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POSTDOCTORAL STUDIES

Derek Richard Tomson

AUTEUR DE LA THÈSE / AUTHOR OF THESIS

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TITRE DE LA THÈSE / TITLE OF THESIS

Julian Little

DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

David Moher

CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR

EXAMINATEURS (EXAMINATRICES) DE LA THÈSE / THESIS EXAMINERS

Brenda Wilson

Bernard Choi

Gary W. Slater

Le Doyen de la Faculté des études supérieures et postdoctorales / Dean of the Faculty of Graduate and Postdoctoral Studies

EVALUATING THE ASSOCIATION BETWEEN ADULT PRIMARY BRAIN TUMOURS AND A FAMILY HISTORY OF CANCER

By Derek Tomson

Thesis submitted to the School of Graduate Studies and Research in partial
fulfillment of the requirements for the M.Sc. degree in Epidemiology

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Thesis Supervisors:

Dr. Julian Little
and
Dr. David Moher

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ABSTRACT

There are very few established causes of primary brain tumours in adults. Associated with short survival times, increasing effort is being put forth in an attempt to better understand the risk factors of these neoplasms, including investigating the possible relationship with a family history of cancer and germline genetic polymorphisms. This thesis was conducted to evaluate both of these potential associations.

Using an international population-based case-control study, the self-reported family histories of cancer were compared between 1089 glioma cases and 1922 matched controls and between 307 meningioma cases and 1095 controls. Significantly lowered odds of glioma were associated with the reporting of any type of cancer in a first degree relative (OR = 0.8, 95% CI = 0.7-0.99) and with any type of cancer excluding brain tumours (OR = 0.8, 95% CI = 0.7-0.9). No significant associations were found amongst the meningioma cases and controls, though elevated point estimates were found for those reporting parental lung and genitourinary cancers, while the presence of breast, lip, oral, pharyngeal and unspecified cancers all produced great reductions in meningioma odds, suggesting that further study is required.

In order to evaluate the association between adult brain tumours and genetic polymorphisms, a systematic review of the literature was completed. A total of 41 case-control studies were included, covering 46 separate genes and more than 100 different single nucleotide polymorphisms. When possible, quantitative data synthesis was performed to establish a more refined point estimate and confidence intervals. Heterogeneity across the studies and variability in the subject matter often prevented any possible data synthesis so establishing associations that were statistically significant was difficult. All told, there were 41 significant associations found amongst the included studies and each varied by the particular polymorphism or histology studied. None of the estimates produced in the quantitative data syntheses suggested a statistically significant association.

The results of this thesis suggest that a family history of cancer is not a risk factor for primary brain tumours in adults and that further work is necessary to better establish the possible association between various genetic polymorphisms and adult brain tumours.

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1.0. INTRODUCTION

1.1. Primary Brain Tumours in Adults

Primary brain tumours (PBTs) are neoplasms that are first formed in the brain, as opposed to secondary brain tumours which metastasize to the brain from other parts of the body. PBT histologies are determined by the type of cell in which they originate. Two of the most common histologies are gliomas, which form in glial cells, and meningiomas, which originate in the meninges. Taken together, these two PBT types make up 65-95 percent of all reported adult brain tumours (1,2).

Currently, there are very few established risk factors for adult PBTs. High-dose exposure to ionizing radiation (3) and hereditary syndromes (4-7) have been associated with increased risk for the development of both glioma and meningioma, but this accounts for less than five percent of the worldwide incidence (8). With survival times estimated at less than one year after diagnosis for the more severe forms of adult PBTs (9-11), gaining a better understanding of the risk factors associated with the disease is important.

1.2. Primary Brain Tumours and a Family History of Cancer

The case-control study reported by Choi et al (12) in 1970 was the first published attempt to establish whether a family history of cancer is associated with a change in odds (henceforth referred to as risk) of adult brain tumours. Since then, numerous other studies have been completed and the results have been highly inconsistent, with multiple studies suggesting increased risk while many other imply that a family history of cancer lowers one's risk of PBT or that no association exists. A great deal of this inconsistency

can be attributed to differences in the study methods, including number and relationship of the relatives studied, the validation of the family cancer history, and the manner in which the controls were selected (13).

1.3. Primary Brain Tumours and Genetic Polymorphisms

Rare genetic familial syndromes such as neurofibromatosis I and II (4), tuberous sclerosis (5), and Li-Fraumeni syndrome (6) have all been established as risk factors for the development of PBTs in adults. The genetic disorder that is passed on from parents to offspring increases the child's likelihood of developing a brain tumour later in life. Based on this, a number of studies have been completed which have investigated the possible association between germline single nucleotide polymorphisms (SNPs) and PBTs.

A great deal of variability exists amongst the studies covering the association between SNPs and adult PBTs due to the vast number of SNPs found within the human genome, not to mention the different types of tumour studied and the population the authors selected from. Assessing all of the different findings and keeping track of all of the possible associations can be a very tedious task. While there are published systematic reviews available (14), these are restricted to a handful of genes and common SNPs. They do not provide a complete overview of the current research available regarding genetic polymorphisms associated with PBTs in adult populations. Such a review could help to establish possible relationships by synthesizing the available data and providing more reliable estimates than single studies can provide.

1.4. The SEARCH Study

The Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH) study was an international, multicentre, population-based, case-control study conducted to investigate hypothesized risk factors for glioma and meningioma in adults. The glioma participants and their matched controls were recruited in Melbourne and Adelaide (Australia), Toronto and Winnipeg (Canada), Grenoble (France), Heidelberg (Germany), Stockholm (Sweden), and Los Angeles (USA). Adults diagnosed with meningioma and their controls were from Adelaide, Toronto, Winnipeg, Grenoble, Heidelberg, and Stockholm. The study was coordinated by the International Agency for Research on Cancer.

Cases between the ages of 20 and 80 with histologically confirmed gliomas or meningiomas diagnosed between 1980 and 1991 were eligible for inclusion in the study. Population-based controls were recruited at each study centre using various methods, such as random-digit dialing, population registries, and census records. Each of the included participants completed either a face-to-face interview with trained interviewers or a self-administered questionnaire. Questions covered the number of first degree relatives (mother, father, siblings, and children) and specific family cancer histories, as well as their age and education level. Proxy respondents, individuals who provided responses on behalf of the intended participant, were allowed and their use was recorded. The most common proxies were the spouse of the study subject. An assessment was made by the interviewer regarding how well the interviewee seemed to understand what was being asked of them.

1.5. Research Objectives

- To examine the potential association between a family history of cancer and adult PBTs.
- To determine whether this possible association varies depending on: the type of PBT (glioma or meningioma), the cancer site in first degree relatives, the relative with the cancer, the age of the participant, the socioeconomic status of the participant, the geographic location of the participant, or the manner in which the relevant information was obtained by the SEARCH study coordinators.
- To conduct a systematic review of case-control studies evaluating the potential association between adult brain tumours and genetic polymorphisms.
- To complete quantitative data synthesis of case-control study results for specific SNPs and adult brain tumour histologies.

2.0. LITERATURE REVIEW

2.1. Biology and Clinical Features of Primary Brain Tumours

2.1.1. Definition

A brain tumour consists of either the growth of abnormal cells or the uncontrolled growth of normal cells in the brain. The specific lineage of the normal cell that experiences this non-regulated growth helps determine the histology of the tumour.

PBTs refer to those tumours which originate in the brain, rather than metastasizing to the brain from another part of the body. The third edition of the International Classification of Diseases for Oncology (ICD-O) (15) is used worldwide for recording cases of tumours of the brain (ICD-0 III location codes 191.0-191.9) and of the meninges (192.1 and 192.3). The classification of these tumours depends on a variety of factors, such as the exact location of the tumour within the brain, the type of tissue involved, and whether the tumour is malignant or benign. The two tumour types of particular focus in this thesis are gliomas and meningiomas. Gliomas and meningiomas represent the most common forms of PBTs in adults, together having been estimated to account for between 65 (1) and 95 percent (2) of all cases.

2.1.2. Types of Primary Brain Tumours

Glioma

Glioma is the general term used for tumours that begin in the glial cells of the brain. They are further categorized by the specific type of glial cell from which they originate, thus PBTs such as astrocytomas and oligodendrogliomas can be referred to more generally as gliomas. These tumours may exist in both benign and malignant

forms, with lower grade gliomas tending to be slower growing, less aggressive, and conferring a better prognosis for the patient, while higher grade gliomas display anaplastic tissue, are fast growing, and are often reported to spread to other tissues throughout the body. This distinction between high- and low-grade gliomas is important because differences exist in the manner in which these different tumour types are treated (16).

Astrocytoma

Primary astrocytomas originate in the neurological cells of the brain called astrocytes. There are four grades of astrocytomas, with grades I and II representing benign tumours that are associated with epileptic seizures due to the tumour irritating the surrounding brain tissue. Diffuse astrocytomas are the most common form of low-grade glioma, typically diagnosed in individuals who are in their late-thirties or older, producing average survival rates of seven years, though approximately 20 percent of cases will survive for more than ten years after diagnosis (17). Grades III and IV refer to the more serious malignant forms of astrocytoma, also known as anaplastic astrocytomas, with average survival rates of 18 and 12 months respectively, depending on the age of the patient and how well he or she responds to therapy (18). A specific sub-type of grade IV astrocytoma is known as glioblastoma multiforme, whose hallmark characteristics are the ability to quickly spread throughout the brain and cause massive areas of cellular necrosis.

Oligodendroglioma

Oligodendrogliomas arise from the oligodendrocytic cells of the brain. These cells, normally responsible for the production of the myelin sheath, will experience rapid

growth in numbers as the tumour develops. It is thought that most oligodendrogliomas arise from oligoastrocytomas, or mixed gliomas, in which tumours originate from both astrocytes and oligodendrocytes (18). Classification of oligodendrogliomas usually consists of low grade/benign, anaplastic, and malignant tumours.

Meningioma

Meningiomas are brain tumours that originate from the meninges covering the brain. They are primarily benign and very slow growing, and they can be present for years without the development of any outward signs of disease. Similar to astrocytomas, the presence of seizures associated with the tumour is due to the irritation of adjacent brain tissue. Occasionally, “atypical meningiomas” will develop which are much more aggressive in terms of growth and causation of symptoms, likening them to a more malignant-like tumour.

2.1.3. Classification and Grading

The World Health Organization (WHO) introduced a system for the classification of central nervous system tumours in 1993, which was further revised in 2000 (15). The purpose of this system was to provide grading guidelines based on tumour prognosis. The advantages of this system are that it is fairly simple, as each tumour type is of a single defined grade from I to IV, and that gradation provides a guide to the appropriate mode of therapy. The WHO classification system stratifies tumours on the basis of their biological potential. Tumours with grades on the lower end of the scale have more favourable prognosis, usually reserved for those tumours with a stable histology, while those with higher grades are more severe malignancies.

As mentioned above, the non-invasive, benign astrocytomas are classified as grade I tumours, as well as slow-growing and benign meningiomas. PBT types which fall under the category of WHO grade II include diffuse astrocytoma, oligodendroglioma, and oligoastrocytoma. Anaplastic and malignant astrocytomas are classified as WHO grade III tumours, as well as anaplastic oligodendrogliomas and oligoastrocytomas. The rare malignant meningiomas are classified under grade II or III depending upon their severity. The most severe PBTs, the grade IV tumours, include the glioblastoma multiforme, which are often more simply referred to as gliomas in the literature.

2.1.4. Signs and Symptoms

There are a number of established signs and symptoms of PBTs. Headaches, vomiting/nausea, and general malaise are common. Often, personality changes, including emotional instability take place. Intellectual decline is associated with PBTs, with cases being faced with impaired judgment, loss of memory, and a reduced level of consciousness. Finally, a number of neurological changes can take place as a result of the tumour. Cases may experience vision problems, such as double vision and decreased acuity; hearing loss, difficulties in normal speech patterns, and they may report feelings of dizziness, clumsiness, and decreased coordination of motor movements (17).

The signs and symptoms described above can result from seizures, cerebral edema, or obstructive hydrocephalus, which is the blockage of the normal flow of cerebrospinal fluid to the brain. The uncontrolled cellular growth that leads to the tumour formation results in the disruption of connections between normal brain cells, as well as introducing a great deal of pressure on the adjacent brain (17). Since there is limited

room for cellular expansion within the skull, even small tumours can induce a great deal of brain dysfunction and death.

2.2. Trends in Primary Brain Tumour Incidence and Mortality

Recent estimates by the National Cancer Institute of Canada have suggested that in 2004 there were 2300 new cases of PBTs in Canadian adults (19). The age-standardized incidence rate of brain cancer per 100,000 Canadians in 2000 was eight for males and six for females, while the age-standardized mortality rate was six males and four females (19). These numbers are consistent with global findings for other developed, industrial nations. The International Agency for Research on Cancer reports that for North America, Western Europe, and Australia, there are 6-11 new cases of PBTs per 100,000 men in these regions and 4-11 new cases per 100,000 women (20).

In less developed countries, the incidence of PBTs is lower (3 per 100,000 men and 2 per 100,000 women) (21). However, due to the lack of consistent information concerning the causes and determinants of PBTs, difficulty exists in interpreting whether or not a true difference exists. It has been suggested that the increased incidence in the developed countries may be attributed to greater access to healthcare, improved diagnostic procedures for case ascertainment, and better reporting of incidence (22,23). Yet, within the subset of developed countries there exists great variability. For example, developed Asian countries such as Singapore and Japan have reported incidence of astrocytomas of less than two per 100,000 males and less than one per 100,000 females compared to Canada, which has an incidence of nearly four cases per 100,000 males and three per 100,000 females (20). Another study found that the incidence of gliomas in

Japan was roughly half of that in the United States (24), suggesting that susceptibility may be influenced by ethnic differences.

Similar to the debate surrounding the differences in incidence rates between developed and developing countries, there is no universally accepted opinion regarding the change in incidence of PBTs over time. Arguments have been made by a number of studies (25-27) that report findings suggesting an increasing worldwide incidence of PBTs, particularly in the elderly. However, it has also been proposed that this is related to improved diagnosis and reporting of intracranial tumours, as supported by the apparent leveling off of PBT mortality and incidence rates after they had greatly increased following the widespread introduction of computed tomography (CT) scans and magnetic resonance imaging (MRI) in the late 1970s and early 1980s (28). This has led to further debate. Werner et al (29) looked at the incidence of PBTs and found that, after controlling for the confounding effect of improved diagnostic techniques, there was a true incidence rate increase over time. Yet, the findings of Gurney et al (30) and Lonn et al (31) both show a stabilization of incidence rates in all age groups taking place in the late 1980s to early 1990s.

Mortality for PBTs is influenced by both the type of tumour as well as the age of onset. In a review by Ohgaki et al (22), median, mean, one-year, two-year, five-year, and 10-year survival data was summarized. For all tumour types, mortality increased as the WHO grade of the tumour increased. Patients with grade II astrocytomas reported median survival of 67 months and one-year survival of greater than 70 percent and 10-year survival greater than 25 percent. Individuals diagnosed with grade IV gliomas could only expect a median survival of 4.9 months, with one- and 10-year survival rates of less

than 30 and less than 2 percent, respectively. The Surveillance, Epidemiology, and End Results Program (SEER) reported that the five-year survival rate following the diagnosis of a primary malignant brain and central nervous system tumour is 28.1 percent for males and 30.5 percent for females (1973-2002) (32). Those diagnosed between the ages of 20-44 years had better five-year survival rates (47.9 percent), while those diagnosed between the ages of 45-54, 55-64, 65-74, and 75 or older had increasingly worse rates of survival (23.1, 10.7, 6.6, and 4.8 percent, respectively).

2.3. Risk Factors

2.3.1. Sex

As suggested in section 2.2, there exists a difference in the incidence of PBTs by sex. In Canada in 2004, the age-standardized incidence of brain tumours in men was roughly two more new cases per 100,000 than in women (19). Surawicz et al (33) found that in the United States there were 80 percent more female cases of meningioma, while glioma tended to occur more frequently in men, with a 40 percent increase compared to females. This 40 percent difference has been shown to increase from the average age of menarche until the average age of menopause, which has prompted the hypothesis that female hormones may serve a protective function against the development of primary gliomas (34).

2.3.2. Age

The Central Brain Tumor [*sic*] Registry of the United States (CBTRUS) found that the average age of onset for a PBT was roughly 54 years of age (32) and 62 years of age when including only those with meningioma and glioma. In a review by Wrensch et al (23), they compared the reported incidence rates of various brain tumour types by the following age groups: 0-19 years of age, 20-34, 35-44, 45-54, 55-64, 65-74, 75-84, and 85 or older. They found that meningioma increased across all age groups until experiencing a very slight decline in the 85 and older category. Glioblastoma and astrocytoma both peaked in the 65-74 year old age group; mixed gliomas, or oligoastrocytomas, in the 55-64 category; and oligodendroglioma at 35-44 years old. When taking all tumour types as a whole, the incidence steadily increased with age until a slight drop in the 85 and older age group. A more recent study by Chakrabarti et al (35) found that age-specific incidence rates of glioblastoma multiforme in Los Angeles County subjects rose sharply after 30 years of age, peaking at ages of 70-74 in males and 75-79 in females.

2.3.3. Ethnic Group

Previous research has indicated that the incidence of all PBTs is higher in whites than it is in blacks (36). With specific regards to gliomas, whites have also reported higher levels of incidence than blacks (37,38) and Asians (24). However, other studies have shown there to be no difference by ethnic group amongst meningioma cases (32) and analysis of the SEER data revealed no survival difference by ethnicity amongst whites and blacks with malignant PBTs (39).

2.3.4. Family History of Cancer and Primary Brain Tumours

Studies have shown that an association exists between primary brain tumours and several familial cancer syndromes, the most common of which are neurofibromatosis I and II (4), tuberous sclerosis (5), Li-Fraumeni Syndrome (6), and von Hippel-Lindau disease (7). The association of increased tumour risk in those individuals with a familial history of these syndromes supports the hypothesis that there exists a genetic predisposition to brain tumour development. That being said, it has been estimated that these hereditary syndromes account for less than five percent of all brain tumours reported in adults worldwide (8).

Another means of investigating the hypothesis of a genetic predisposition is the examination of the proband's family history of various forms of cancer. While a family history of cancer may be due to similar environmental exposures, it is also thought that it may be an indication of the inheritance of rare, highly penetrant mutations which do not have a great impact on cancer risk in the general population, including mutations in the *p53* and the *xeroderma pigmentosum complementation group D* genes (11,40).

Relatively few observational studies have been conducted so far that examine the potential association of a history of cancer in first degree relatives and brain tumour risk (11). At this point, there seems to be little agreement as to whether or not a family history does impact PBT risk in adults.

Malmer et al (1) compared the risk of glioma between spouses of patients with PBTs and their first degree relatives with the purpose of distinguishing between environmental and genetic effects. Their cohort study found that the risk for a PBT of any type was significantly increased by two to three times amongst first degree relatives,

while for spouses there was no effect, supporting the notion of a genetic predisposition. Other investigators have focused on using cancer-based registries or case-control studies to assess the significance of a family history of a wide variety of cancers, comparing the incidence of cancer in families of cases with PBTs to the families of cancer-free controls.

A great deal of the focus has been on the relation to glioma risk in particular. A number of case-control studies (8,12,41,42) have found that the risk of glioma was elevated amongst those individuals reporting a first degree relative with some form of central nervous system cancer, whereas others (9,43-46) have suggested that there is no change in risk. Taken together, the odds ratios from these studies form a range of 0.7-3.6 and do not achieve statistical significance (11). Similarly, a second review of the literature by Wrensch et al (23) found that there was no general consensus concerning the reported relative risks of brain tumours amongst family members of brain tumour cases, including those that were restricted to siblings and twins. In an attempt to assess the risk of glioma in relation to a family history of cancer, while controlling for the effect of family size and age of the individual, investigators in the United States (47), Sweden (48,49), and Iceland (50) utilized genealogical information provided by cancer registries. Each of these studies found non-significant elevated risks of glioma in those who had a first degree relative with some form of central nervous system cancer (RR = 2.0, 1.6, and 1.7, respectively).

Other cancers studied in first degree relatives as risk factors for PBTs in adults have included oral (11), stomach (11,47), colon (11,51), lung (11,42,44), breast (11,42,44), melanoma (11,47,52), prostate (11,47,53-55), and Hodgkin's disease (11,56,57). The study by Hill et al (11) covered all of these cancers, as well as cancer of

the ovary, leukemia, and skin, bone, bladder, and cervical cancer. The Hill case-control study consisted of 468 adult cases with glioma and 768 cancer-free hospital-based controls from the United States and after adjusting for age, ethnicity, sex, location, and proximity of residence to hospital, they found that only a family history of stomach (OR = 2.2, 95% CI = 1.0-4.6) and prostate cancer (OR = 2.1, 95% CI = 1.1-3.8) were statistically significant. This increased odds of glioma associated with familial stomach cancer has been seen in a previous study using a United States cancer registry (47), but was not found in the analysis of a Swedish population-based cancer registry (52). The presence of first degree relatives with prostate cancer has been linked to an increased risk of glioma in three previous studies (47,53,54), but not so in a fourth (55). Hill et al did not find an elevated odds of glioma associated with a family history of lung cancer (OR = 1.0, 95% CI = 0.6-1.6) and only a slight increase in breast cancer (OR = 1.2, 95% CI = 0.8-1.9), in contrast to previous studies (42,44) which found a significantly elevated risk. Likewise, the previous research covering oral and colon cancers, melanoma, and Hodgkin's disease in first degree relatives has produced inconsistent results (11).

Care must be taken in interpreting the results of the possible association between a family history of cancer and PBTs in adults. Studies that do not take into account potential confounders such as the number of relatives at risk, the age distribution of the relatives, and the accuracy of the reporting are prone to produce biased results (11). While case-control studies must account for recall bias in their subjects, cohort studies will be faced with dealing with limited statistical power due to the fairly low incidence rates associated with adult brain tumours.

2.3.5. Genetic Polymorphisms

Previous research has found a clustering of PBTs amongst families with hereditary syndromes that are caused by inherited rare mutations in highly penetrant genes, such as tuberous sclerosis and neurofibromatosis (4-7), but as mentioned previously, these cases do not represent a large portion of the worldwide incidence of PBTs (8). Therefore, a recent focus of research has been to examine the possible associations involving more common genetic aberrations (found in greater than one percent of the population), termed polymorphisms, in genes that have been postulated to influence tumour susceptibility. Investigators have looked at genes involved in metabolizing chemicals, regulating the cell cycle, tumour suppressor genes, DNA damage repair, and cellular growth and development for polymorphisms which might be associated with a change in risk of PBTs in adults.

There have been more than 40 case-control studies published in the past 12 years evaluating the association between genetic polymorphisms and adult-onset PBTs, covering variants on more than 40 different genes. Great variation exists in their methodology. Some reports focused on a specific histology, others looked for differences in distinct geographic locations, while a few studies have attempted to establish the presence of a genetic polymorphism and environmental exposure interaction term that could impact tumour susceptibility.

To this point, the results have been highly inconsistent. Depending on the specific polymorphism being investigated, significant findings have been published suggesting both protective and harmful effects associated with the variant genotype. The glutathione *S*-transferase genes *M*, *T*, and *P* have been investigated to the greatest extent

thus far, but associations between PBTs and genetic variants coding for cytochrome *P450*, enzymes of the *excision repair cross-complementing* genes and the *p53* gene have all been investigated in multiple studies. These case-control studies are discussed in detail in the systematic review of the association between genetic polymorphisms and PBTs presented in section 4.3 of this thesis.

2.3.6. Socioeconomic Status and Education Level

Since there has already been shown to be a difference between the incidence rates of PBTs amongst developed and developing countries, an area of focus for potential risk factors of brain neoplasms in adults has been the reported income and highest level of education achieved. This has been done as a means of estimating a participant's socioeconomic status. At this point, there are no definitive associations between socioeconomic status and PBTs, though a few significant and similar trends have been found across a number of studies.

Separate studies in the United States (58), Australia (59), and New Zealand (26) have reported that brain tumours were more likely to exist amongst men of higher socioeconomic status or living in more affluent neighborhoods. Men classified as “white collar workers” have been found to have an elevated risk of glioma (60). In the analysis of the association between cancer in first degree relatives and the risk of glioma in adults, Hill et al (11) found that the glioma cases tended to have both a higher education level and a greater reported income than the control subjects. A study of glioma cases and controls from three different American hospitals established that, for their participants, a significant positive association existed between household income and low-grade glioma

and meningioma, but there was no significant association for high-grade glioma (61). The same study found a positive association between increasing level of education and risk of low-grade glioma, but not for high-grade glioma or meningioma. Finally, one group looked at whether or not Medicaid enrollment in the state of Michigan may be associated with PBTs (62). The hypothesis was that individuals on Medicaid would be representative of lower socioeconomic status compared to those who were not enrolled in the program. In contrast to the general trend that higher socioeconomic status is linked to greater risk, this study found that those signed up for Medicaid were actually at a greater risk of developing both glioblastoma multiforme and astrocytoma.

2.3.7. Ionizing Radiation

Exposure to high doses of ionizing radiation remains, along with the familial cancer syndromes mentioned earlier, the only established risk factors for glioma and meningioma (23,63-65). Previous studies have shown that an increased risk for the development of brain tumours arises with both acute and episodic exposures. Analysis of the cohort of survivors of the atomic bombings of Hiroshima (66,67) and Nagasaki (67,68) revealed a dose-related excess of nervous system tumours, with an increased risk for both gliomas and meningiomas. A case-control study conducted by Ron et al (69) examining the risk associated with low-dose therapeutic radiation in childhood for the treatment of tinea capitis and subsequent tumour development found increased incidence of glioma and meningioma. A number of studies have shown elevated risk of adult brain tumour development associated with patients who had undergone radiation therapy during childhood for lymphoblastic leukemia (70-72) and for cancers other than leukemia

(73,74). A recent case-control analysis by Phillips et al (75) found a nearly four-fold significantly elevated risk of meningioma in patients previously receiving radiation therapy to the head and neck.

Debate does exist concerning exposure to ionizing radiation as a result of diagnostic techniques. Of particular interest has been the episodic exposure that comes with diagnostic X-ray application in dental offices. The general findings seem to be that there is a positive association between episodic exposure and meningioma in adults (76-78), with each of the three studies finding a greater than two-fold significantly increased risk. Interestingly, there was a stronger effect for those X-rays that were taken more in the past, which suggests that the manner in which they are now being used may reduce their potential for harm. At this time, it is unclear whether this reduction in effect is due to a latency period that is still confounding the more recent exposures or as a result of different methods of practice. For glioma, the results have been much more inconsistent (79,80), with no clear association or lack thereof currently established.

2.3.8. Electromagnetic Fields

Exposure to electromagnetic fields (EMFs), both in the home and as a result of occupation, has been a topic that has been extensively studied in relation to brain tumour development. Since EMFs have not been proven to cause chromosomal damage, it is thought that they may act as tumour promoters, as opposed to tumour initiators (81). Tumour promoters have an exposure threshold at which point they become active and display a reversibility of effects (82), so researchers have tried to differentiate possible relationships based on the magnitude of the EMF and the aggressiveness of the tumour.

Despite the specification of different frequencies of exposure, duration of exposure, and tumour histology, the results remain highly inconsistent.

Previous case-control studies have been carried out examining the risk of brain tumours in relation to EMFs from high-voltage power lines close to one's permanent residence and no clear association was established in any of them (81,83-86). However, the findings from these studies should be interpreted with caution, since none of them are based on personal measurements of exposure, but rather on expected EMF exposure found from calculated magnetic fields based on approximated exposure variables such as residential proximity and power line load records.

There are two separate reviews of the available literature concerning the possible association between occupational EMF exposure and brain tumours. Ahlbom et al (87) reviewed 10 studies, of which five suggested a positive association and five suggested no association. A meta-analysis of 29 studies by Kheifets et al (88) did find a very small, though statistically significant, overall increase in risk of brain tumours related to occupational EMF exposure. Significant results have also been found for particular groups, including increased risk of glioblastoma multiforme for men with occupational EMF exposure (82) and increased risk of brain tumours for men enlisted in the United States Air Force who were exposed regularly to EMFs (89), but the majority of the results point to no association. One major concern in interpreting these results is the accuracy of the exposure classification. There is concern that relying on job titles to determine exposure over a long period of time does not take into account the effect of working across a multitude of locations and exposure to other potential risk factors (2,90).

However, others have found that relying on self-reporting of exposures and not occupational title leads to lower validity and reliability of exposure status (91).

A third area of EMF exposure that has received attention as having a possible link to increased risk of brain tumour development is the use of various household appliances. Kleinerman et al (92) looked at the self-reported use of 14 different commonly used electrical items which emit extremely low frequency EMFs. While 12 of the 14 listed appliances were not associated with a change in risk, “ever” versus “never” use of a hair dryer was associated with an increased risk of glioma (OR = 1.7, 95% CI = 1.1–2.5) and the use of electric shavers by men was associated with a significant increase in the risk of meningioma (OR = 10.9, 95% CI = 2.3–50). The authors do advise caution in interpreting the latter result since it is based on only two cases. A second study by Mutnick and Muscat (93) found that no risk of brain cancer was present with the regular use of personal computers, electric heaters, electric hair dryers, or electric razors, while Ryan et al (46) reported elevated risks of glioma with regular use of an electric blanket and meningioma with electric waterbed heaters. Further study of brain tumour risk related to household appliance usage would be helpful in assessing whether EMFs may act as tumour promoters or not. If they indeed are tumour promoters, one would expect that odds ratios would fluctuate based on the time since the last use and the amount of use, due to the reversibility of effects and threshold nature, respectively, of tumour promoting agents.

2.3.9. Occupational Exposures

Occupational risk factors for the development of glioma and meningioma in adults have been extensively discussed in previous literature with little agreement about the results. A wide range of jobs and the relevant chemicals, compounds, and electromagnetic forces associated with each have been examined in numerous case-control and cohort studies, but no single exposure has emerged as a definitive risk factor to this point. Some of the more common occupations and industries that have been studied are those which include likely exposure to neurotoxic or carcinogenic substances, such as organic solvents, phenols, and polycyclic aromatic hydrocarbons (PAHs).

The petrochemical industry in particular has been one of focused study. While there have been a number of case-control and cohort studies that have found elevated risks for both glioma and meningioma (94-97), evidence also exists which suggests that there is no association between job-related exposure to petrochemicals and elevated risk of brain tumours (2,98). A problem confounding the possible association is the lack of the identification of a single responsible agent. Petrochemical workers may be exposed to both aromatic and aliphatic petroleum hydrocarbons, as well as numerous other carcinogens (98), making it extremely difficult to assess the impact of one compound.

A second area that has generated a great deal of interest is exposure to the common chemicals used in the farming industry associated with PBTs. Pesticides, organochlorides, and alkylureas are all potential exposures for those employed in agriculture, and each has been shown to induce cancer in animal experiments (23). Khuder et al (99) conducted a meta-analysis of brain tumours and farm occupation which included 33 papers. The overall odds ratio was found to be 1.3 (95% CI = 1.1-1.5),

suggesting a weakly positive association with farming. This finding has been further supported by studies looking at insecticide and fungicide exposure in women (100) and herbicides in wheat farmers (101). However, one of the largest case-control studies conducted on adults with incident cases of brain tumours (2) did not find any association with self-reported employment in the agriculture industry. These findings are comparable to the recent results produced by Pan et al in a similar study (102).

Industries related to the production of rubber and plastics have also been considered a great deal in previous literature, with a focus on the exposure to vinyl chloride. Increased risk of brain cancer with exposure to vinyl chloride has been found in some studies (103,104), but a greater number have been unable to establish a statistically significant elevated risk (102,105-107). Other potential carcinogens that have been explored include polyethylene, polystyrene, and polyurethane, but the results have not been consistent.

As mentioned, a wide range of occupations have been assessed for potential associations with increased risk of glioma and meningioma. Studies examining police officers, medical professionals, textile workers, computer programmers, childcare professionals, metal workers, and painters are just a few of the litany of professions that have been considered. Despite the effort, there is no conclusive evidence to suggest that any one profession, and especially one particular exposure associated with that profession, can be considered as a definitive risk factor. Limitations due to small sample sizes in case-control studies, low incident rates of brain tumours in cohort studies, and the difficulty in establishing individual exposure based on job descriptions makes any interpretation of these results challenging and it should be done so with caution.

2.3.10. Cellular Telephones

Concern has been raised over whether the use of cellular telephones is associated with a higher risk of brain tumour development, stemming from the fact that they operate at radio frequencies, a form of electromagnetic energy that has long been a subject of public concern (22). To date, there seems to be little evidence to support the idea of an association between cell phone usage and either meningioma or glioma. Only one case-control study (108) found a significantly increased risk ($OR = 1.85$, $95\% CI = 1.12-3.39$), while there have been a large number which report no significant associations (86).

Recent interest has been generated in determining whether there is a significant association with cell phone use restricted to the same side of the temporal, tempoparietal, and occipital areas of the head where the tumour is located. Though an elevated odds ratio was found ($OR = 2.42$, $95\% CI = 0.97-6.05$) in the Hardell study (109), this result did not achieve statistical significance and was based on only 13 cases. The largest case-control study completed to date on the subject of cellular phone use and PBTs found an association between the tumour location and the side of the head that the participants reported to use most frequently to make calls (110). However, when they controlled for handedness of the participant, since right-handed people most often hold the phone to the right side of their head and left-handers to their left side, the association was null. The authors suggest that this perceived association was more likely due to recall bias in an attempt by the cases to help explain the cause of their tumour.

Although the majority of the current research suggests that no association exists between cell phone use and brain tumours, it would seem reasonable to continue to examine this potential relationship. Not only is cell phone use increasing in both the

number of people and the number of hours by individuals, but there may be a latent period that has yet to be revealed due to the relative newness of cellular telephones (23).

2.3.11. Diet

The possible role of diet in the etiology of adult brain tumour development remains highly controversial. Not only are there questions concerning the activity of different chemical compounds in the brain, but there remain unresolved issues about the validity of diet studies themselves. The areas of concern include the lack of a distinction between those who self-report consuming high levels of a specific compound as opposed to those who report consuming high levels of all compounds, the need for a food composition database which can provide complete nutrient and non-nutrient information on food composition, and more reliable analytical chemical techniques for determining food composition (111). With such levels of uncertainty, caution must be exercised in interpreting diet study results, particularly those which combine results from heterogeneous populations.

Numerous studies conducted in animals have shown that various *N*-nitroso compounds, in particular the nitrosoureas such as methylnitrosourea, ethylnitrosourea, and alkyl nitrosourea, can induce brain tumours (112-114). Studies have also demonstrated that the ingestion of nitrites and alkylureas results in the formation of alkyl nitrosoureas in the human stomach (113). Nitrites and other *N*-nitroso compound precursors are commonplace in industrialized society, with uses ranging from cosmetics to a wide variety of processed foods, especially cured meats. In contrast, the consumption of products with high concentrations of anti-oxidants, such as fresh fruit

(41,115), fresh vegetables (114,116), fresh fish (114), and an assortment of vitamins (43,112), have been suggested to provide a protective effect against brain tumour development. These anti-oxidants block the endogenous nitrosation of *N*-nitroso compounds in the stomach due to their nitrogen scavenging nature (114). Based on this information, a hypothesis has been put forward that a diet high in the consumption of cured foods and low in the consumption of fresh fruits and vegetables be considered high risk for the development of adult brain tumours (112).

Table 1 summarizes previous studies that have looked at the possible role of diet associated with brain tumours. Based on the different foods studied, the manner in which the diet was ascertained, and the type of tumour investigated, comparing the various results becomes difficult. Added to this is the fact that the assessment of exposure to *N*-nitroso compounds from dietary sources is considered to be problematic (117). It appears that there tends to be a slightly increased risk of tumour development among those reporting consumption of cured or processed foods, while the average risk tends to decrease among those eating fruits and vegetables and/or taking vitamin supplements, but these results vary greatly from study to study. This inconsistency has also been shown in a recent meta-analysis by Huncharek et al (118), which pooled the results of nine studies examining the possible association of dietary *N*-nitroso intake from cured meats and the risk of glioma in adults. They found that there was a lack of statistical heterogeneity amongst the studies ($p=0.58$) and concluded that the available data does not provide clear support of the hypothetical association between cured meat intake and subsequent adult brain tumour development.

Some studies have tried to establish a possible dose-related association between different foods and the risk of brain tumours. This has added to the variability of the results, as some found protective effects in the lower exposure groups and harmful effects at the mid-range and highest exposure levels, while others report opposite findings (114,117,119). Investigators have also examined whether certain combinations of foods or diet types can be linked to brain tumour development. Significant associations have been found in men who report high consumption of cured foods and low consumption of fruits and vegetables rich in vitamin C (OR = 2.0, 95% C.I. = 1.2-3.5) (112), a diet high in nitrite and low in vitamin C for men only (OR = 2.1, 95% C.I. = 1.1-3.8) (112), and for those who ate bacon with citrus juice less than 50% of the time (OR = 2.5, 95% C.I. = 1.1-5.5) (114), though each of these results are restricted to a single paper.

It has been suggested that the relationship seen between cured meat consumption and glioma risk may be confounded by total energy intake (120). A subsequent case-control study that took this value into account found that the positive associations between different cured meats and glioma development did decrease as a result of adjusting for caloric intake, but the sample size used was very small ($n = 40$), bringing the validity of the results into question. Kaplan et al (121) found a significantly elevated risk of both glioma and meningioma development associated with high protein intake, which would support the hypothesis of the link with cured meat, but at the same time they report that high sodium intake served as a significant protective effect, and that a diet high in fat and cholesterol was inversely associated with tumour risk, though these findings were not statistically significant.

Table 1. Description of studies that have evaluated the potential association between diet and adult brain tumours.

First Author, Year	Type of Tumour Studied	Dietary Associations				Vitamin supplements
		Cured/processed foods	Fruits and vegetables	Dietary nutrients		
Ahlbom, 86	Glioma	Bacon/ham (++), smoked sausage (+), smoked fish (+)	Not reported	Not reported	Not reported	
Burch, 87	Glioma	Meat (-), fish (+)	Fruit (-)	Not reported	Vit C (-), vit E (-)	
Mills, 89	Glioma	Not reported	Fruit (-), vegetarian (-)	Not reported	Vit C (+)	
Preston-Martin, 91	Glioma	Meat (0)	Citrus (-)	Not reported	Any (-)	
Boeing, 93	Glioma, meningioma	Glioma: Meat (++) Meningioma: Meat (+)	Glioma: Potatoes (-) Meningioma: Potatoes (-) All: Fruit juice (0), fruit (+), other veg (-), veg juice (-)	Glioma: Vit C (0), NDMA (++) Meningioma: Vit C (0), NDMA (+)	All: Any (+)	
Giles, 94	Glioma	Men: Meat, fish (+) Women: Meat, fish (+)	Men: Fruit (+), veg (+) Women: Fruit (+), veg (+)	Men: Vit E (++) Women: Vit E (+), vit C (-)	Not reported	
Blowers, 96	Glioma	Bacon (++) other cured meat (+)	Any veg (+), citrus (+), other fruits/juices (-), celery (-), carrots (-), bell peppers (-)	Nitrite in all foods (0), nitrite in cured meats (+), nitrate (-), vit A (-), vit C (+), vit E (+), retinol (+)	Multiple vit (-), vit C (-), vit E (-), mineral supplements (-)	
Lee, 97	Glioma	Men: Bacon(+), cured meats (+), cured fish (+), cured foods (+) Women: Bacon (-), cured meats (++) cured foods (++)	All: Veg/fruit high in vit A (-), veg/fruit high in vit C (-), green beans & legumes (-), other fruits (-), other veg (-)	Men: Nitrates (-) Women: nitrates (-) All: nitrites (+), vit C (-)	Men: Vit C (-), other vit (-) Women: Vit C (-), other vit (-) All: Vit E (-), multiple vit (-)	
Hu, 99	Glioma, meningioma	Meat (-), salted fish (++) salted Chinese cabbage (-)	Potatoes (-), Chinese cabbage (-), fresh veg (-), fruit (-)	Calcium (-), beta-carotene (-), vit E (-), vit C (-)	Not reported	
Chen, 02	Glioma	Meat (+)	All veg (-), dark green veg (-), dark yellow veg (-), tomatoes (-), beans (-), citrus fruit (-)	Nitrate (+), nitrite (+), vit C (-), vit E (-), lycopene (-), lutein (-), retinol (-), pro-vit A carotenoids (-), alphacarotene (-), betacarotene (-)	Not reported	

(++) Significant positive association for cases vs. controls (odds ratio > 1.0) (-) Significant negative association for cases vs. controls (odds ratio < 1.0)

(+) Nonsignificant positive association for cases vs. controls (odds ratio > 1.0) (-) Nonsignificant negative association for cases vs. controls (odds ratio < 1.0)

(0) No association (odds ratio = 1.0) NDMA *N*-nitrosodimethylamine

Based on the lack of consistent findings across the different studies, coupled with the general consensus that it is difficult to obtain accurate reporting of ‘usual’ diet and even more difficult to determine *N*-nitroso compound exposure due to diet (114), diet is not considered to be an established risk factor for adult PBTs. Further epidemiological study is required to gain a better understanding of the impact, if any, that one’s diet may have on their individual risk of developing an adult-onset brain tumour.

2.3.13. Alcohol

The hypothesis that the consumption of alcoholic beverages may lead to an increased risk of brain tumours in adults is based on the idea that certain alcoholic beverages, such as dark beers and spirits, contain high levels of *N*-nitroso compounds and their precursors nitrate and nitrite, which have been shown to induce brain tumours in studies involving animals (122). As well, studies evaluating the effects of alcohol consumption have found that they can deplete blood levels of anti-oxidants (117). At this time, only a few studies have been carried out that investigate this potential causal link, and the results that have been generated are highly variable.

While Burch et al (41) found that there was a significantly elevated risk of brain tumour associated with the consumption of wine, a second study by Ryan et al (46) discovered a decreased risk of glioma and meningioma among those who reported regular drinking of white wine. Ten other studies (12,42,43,45,112,122-126) all looked for a potential association and reported that a significant relationship between liquor consumption and brain tumour incidence did not exist among their respective participants. One case-control study (117) did find a significantly increased risk of

glioma in males whose reported lifetime consumption of liquor exceeded 1000 litres versus those who never drank, but the risk was not significant for those whose stated consumption was less than 1000 litres. Finally, a retrospective cohort study involving World War II veterans (127) found that there was a significantly greater risk of death caused by brain tumours among those participants that were alcoholics as compared to those who were not.

2.3.13. Tobacco Smoke

There are a large number of observational studies that have been previously conducted that looked at smoking as a potential cause of brain tumours in adults. The hypothesis that there may be a causal link is based on the fact that cigarette smoke contains high levels of *N*-nitroso compounds and other carcinogenic compounds that can be absorbed in the lungs and transported to the brain, potentially leading to an increased risk of tumour development (125,128). However, the general trend found in the results is that there is no association. One previous review looking at cigarette smoking and glioma included 10 studies, of which four reported nonsignificant relative risks of less than 1.0, two found a relative risk of 1.0, one found nonsignificant relative risks of less than 1.0 in hospital-based controls and slightly more than 1.0 in population-based controls, and three studies reported nonsignificant relative risks of greater than 1.0 (112).

Efird et al (125) conducted a cohort study of 133, 811 participants that were followed for up to 21 years which aimed to assess the possible relationship between cigarette smoking and the development of primary adult-onset glioma. Though they reported a significant trend for increased risk of glioma with increasing number of packs

of cigarettes per day in women, the odds ratios for each of the exposure categories was non-significant. Other cohort studies conducted include white male veterans, which found no association between current or former smokers and death from cancer of the brain, and Seventh Day Adventists, in which no association between cigarette smoking and incidence of brain tumours was reported. It should be noted that cohort studies such as these may have a difficult time establishing sufficient power to detect a true effect due to the low incidence rates associated with PBTs in adults (125).

Philips et al (129) looked at “ever smoked” versus “never smoked” and found a significant increased risk of meningioma among males, with a significant trend of increasing risk as number of cigarettes smoked per day increased. However, the risk was not significantly elevated in either females alone or in the entire study population as a whole. Another case-control study (122) found a statistically significant increase in risk of glioma among male smokers, but failed to find a significant difference in both females and the combined group of smokers versus non-smokers.

A few experiments have looked at the possibility of an increased risk in brain tumours due to passive exposure to tobacco smoke among non-smokers. Again, the findings have lacked consistency. Efird (125) found no significant association between the development of glioma in adults whose father smoked during their gestation or during their childhood. The cohort study conducted by Hirayama et al (130) found a significant increase for brain tumours among non-smoking females whose husbands smoked, but this was based on only 34 cases of brain tumours. Three other studies (46,114,129) reported a positive association between passive exposure and elevated risk of brain tumours, but of

these three, two (46,129) failed to find a significant link between active smoking and increased risk.

2.3.14. Other Risk Factors

Allergies

Schlehofer et al (131), using the SEARCH dataset, evaluated the possible associations between allergic diseases, separated as asthma, eczema, and 'other', and glioma and meningioma. Their findings suggested a significant inverse association between allergies, taken as a whole, and glioma (OR = 0.6, 95% CI = 0.5-0.7), and significant associations specifically with eczema (OR = 0.6, 95% CI = 0.5-0.9) and allergies other than eczema and asthma (OR = 0.6, 95% CI = 0.5-0.7). An inverse effect was also detected amongst meningioma cases, though this result was not statistically significant (OR = 0.9, 95% CI = 0.6-1.2). In a separate publication which utilized the participants from the Adelaide SEARCH study centre only, Ryan et al (46) detected a significant inverse relationship between gliomas and allergens (OR = 0.5, 95% CI = 0.3-0.9), but not glioma and asthma. All findings pertaining to meningiomas were not statistically significant.

More recent reports have echoed this relationship found between allergens and glioma incidence in adults. Brenner et al (132) found that the reporting of any allergy provided a significant protective effect for glioma cases (OR = 0.7, 95% CI = 0.5-0.9), but not for meningioma (OR = 1.0, 95% CI = 0.7-1.4). Significantly lowered odds of glioma were also found to be associated with asthma and allergies to chemicals. Another case-control study using adult cases with newly diagnosed glioma found that, after

controlling for age, sex, and ethnicity, the reporting of any allergy served a statistically significant protective effect (OR = 0.5, 95% CI = 0.3-0.7), with specific allergies to nuts, pollen, and dairy products also significantly reducing odds (133).

The similar findings amongst the case-control studies of allergies providing a protective effect for glioma suggest the possibility that immunological factors are of etiological importance. However, to this point, no molecular basis to this relationship has been determined (22,131). Lowered risk of other tumour types associated with allergies has led to the suggestion that allergies may cause excessive immune reactions that interfere with the uncontrolled growth of cancerous cells (12,45).

Head Injuries

The association between head trauma and PBTs in adults has been one of great controversy. There exist a number of case-control studies which suggest that prior head trauma leads to an increased risk of brain tumours, as well as those that did not detect any relationship (134). The argument for an association is based on the idea that a severe trauma will induce a strong proliferative astrogliosis at the site of injury, though proving this relationship is considered to be very difficult, as well as eliminating the possibility that diagnostic bias may influence the results (22). Seizures, diminished consciousness, and loss of mental sharpness or difficulty concentrating are just a few of the symptoms associated with PBTs that may cause an accident, which could in turn lead to investigation by X-ray and the eventual diagnosis of a previously undetected neoplasm (17).

The SEARCH study did include questions pertaining to head trauma from injury or from sports participation. Preston-Martin et al (134) did not find any significant associations between medically treated head injuries at least five years prior to diagnosis and either glioma or meningioma, though the risk of glioma in males with more than one head injury did approach significance. When the authors stratified the participants by the latency period between the time of injury and diagnosis of the PBT, males who were injured 15-24 years before being diagnosed with meningioma were at a significantly elevated risk (OR = 5.4, 95% CI = 1.7-16.7). However, the authors warn that this is based on only seven cases and 18 controls. No elevated risk of glioma or meningioma was found to be associated with participation in boxing, rugby, or football.

Exposure to Animals

Exposure to animals has been considered as a possible risk factor for PBTs. This is not to be confused with studies that have evaluated the possible association of tumours with residing on a farm or working in agriculture. Instead, these publications specifically address contact with animals, including domestic pets. The hypothesis is founded on the idea that various infectious agents may be transmitted from animals to humans that can have an effect on the meningeal and glial cells of the brain.

Menegoz et al (135) used the SEARCH study data to evaluate the association between dairy cattle, beef cattle, pigs, horses, sheep, goats, poultry, dogs, and cats and the risk of glioma and meningioma. 'Contact' was defined as if a subject had ever come in contact with the specific animals at least twice a month for a total of at least 12 months. When stratified by sex and modeled to control for age, study centre, years of schooling,

and exposure, no significant associations were found for either glioma or meningioma. In fact, all of the odds ratios were very close to 1.0 (range for men = 0.9-1.0, range for women = 0.8-1.0). Centre-specific analysis was done, which yielded significantly elevated odds of glioma in males from the Winnipeg centre who reported dairy cattle, pig, and cat exposures, while significantly reduced odds of glioma was found in Heidelberg males exposed to horses and Adelaide women exposed to dogs. The only reported finding that achieved statistical significance for meningioma was in Grenoble women exposed to dogs (OR = 0.28, 95% CI = 0.10-0.78). It should be noted that for every exposure considered, the findings varied greatly from centre to centre. Even for those significant findings listed above, other centres reported an opposite association, just not at the specified level of statistical significance. Further work investigated the possibility of an association between PBTs and the lack of exposure to animals or between PBTs and an increasing number of animals that the subjects were in contact with. No significant findings were reported.

At this time, the majority of the literature concerning animal exposure as a risk factor is restricted to studies of childhood PBTs. Three studies were found that looked at animal exposure as a risk factor for adult PBTs. Burch et al (41) conducted a hospital-based case-control study which included 215 cases diagnosed in Canada between 1979 and 1982. There were no significant associations between contacts with pets and tumour risk. Ahlbohm et al (123) looked at non-occupational risk factors for astrocytomas in 78 cases and 289 controls, but did not find any indication that animal contact impacted the risk of astrocytoma development in adults. Finally, a case-control study conducted in the United States that included glioblastoma, grade III and IV astrocytoma, and anaplastic

astrocytoma cases also did not find any association between brain tumours and exposure to either pets or animals in a farm environment (45).

2.4. Systematic Reviews and Meta-analyses

2.4.1. Use of Systematic Reviews and Meta-analysis

The task of keeping abreast of all of the new and pertinent published information has become nearly impossible for workers in the health care profession. It was estimated in 1995 that physicians would need to read, on average, 19 original articles a day to stay on top of the medical literature (136), a number that is surely higher today. In order to help cope with the flood of information, systematic reviews and meta-analyses have been developed as a tool for consolidating information from a wide variety of sources, while also helping in the assessment of the quality of evidence and evaluating the potential impact of biased results.

A systematic review has been defined as “a review in which there is a comprehensive search for relevant studies on a specific topic, and those identified are then appraised and synthesized according to a predetermined and explicit method” (137). Based on this definition, it is clear that a sound systematic review requires a specific question to be examined. This question should clearly identify the population of interest, the intervention or exposure being evaluated, the particular outcome, and the design of the study. The fact that it is all predetermined suggests that all of the methods employed must be developed *a priori* through the use of a detailed protocol. In 1992, the Cochrane Collaboration was founded. This international group of health care professionals has taken on the responsibility of preparing, maintaining, and disseminating systematic

reviews of health care research, creating a standard for assessing the quality of a review, including the details of the protocol developed prior to the start of the review process.

“A comprehensive search” means that, ideally, all relevant studies pertaining to the question developed should be included. This is possible only by searching all available bibliographic databases; hand searching all journals, abstracts, and proceedings; and searching all of the relevant grey literature, which may include unpublished reports and ongoing studies (138). This is by no means an easy task and for most it is not feasible due to both time constraints and a lack of sufficient funding. Therefore, the rule of thumb that has been developed is that researchers should select the maximum number of sources to be searched as their resources will allow (139), with detailed information about the sources searched and the methods used to search them provided in the final report.

A meta-analysis, or quantitative data synthesis, is described as “the statistical combination of at least two studies to produce a single estimate of the effect of the health care intervention under consideration” (137). This means that quantitative pooling of data abstracted from the included studies in the review can be performed. While a meta-analysis is useful in that it can provide a more accurate estimation of a proposed association due to the inclusion of larger numbers of participants, it is not always feasible. Statistical heterogeneity due to differences in outcome measurement and clinical heterogeneity resulting from variation in the populations used across the different studies are just two possibilities that would make meta-analysis inappropriate.

2.4.2. Limitations of Systematic Reviews and Meta-analyses

Identifying all of the relevant literature for inclusion has been labeled the most fundamental challenge of any systematic review (140). Typically, electronic searches of the literature will yield approximately 74 % of all relevant articles (141), and further hand searching and scanning of the grey literature is not always feasible and the usefulness of unpublished data has been the subject of debate (142). Furthermore, there is the issue of variable quality of reporting amongst the included studies. Quality assessment of the included articles in a review may lead to fluctuations in the estimated effect depending on the inclusion or exclusion of low quality studies from the meta-analysis (143).

Bias is also of concern in systematic reviews and meta-analyses, since failure to recognize its effect can result in an incorrect analysis of the available literature. Inclusion criteria bias results from the creation of selection criteria for a systematic review based on a preliminary review of the literature, rather than the development of selection criteria *a priori* (137). Thus, the development of a sound protocol before the start of a review is required to minimize this bias. Reference bias has been suggested to evolve as a result of the tendency of authors to more frequently refer to those studies that show positive outcomes favoured by the author of the review. A recently shown example of this is that searching for trials limited to those sponsored by pharmaceutical companies can increase the chances of finding a positive effectiveness for the drugs manufactured by these companies (144). In order to help recognize the possibility of reference bias, reviewers should make available all of the cited sources of funding of their included studies.

A third major form of bias that may be introduced in a systematic review is publication bias. There has been some evidence that investigators are more likely to

submit, and editors are more likely to publish, those results which have significant findings (145-147). Therefore, reviews which fail to include unpublished material run the risk of overestimating the effect of the intervention or exposure of interest as a result of introducing this bias. Tied into this is the risk of bias due to selective reporting, in which authors or publishers will only include those results in a study which were significant. However, it is impossible to be aware of all of the available grey literature and a number of editors are reluctant to publish reviews which include grey literature, thus defeating the very purpose of a systematic review (139). A possible solution is to make clear all efforts performed to identify unpublished data by the author so that the reader is aware of the potential for publication bias. A common method employed is the funnel plot (148), a graphical representation of both the sample size of the study and the estimated effect. Provided there are a sufficient number of included studies to assess graphically, an inverted funnel with no obvious gaps suggests a lack of publication bias. If, for example, there are little or no plots where effect size is minimal, the possibility exists that the results of the review are being influenced by publication bias.

2.4.3. Systematic Reviews and Meta-analyses for Case-Control Studies

When conducting systematic reviews and meta-analyses of randomized control trials, one is making the assumption that each study provides an unbiased estimate of effect and any variability seen from study to study is simply a result of random variation. As a result of the randomization in assigning participants to either receive the intervention of interest or not, investigators can hope to severely minimize the effect of possible confounders. The same cannot be said for non-randomized studies, in particular

case-control investigations. Cases are identified as a result of having the condition of interest, while controls are selected on the basis that they do not have said condition. While some case-control studies will attempt to control for potential confounding factors, such as sex, age, and ethnicity, by using either frequency or individual matching strategies, it is not always the case. Consequently, meta-analyses of case-control studies become vulnerable to biases and confounding present in the included studies, prompting some authors to argue that quality assessment and evaluation of heterogeneity becomes critical (14).

2.4.4. Quality Assessment Tools for Systematic Reviews

There seems to be a great deal of disagreement in the literature concerning whether or not to include quality assessment of the selected studies in the review. The inclusion of study quality has received the support of the Cochrane Collaboration, the Evidence-based Practice Center Program of the Agency for Healthcare Research & Quality (AHRQ), and numerous journal editors. Also, empirical evidence has suggested that those articles of lower quality tend to report greater treatment effects (149), indicative of a need to eliminate potential bias by controlling for study quality. In contrast, studies exist which suggest that there is no relationship between quality score and effect size, with one review even finding that lower quality studies produced smaller effect sizes than ones of greater perceived quality (149).

Part of the problem is the lack of a general consensus on which method to use for evaluating study quality. Different quality assessment tools available include assessing individual quality components or items, in particular individual aspects of study

methodology; quality checklists, which are based on a number of quality items, but do not have a numerical value attached; and quality scales, which are also based on a variety of quality items, but are numerically scored to provide an estimate of overall study quality (150). Most of these checklists and scales tend to target the same four quality constructs for evaluation: methodological quality, bias or systematic error, internal validity, and external validity or generalisability.

A review by Deeks et al (151) examined all of the relevant literature pertaining to quality assessment tools available for non-randomised studies. To be deemed satisfactory for use, a tool had to include a minimum of four core items which were: identifying how allocation occurred (i.e. were the cases and controls recruited from the same population?), discussing whether or not there was any attempt to balance the groups by design of the study (i.e. matching), the identification of prognostic factors (i.e. are the distributions of principal confounders discussed?), and finally, was case-mix adjustment covered (i.e. was there adequate adjustment for confounding in the analyses?). The authors identified a total of 194 different methods of quality assessment, of which only six were considered to be applicable to evaluating non-randomised studies as part of a systematic review based on the above core quality constructs. Included in this group is the Black and Downs checklist, which has been selected as the quality assessment tool for the included studies in the systematic review component of this thesis (152).

2.4.5. The Black and Downs Checklist for Non-randomised Studies

Developed in 1998 (152), the Black and Downs checklist for measuring study quality consists of 27 questions, with individual sections that address the reporting of

methods and results (10 questions); external validity (3 questions); internal validity, specifically concerning bias (7 questions); internal validity with regards to confounding and selection bias (6 questions); and finally, power (1 question). Due to these sub-scales, one is able to generate a profile of the strengths and weaknesses of the included studies for each of the areas of methodological concern. The checklist is intended to be used for both randomised and non-randomised studies, so as a result, not all of the questions are applicable when reviewing case-control studies.

The pilot version of the Black and Downs checklist was developed on the basis of existing epidemiological principles, study designs, and quality assessment checklists, and after testing inter-rater reliability and test-retest reliability, a revised version was developed. Taking into account internal consistency, test-retest reliability, inter-rater reliability, criterion validity, and respondent burden for both the checklist as a whole and each of the sub-scales, it was felt that a feasible checklist for the assessment of the methodological quality of non-randomised studies had been established (152).

The author of this thesis recognizes that the Black and Downs checklist is not without its shortcomings. The reliability of the checklist was based on only two separate reviewers, each of whom had Master's level education in epidemiology, and the retest was taken merely two weeks after the initial one. Each of these drawbacks is also acknowledged by the creators of the checklist, who realize that more rigorous testing of the checklist is required. However, at this time there is no conclusive evidence that would suggest the superiority of one quality assessment tool over another, so the Black and Downs checklist was selected for its ease of use and inclusion of sub-scales (151).

3.0. METHODS

3.1. Methods of the Case-Control Study Analysis

This section outlines the Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH) adult brain tumour case-control study, including the general design, the ascertainment of cases and controls, the data collected, and the questionnaire used. Also covered are the inclusion and exclusion criteria, the handling of missing values, the selection of covariates, defining derived variables, and the exposure variables that were evaluated. Finally, an overview of the various forms of analysis employed is provided.

3.1.1. General Design

The SEARCH study was an international, multicentre, population-based, case-control study conducted to investigate hypothesized risk factors for primary brain tumours in adults, specifically glioma (ICD-O 191) and meningioma (ICD-O 192.1) (15). The glioma data was collected in eight different centres within six different countries. These centres were: Melbourne and Adelaide (Australia), Toronto and Winnipeg (Canada), Grenoble (France), Heidelberg (Germany), Stockholm (Sweden), and Los Angeles (USA). The centres in Melbourne and Los Angeles did not include meningioma cases. The design and conduct was not the exact same at each centre due to varying local circumstances. For details of the study design for each of the centres, please see Appendix A. The study was coordinated by the International Agency for Research on Cancer, based out of Lyon, France. The coordinators were responsible for compiling and merging all data into pooled sets.

3.1.2. Ascertainment of Cases and Controls

Eligibility criteria for the cases were similar for all of the centres. Cases were recruited based on either neurosurgical clinics or cancer registries. Entry into the study required that the patient be between the ages of 20-80 at the time of diagnosis, with a histological confirmation of the diagnosis, and the date of diagnosis to be between 1980 and 1991. The completeness of case ascertainment was verified through the respective pathology departments or via cancer registries (2). With few exceptions, all incident cases were included. Data were collected from 1582 cases. 53 of these cases had to be excluded because more than 12 months had elapsed between the time of diagnosis and the interview; two cases were removed because their histology could not be verified; one case was eliminated since the date of diagnosis was unknown; finally, 15 glioma and two meningioma cases were deemed ineligible because it was not possible to locate matching controls. Therefore, the final number of cases included in the SEARCH adult brain tumour study dataset was 1178 glioma cases and 331 participants with meningioma.

Population-based, healthy adult controls were recruited in each centre, using different methods in each location, such as random-digit dialing, registries, and census records. In some of the centres, the controls were matched with cases on age (five-year age groups) and sex. In the others, frequency matching by age and sex was used. A total of 2493 controls were identified. 257 of these were excluded because they could not be matched to a case, resulting in 1987 glioma controls and 1123 meningioma controls.

While the number of participants included in the SEARCH study is fixed, it is still required to evaluate whether or not there is a sufficient number of subjects to detect a significant difference in the risk of developing a PBT based on whether or not someone

has a family history of cancer. In order to do this, power calculations were performed based on rejecting the null hypothesis that there is no difference in odds of developing a PBT between those exposed and those not exposed; that is, an odds ratio of 1.0, at the five percent significance level.

Power calculations were conducted for a range of values for the pooled data set. In order to determine the power for different magnitudes of difference in odds, the expected odds ratio was also varied. The range of values reported here are based on discussions with Dr. Little. It should be noted that for all of the power calculations, the hypothesis tested was two-sided.

Table 2. Power calculations for the pooled SEARCH dataset (number of cases = 1509 and number of controls = 1987).

EXPECTED ODDS RATIO	PROPORTION OF CONTROLS EXPOSED (REPORTING A FIRST-DEGREE RELATIVE WITH CANCER)				
	0.05	0.10	0.15	0.20	0.25
1.2	0.251	0.422	0.522	0.644	0.709
1.4	0.692	0.919	0.977	0.992	0.997
1.6	0.943	0.998	1.000	1.000	1.000
1.8	0.995	1.000	1.000	1.000	1.000
2.0	1.000	1.000	1.000	1.000	1.000

Based on table 2, it can be seen that the pooled data will be sufficient to produce resultant power of greater than 80 per cent, a commonly accepted cut-off value, for nearly every instance when the expected OR is 1.4 or above. The only situations where a true underlying association could be missed are when the expected odds ratio is low (1.2 or less), and if the proportion of those exposed is low (five percent or less) while the expected odds ratio is low (1.4 or less).

3.1.3. The Questionnaire

A standard questionnaire was developed by the investigators involved in gathering the SEARCH study data, which was later translated into the native language of the different centres. For nearly all of the study centres, information was collected from the cases and controls via face-to-face interview by specially trained interviewers. At the Stockholm study centre, self-administered questionnaires were mailed out to the participants. As well, information pertaining to some of the Melbourne-based participants was gathered through mailed self-administered questionnaires. The reason for this was that these centres covered a very wide geographical area and getting the trained interviewers to all of the cases and controls was not feasible. Generally, cases were interviewed either at home or in the hospital within 6 months after diagnosis. The controls were interviewed at home. It should be noted that for 325 of the cases and 65 controls, information was obtained by interview with a proxy, such as a spouse.

Subjects were asked a number of questions pertaining to such topics as the size of their first degree family, their education level, and the history of cancer within their family. Also included in the data was a measure of how well the interviewer felt the subject understood the questions, the interviewer's impression of the quality of the information provided, the type of matching that was used for each subject, and the type of interview used to gather the information.

3.1.4. Inclusion and Exclusion Criteria

Checks were made to ensure consistency in the participants' responses. Those individuals who provided inconsistent information about questions relevant to the

association between a family history of cancer and adult PBTs were eliminated. Table 3 summarizes the different instances of contradiction found in the study data, including the number of cases and controls that were excluded and the respective percentage of the total pool of cases and controls that each represents. Those who gave inconsistent information pertaining to a specific cancer exposure were eliminated for the analysis of that cancer-type only. Missing data was also treated as grounds for exclusion from analysis. However, since all of the missing data was relevant to the total number of first degree relatives and not just a specific form of cancer, these participants were excluded entirely from the statistical analysis. For the meningioma data, missing information existed for the number of relatives at risk, the number of relatives with any form of cancer, and the education level of the study subject. Only those participants missing data regarding the family size at risk and the number with cancer were eliminated from all analyses. There were no inconsistent responses found amongst the meningioma cases and controls.

After eliminating any participants with missing information or conflicting answers, a total of 2997 participants remained (94.7% of original total) for the glioma data analysis, 1085 glioma cases (92.1% of original number of cases) and 1912 controls (96.2% of original number of controls). As mentioned, only those cases and controls with missing information were removed from all analyses, which represent 4.9% (n = 154) of the total glioma study population. 16 participants (1.1%) from the meningioma data were completely removed due to missing responses concerning family size and number of relatives with cancer, leaving 325 eligible meningioma cases (98.2% of original number of cases) and 1113 controls (99.1% of original number of controls).

Table 3. Reason for exclusion from the SEARCH adult brain tumour study: missing data and inconsistent responses.

Reason	Total # excluded for glioma (% of total)	# of glioma cases (% of cases)	# of glioma controls (% of controls)	Total # excluded for meningioma (% of total)	# of meningioma cases (% of cases)	# of meningioma controls (% of controls)
Missing the number of siblings	130 (4.1%)	73 (6.2%)	57 (2.9%)	7 (0.5%)	1 (0.3%)	6 (0.5%)
Missing the total number of first-degree relatives with cancer	24 (0.8%)	16 (1.4%)	8 (0.4%)	9 (0.6%)	5 (1.5%)	4 (0.4%)
Missing information about ever having a relative with a brain tumour	0 (0.0%)	0 (0.0%)	0 (0.0%)	28 (1.9%)	14 (4.2%)	14 (1.2%)
Missing the number of years of school	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (0.4%)	3 (0.9%)	3 (0.3%)
Missing the highest level of tertiary education received	0 (0.0%)	0 (0.0%)	0 (0.0%)	31 (2.1%)	14 (4.2%)	17 (1.5%)
Reported having 2 parents with lung cancer, but not having a father with lung cancer	10 (0.3%)	3 (0.3%)	7 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reported having 2 parents with lung cancer, but only 1 first-degree relative with cancer	1 (0.0%)	0	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reported having 2 parents with gastrointestinal cancer, but only 1 first-degree relative with cancer	1 (0.0%)	0	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reported having 2 parents with gastrointestinal cancer, but not having a father with cancer	1 (0.0%)	1 (0.1%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reported having 2 parents with unspecified cancers, but only 1 first-degree relative with cancer	1 (0.0%)	0	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

3.1.5. Selection of Covariates

Sex, age, and study centre were included as covariates in all analyses since the control group was selected using either frequency or individual matching based on these variables. Due to the matching, it is inappropriate to compare unadjusted univariate statistics of particular cancer histories and other variables between cases and controls. The five-year strata used for age groups were based on the matching methods of the individual study centres.

As previously outlined in the literature review, very little conclusive evidence exists that identifies particular risk factors for the development of primary brain tumours in adults or is associated with a family history of cancer (2,9,135,153,154). Therefore, variables such as smoking history, occupation, or diet, were not considered as covariates when constructing the models used for the conditional and unconditional logistic regressions.

3.1.6. Other Potential Covariates

Other potential covariates were examined for their impact on the results. These covariates were: number of first degree relatives, the type of interview, the quality of interview, the number of years of schooling and the level of training reported after secondary school, and the presence of a first degree relative with a brain tumour. Each was examined separately and the impact created on the point estimates of the association of a family history of cancer with PBTs in the adults included in this dataset was determined.

Biased results can be created if one ignores the number of family members that are actually at risk of developing cancer (155). To adjust for this, participants were asked to report the number of siblings and children that they had, which allowed for the generation of a variable which indicated the total number of first degree relatives at risk of cancer. The created variable indicated the sum of the number of reported children and siblings plus the addition of two to account for the parents of the respondent.

The type of interview was considered because not all of the participants were able to provide their own responses for the questionnaire. The use of proxy or assisted responses introduces the potential for recall bias, as the proxy may be less likely to accurately recall the family history of cancer. As a result, the impact of the type of interview was evaluated, comparing those who completed the questionnaire without assistance to those who required help or a proxy. This analysis was included as a potential method for accounting for reporting quality. A second method for measuring the impact of the interview was the quality of the interview and the responses provided as deemed by the interviewer. This covariate was assessed using five different categories: very good, reliable, questionable, unsatisfactory, and unknown.

The number of years of schooling and the level of training reported after secondary school were used as a measure of the socio-economic status of the participants. There has not been any conclusive evidence that socio-economic status affects risk of brain tumours in adults so it was not considered as a variable that must be included in the regression analysis (26,58,59,62). However, previous analyses of the SEARCH adult PBT dataset have shown that cases tended to be slightly less educated than controls (134), so the impact of reported education was assessed.

Participants were asked to report whether or not they had a first degree relative with a brain tumour. Previous studies (47-50) have reported an elevated risk of glioma and astrocytoma associated with a family history of brain or central nervous system cancer. For the SEARCH study, respondents were asked to give a “yes or no”-type response concerning having a relative with a brain tumour. As a result, the possible association was restricted to having at least one first degree relative with a brain neoplasm and did not take into account the effect of having multiple afflicted relatives.

3.1.7. Derived Variables

Age

The age variable was based on the age of the cases at the time of diagnosis and the age at the time of interview for the controls. Ages ranged from 20-79 years. Based on the methods of previous case-control studies that analyzed the SEARCH data, age was grouped into five-year bands, except for the final group which covered nine years due to lower numbers of older participants. The resultant groups are: 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, and 70+.

Number of First degree Relatives

The number of first degree relatives reported by each of the study participants was used to eliminate the bias that would have been introduced by not taking into account the actual number of relatives when considering family history as a potential risk factor for brain tumour incidence in adults (155). This variable was created by adding together the number of siblings and the number of children reported and then adding two to the total to account for the mother and father. Values ranged from 2 to 24, but cell sizes were less

than 10 for cases reporting 16 or more first degree relatives and for controls reporting 18 or more relatives. To ensure adequate power in conducting the statistical analyses, strata were collapsed based on categories used in previous case-control studies on the same area (11). These strata were: 2 (0 children and 0 siblings), 3-4, 5-7, 8-10, and more than 10 first-degree relatives.

Type of Interview

Type of interview was grouped into two different categories. The first group, “Direct”, consisted of those participants who provided all of their answers directly with no assistance. The second group, “Assisted/Proxy”, was those who required help in answering (assisted), or had someone else provide some answers (part proxy) or all answers (proxy).

Socioeconomic Status

As mentioned, socioeconomic status was estimated on the basis of highest educational qualification obtained and the number of years of schooling completed. A seven-point scale was created, based on the methods of previous analysis done using the SEARCH study data set (134) to categorize the participants. The points of the scale were: 7 = university/college degree; 6 = some university/college, no degree; 5 = technical training, apprenticeship, or adult evening classes; 4 = high school graduate; 3 = some high school; 2 = 7-9 years of schooling; and 1 = < 7 years of schooling.

3.1.8. Exposure Variables

A total of 20 different exposure variables were assessed to examine the potential association between a family history of cancer and primary brain tumours in adults.

Table 4 lists each of these 20 variables. Each was answered as either “Yes” or “No”. It should be noted that the number of cases and controls included in the analysis of each of the exposure variables was not always the same due to the removal of those participants with conflicting answers outlined in table 3 above.

Table 4. Included cancer exposure variables in the SEARCH adult brain tumour study.

VARIABLE
Relatives with any kind of cancer
Relative with brain tumour
Relatives with cancer other than brain tumour
Mother with cancer other than brain tumour
Father with cancer other than brain tumour
Sibling with cancer other than brain tumour
Children with cancer other than brain tumour
Parent with lung cancer
Father with lung cancer
Sibling with lung cancer
Mother with breast cancer
Sister with breast cancer
Parent with lip, oral, or pharyngeal cancer
Sibling with lip, oral, or pharyngeal cancer
Parent with gastro-intestinal cancer
Sibling with gastro-intestinal cancer
Parent with genito-urinary cancer
Sibling with genito-urinary cancer
Parent with unspecified cancer
Sibling with unspecified cancer

3.1.9 Statistical Analysis

Descriptive analyses were performed, comparing the frequency distribution of the included cases and controls amongst the different categorical variables. These distributions were expressed in terms of raw numbers and percentages. The purpose of these analyses was to describe any differences between the cases and controls, as well as to explore potential patterns amongst the missing data and to detect potential outliers or implausible values.

The association of a family history of each of the various forms of cancer in first-degree relatives with primary brain tumours in adults was assessed via logistic regression. All analyses were performed separately for the glioma dataset and the meningioma dataset. The primary analysis employed was an unconditional logistic regression for those centres in which frequency matching was used and a conditional logistic regression for the study centres which utilized individual matching between cases and controls based on the standard approach established by Breslow and Day (156). For those who were frequency matched, strata were defined by study centre, sex, and five-year age groups. Strata for individually matched participants were the matched sets. Unconditional logistic regression was performed on the entire data set by breaking the individual matching *post hoc* and assigning the individual cases and controls to their respective five-year age groupings. The associations between the independent variables and the risk of glioma and meningioma were examined by generating odds ratios and 95 percent confidence intervals. For all regressions, the probability modeled was that a person was a case, thus an odds ratio of greater than 1.0 suggests an increased risk of primary brain tumour development and a point estimate of less than 1.0 implied that the exposure was associated with a lowered risk of glioma. For rare diseases, the odds ratio is a good approximation of relative risk in case-control studies. The odds ratio is the appropriate measure because the sampling fraction of the cases and controls is not known (213).

All of the unconditional logistic regression models created included adjustment for the three matching variables, study centre, sex, and five-year age groups. Additional models were created which included the various potential covariates outlined in section 3.2.6 above. A number of model-fit statistics were used to assess the value of including

each of the covariates in the final model. These include R-square, c-statistic, Wald chi-square, -2 log likelihood ratio, and the Hosmer and Lemeshow goodness-of-fit test. Descriptions of each of these statistical tests can be found in appendix B. For those variables where units increased in a numerical fashion, such as number of first degree relatives and socioeconomic status, logit plots were created in order to examine the patterns of relationships between the independent variable and the log odds of primary brain tumours in adults. The purpose of these plots was to determine the best scale of the variable to be included in the final models.

Based on previous studies which used the SEARCH adult brain tumour dataset (2,131,134,135), the referent groups for the study centre variable were those centres which contributed the greatest number of participants. This was the Melbourne centre for the glioma analysis and the Heidelberg centre for the meningioma analysis. Females were used as the referent value for sex because there were no males included in the Los Angeles centre for the glioma data and there were larger numbers of female meningioma cases compared to males. Since only the Melbourne, Toronto, and Winnipeg centres included participants in the 20-24 age category, the 25-29 grouping was selected as the reference. Those individuals with only two first degree relatives served as the reference value for the family size variable following the methods of Hill et al (11) and the lowest socio-economic status, as estimated by those who reported having less than seven years of schooling, and the most reliable form of interview, direct, were the reference value for the SES and interview type variables, respectively, based on previous SEARCH papers.

The conditional logistic regression was carried out using the participants from the study centres which employed individual matching strategies (Melbourne, Grenoble,

Stockholm, Winnipeg, and Los Angeles). Strata were the matched pairs (one glioma case and one control) in Melbourne, Stockholm, and Los Angeles. Grenoble and Winnipeg used a one-to-two case:control ratio and all three participants were treated as an individual stratum. Odds ratios and 95 percent confidence intervals were generated for each of the different cancer exposures and compared to the results of the unconditional logistic regression when restricted to including only the same five centres. If the point estimates of the conditional and unconditional regressions were similar, data from all of the centres was pooled and the results of the unconditional regression were reported.

In order to test for heterogeneity between study centres, centre-exposure interaction terms were produced and the corresponding deviance between models was measured using the -2 log likelihood ratio test. Following previous studies using the SEARCH data set (131,134,135), a p-value of less than 0.05 was defined as heterogeneous. Where appropriate, centre-specific results are presented and possible reasons for the heterogeneity are discussed.

Tests for an increasing or decreasing trend of exposure and risk were performed, based separately on the size of the family at risk and the socioeconomic status of the individual. The trend test statistic was obtained by running the model with each of the listed variables considered as a continuous variable and then finding the Wald chi-square statistic. Ordinal values were used, with the socioeconomic status values coming from the seven-point scale that has been described previously. If the resultant Wald chi-square value was greater than or equal to 3.84, the cut point for a p-value of 0.05 using a two-tailed chi-square test, the trend of increasing or decreasing risk for the continuous variable was considered statistically significant.

All analyses were performed in the SAS system, using Proc Freq and Proc Logistic (Version 9.1).

3.1.10. Sensitivity Analyses

Sensitivity analyses were performed to evaluate the impact of the individual study centres, the type of interview, the age of the participant, and the socioeconomic status of the individual. Based on the work of previous research which evaluated the association of a family history of cancer with primary brain tumours in adults (11), the type of interview compared was self-respondent (direct and assisted) versus proxy (part proxy and proxy), and the ages of the participants compared were 20–49 years old (at time of diagnosis for cases and time of interview for controls) versus 50 years or older. Comparisons made for socioeconomic status were any university/college education (degree and some university/college – no degree) versus those without any university/college education, including those reporting technical training, apprenticeship, and adult evening classes.

3.2. Methods of the Systematic Review

This section outlines the different search strategies that were used to identify the pertinent literature concerning associations between genetic polymorphisms and PBTs in adults. Explanations regarding the different electronic databases that were searched are given and details about the inclusion and exclusion criteria that were used in screening the literature are also provided, as well as the variety of data that was abstracted from the included studies and the methods of data synthesis and analysis. The quality assessment tool that was used, the Black and Downs checklist, is also reviewed.

3.2.1. Search Strategy

An extensive search of the literature was conducted in an attempt to retrieve all of the available evidence relating to the evaluation of associations between various genetic polymorphisms and primary brain tumours in adults. Content experts were consulted in order to ensure that all relevant terms were included in the search. Information scientists at the University of Ottawa Health Sciences Library provided their expertise for refining the search strategy and maximizing its effectiveness.

For the purpose of this systematic review, three different electronic databases were searched: Medline and Embase, using the OVID interface, and PubMed, whose search interface is produced by the National Center for Biotechnology Information (NCBI). The initial search strategy was created in Medline, but had to be slightly modified for Embase, as a result of the different indexing methods that exist between the two, and for PubMed, due to slight differences in the truncation of terms.

Medline is a comprehensive literature database compiled by the NCBI of the United States National Library of Medicine. Covering a variety of life sciences, including medicine, nursing, dentistry, and veterinary medicine, Medline contains over 14 million records from more than 7 300 publications, from 1966 up to within one week of the date of use. The majority of the publications found in Medline originate in the United States and are written in the English language, but more than 70 different countries produce works that can be found within the database, written in a variety of languages with an English abstract provided. Due to its extensive global breadth, Medline facilitates evidence-based medicine and is a useful tool for conducting systematic reviews.

Embase, also known as the *Excerpta Medica* database, is a current, comprehensive database tailored to the pharmacological and biomedical fields of study. Containing more than 9 million records from over 4 000 journals published from 1974 to the present, Embase is updated weekly allowing for articles to appear in the database within 2 weeks upon receipt, on average. Though Embase covers a variety of disciplines, including clinical medicine, health policy, and basic biological research, its strength is drug-related searches.

The more than 1 700 journals that are unique to Embase provide validation for including an Embase search alongside a Medline search. While Medline offers the largest collection of references, as well as the longest retrospective access, Embase has greater coverage of European journals and publications in languages other than English (157). Also, the longer lag time in indexing the articles in Medline can have an impact on the rate of retrieval as compared to Embase (158). Reports on the extent of overlap between the two databases vary, depending on the subject of interest, most commonly falling somewhere between 30 and 50 per cent (159,160). This suggests that a more comprehensive search of the literature for relevant information should include both Medline and Embase.

The third electronic database searched was PubMed which, similar to Medline, is published by the United States National Library of Medicine. Covering all health and biomedical sciences, PubMed contains over 15 million articles from nearly 5 000 journals published from 1966 onwards, including health and life sciences publications that are not found in Medline. While the medical subheadings (MeSH terms) are the same in Medline and PubMed, the search interfaces are not. As previously mentioned, Medline

was searched through the OVID interface and PubMed through the NCBI interface. Therefore, different results are found when the same search strategy is employed in each database. As well, the inclusion of the Pre-Medline database in PubMed allows for access to citations that have not yet been indexed in Medline, marking the necessity for including PubMed in this systematic review.

The author consulted previous research in an attempt to find established guidelines for constructing an effective search strategy particular to the association of genetic polymorphisms and primary brain tumours in adults. While there were numerous publications available concerning the searching of electronic databases, the majority focused on randomized controlled trials. Only two systematic reviews on the topic area were found (14,161). The first, conducted in 2000, provided an overview of the genetic alterations in adult diffuse glioma, highlighting their occurrence, significance, and prognostic implications. However, there is no mention of the search strategy employed by the authors. The more recent review by Lai et al (14) focused solely on the association between adult brain tumours and polymorphisms on the *GST* genes. There were no reviews found which considered all potential polymorphisms on the human genome. This lack of guidance from previous literature highlights the import of building a sound search strategy based on the advice of content experts and information retrieval specialists.

The basic search strategy for the electronic databases consisted of three main topic areas searched separately using the Boolean operator “OR” and then the combination of these independent sub-searches using the Boolean operator “AND”. The three sub-searches consisted of: (a) genetic polymorphism studies; (b) genetic studies,

including those that look at genes and chromosomes, as well as molecular components that have been shown to be impacted by genetic polymorphisms, such as enzymes and heterocyclic compounds; and (c) brain neoplasm studies. Where possible, terms of interest were mapped to subject headings using the United States National Library of Medicine's MeSH vocabulary which allows for powerful and unambiguous queries (162). For each of these MeSH terms, the "explode" feature was used to permit the retrieval of all articles under the subheading. In an effort to increase the breadth of the search, the author selected MeSH terms that were fairly broad, such as "gene", "chromosomes", and "brain neoplasms". While this led to the retrieval of very large numbers of citations, it helped to limit the potential for missing relevant information. Queries were also inserted that looked for terms using the "mp" function, which scans titles, original titles, abstracts, name of substance words, and subject heading words. At this step truncation was used, represented by "\$" in Medline and Embase, and by "*" in PubMed, to permit alternative versions of the word in the search. For example, "brain tum\$" will identify brain tumor, brain tumors, brain tumour, brain tumours, brain tumorogenesis, and brain tumourogenesis. In an effort to keep the search as comprehensive as possible, no filters or limits that are available for these electronic databases, such as restricting the search to case-control studies or removing those that involve drug analysis, were used.

The specific search strategy employed for Medline (1966 to June Week 4 2005) can be found in appendix C. The modified version used for Embase (1980 to Week 24 2005) appears in appendix D. The discrepancies between the two strategies are based on the differences in the MeSH vocabulary used in the indexing of articles in Medline and

Embase, but the topics are searched to the same extent in each. For example, Medline uses the term “neoplasm proteins”, while Embase searches “tumor protein”. Appendix E details the search employed in PubMed. There were slight differences between this search and the Medline search due to the different notation used in each database.

A final updated search of the literature was performed on February 1, 2006 and consisted of the re-running of the three search strategies for the time period covering from June 2005 to the end of January 2006.

3.2.2. Screening the Literature

Upon completing the search of the electronic databases, all of the identified citations were imported into the reference management program RefWorks. This program issues a unique identifier number to each of the citations and retains all of the bibliographic information that can be found in the various databases, including the abstract when available. Once this was completed, the citations were moved into the systematic review software package SRS 3.0 (TrialStat!, Ottawa, ON).

The first step taken after the citations were transferred to SRS 3.0 was to remove any duplicates. The SRS 3.0 program offers three different methods of scanning for duplicates, with each ascending level increasing the chances of detecting false positives. The first level is the match scan. This duplicate search looks for near matches in all of the bibliographic details included. Though there is little chance for false positives at this step, the identified duplicates are highlighted, rather than removed, to allow the researcher to check that the article is indeed a duplicate. The next step is the mid scan, which scans only the titles and authors for near matches. This allows for the detection of

duplicates that differed in other areas, such as whether or not the abstract was included, that would have been missed in the match scan. Great caution was exercised here as a result of the increased likelihood of false positives being found. The last duplicate search was the title scan, which looks for near matches only within the title. This is useful for identifying duplicates that differed in the order of bibliographic details, for example the date of publication. Once again, care was taken to avoid labelling false positives as duplicate articles.

All of the titles and abstracts of the remaining citations were scanned by the author to assess the validity of including the publication for further review. A second individual (Dr. Julian Little) independently scanned a randomly selected 10 per cent portion of the citations for their potential relevance. This subset was selected using the RANUNI function in SAS, which uses a prime modulus multiplicative congruent generator as a random number generator.

The screening process was based on the application of the broad eligibility criteria outlined below. Any study that was deemed by either reviewer to be potentially relevant was retained for further assessment. Upon completion of this scanning process, a Cohen kappa score was determined in order to assess the inter-rater reliability between Dr. Little and the author. It should be noted that the screening process was conducted in an unblinded manner with regards to the bibliographic details, but there exists no conclusive evidence that failing to blind such information at this step introduces bias to the systematic review (163).

3.2.3. Study Inclusion/Exclusion Criteria

The initial screening eligibility criteria were structured around four different components: the design of the study, the population under study, the exposure measured, and the outcome assessed. For the purposes of this systematic review, the desired study design and population of interest was case-control studies involving cases with PBTs. The relevant exposure measured was the presence of at least one genetic polymorphism and the primary outcome was the overall magnitude of effect between the cases and the control group, in terms of an odds ratio, of the difference in the genetic frequency of the polymorphism studied.

Consideration for further assessment of the article required that it met all of these criteria. Possible responses to each of the screening questions were yes, no, or unclear. In an attempt to avoid discarding relevant studies, those publications where criteria were deemed unclear were not excluded and kept for further consideration. If a citation satisfied these requirements, it was maintained in a separate file for later retrieval of the entire document. Those that were not deemed to be applicable were removed and placed in the quarantine folder that is provided by SRS 3.0, meaning that they could still be retrieved at any time and their unique identifier provided by RefWorks was maintained. The total number of articles both retrieved and rejected was recorded, as well as the reason for exclusion (inappropriate design, population, exposure, or outcome). Any disagreements between the author and Dr. Little about the relevance of a citation was discussed and if a resolution could not be found, a third party (Dr. David Moher) would make the final decision about whether it was to be included for further assessment. All

relevant review articles were included so that their complete reference lists could be scanned for possible pertinent articles not found in the electronic searches.

The next step taken was to conduct a more thorough investigation of those articles that passed through the initial level of screening. At this stage, more strict screening guidelines were applied to each of the citations. As before, the author examined all of the references and Dr. Little studied a randomly selected 10 per cent portion of these for relevance, with another measure of inter-rater reliability found by way of a Cohen kappa score. Dr. Moher was again responsible for resolving any conflicts. In order for an article to pass through this phase, it had to satisfy the initial screening criteria as well as the following conditions: (a) the study includes participants that were 18 years of age or older; and (b) the article is written in either the English, French, Spanish, Italian, Portuguese, or German languages. Studies which had participants both older and younger than 18 were not excluded, provided that matching by age was done so as to allow for comparison of only those cases and controls that met the requirements of the review. Due to limited resources, it was not possible to include those articles written in languages other than those listed above. The effect of language-restriction on systematic reviews has been debated. Previous research (164,165) indicates that restricting included studies by language of publication does not induce bias, so long as the initial search strategy employed is language inclusive, but a recent article found evidence of bias in using PubMed to search for genetic epidemiology studies with language restrictions (166). As in the previous phase, those articles that were removed were maintained in the quarantine folder and their reason for exclusion was recorded.

Once all of the articles produced by the electronic searches were scanned and evaluated for inclusion, attempts were made to contact the authors of the included studies for any missing information, such as confidence intervals and ages of the participants. If a response was not received before February 1st, 2006 the article would be included in the review but removed during sensitivity analysis to assess the impact of excluding studies in which it was unclear whether they met all of the inclusion criteria. After this was completed, the final step taken was to search the reference lists of all of the included articles for any other pertinent articles that had yet to be retrieved.

3.2.4. Data Abstraction

All relevant data was extracted from each of the included studies using a standard data extraction form created by the author with support from Dr. Little and Dr. Moher (see Appendix F). The form consists of four main components: data pertaining to publication details, data regarding the characteristics of the study, data concerning the methods of the study, and finally, the study results.

3.2.5. Assessment of Study Quality

The methodological quality of the included studies was evaluated using a modified version of the Black and Downs checklist for the assessment of the methodological quality of non-randomised studies (152). This rating scale was used due to the fact that it is a published scale and there is some evidence that using an unpublished rating scale can lead to biased results (167). The Black and Downs checklist was originally developed for use on both randomised and non-randomised studies. Thus,

a number of questions were irrelevant for this review since they pertained to topics that do not exist in case-control studies, such as blinding. Both the author and Dr. Little selected the questions to be excluded and were in complete agreement on what questions were retained. This modified version scored included studies out of 17: nine points concerning the reporting of methods and results, two points for the external validity of the paper, three points regarding the internal validity, and finally, three points on the subject of confounding and selection bias. Each of the included studies was assessed and scored independently by two reviewers (the author and Dr. Little), with a Cohen kappa score found for the final total scores to assess inter-observer agreement.

3.2.6. Data Synthesis and Analysis

Those studies which evaluated the association of the identical genetic polymorphism with the same tumour type were considered for meta-analysis. Due to the fact that our review considered the global population of adults with PBTs and there exists evidence that PBT incidence varies by geographic location (24,168,169), a random effects model was used. Random effects models factor in the effect of both within-study variation, which results from the uncertainty that comes with the sampling of the individual study's participants, and between-study variation, which arises due to the fact that the included studies may be selecting their participants from different populations. Random effects models are more conservative than fixed effect models, which only consider within-study variability. The weight of an individual study in the meta-analysis reflects the size of the study and the variability of its results since it is determined by the inverse of the square of the standard error of the odds estimate. Any potential association

that was restricted to one included study was not eligible for quantitative synthesis, but its findings were evaluated and discussed.

The RevMan statistical package (170) was used to pool the data abstracted from the included studies. RevMan allows for the generation of forest plots to display the individual results of the studies, as well as the estimated cumulative effect of the different genetic polymorphisms on brain tumour risk. The log transformed odds ratios and their 95 percent confidence intervals generated using a random effects model were plotted, with “No Effect” being represented by a vertical line at a log (odds ratio) value of 1.0. The orientation of the forest plots were such that values to the left of the “No Effect” line represented a lowered risk of brain tumour development, while values to the right of “No Effect” implied elevated risk. The association between genetic polymorphisms and PBTs for individual studies and pooled results were considered not to be statistically significant if their 95 percent confidence intervals crossed the “No Effect” line ($p > 0.05$).

As well as the forest plots, tests for overall effect and heterogeneity were also reported. A significant association between a polymorphism and PBTs would produce a Z-score of greater than 1.96 ($p = 0.05$) since it is assumed that the observed effects in each study are normally distributed and the more conservative two-tailed test was used. The test for heterogeneity was determined via the I^2 statistic. An I^2 value of 0 percent means that the included studies are in complete agreement; as the I^2 value increases and approaches 100 percent, it means that the odds ratio estimates of the included studies are more and more dissimilar. While there are no specific guidelines for interpreting I^2 values, less than 25% is commonly interpreted as low heterogeneity, 25-75% is moderate heterogeneity, and greater than 75% is considered high heterogeneity (171).

The chi-square test for heterogeneity is a poor method for producing a p-value pertaining to the null hypothesis that all studies are similar in a meta-analysis (172). In particular, instances where there are low numbers of included studies there is a reduced ability to detect true heterogeneity as significant because the power is low. I^2 is more appropriate because it describes the percentage of total variation across the included studies that is due to true heterogeneity, not due to chance. The principal advantage of the I^2 statistic is that it can be compared across meta-analyses of different sizes and using different types of outcome data (172).

3.2.7. Sensitivity Analysis

Sensitivity analysis was used to assess the robustness of the quantitative syntheses. Stability between the estimated odds ratios and 95 percent confidence intervals for all of the available studies for a particular association and the estimates produced in the sensitivity analyses would suggest robust results, bringing more credibility to the findings. For this review, sensitivity analyses examined the impact of study quality, as determined by the Black and Downs checklist; type of controls, whether the study used population-based or hospital-based controls; and reporting quality regarding ages of the participants, meaning those studies in which it was not clear whether all of the participants were over the age of 18 were dropped from the analysis.

3.2.8. Publication Bias

Publication bias refers to the tendency of studies which report statistically significant results to be published and those with non-significant findings less likely to be

accepted by journal editors (173). Publication bias can originate from either the authors, the sponsors of the study, or the editor and reviewers of the journals, with previous research suggesting that it is the authors who are most likely to create the bias because they are less likely to submit statistically null findings (174).

In accordance with the suggestion of Light and Pillemer (175), the author used a funnel plot in order to examine the possibility of publication bias. The funnel plot used in this thesis measures the precision of the study estimates on the Y-axis and one minus the effect size on the X-axis. Precision estimates that may be used include the number of participants, the inverse of the standard error, or log sample size (176). For this review, the included number of study subjects was used for the Y-axis. The X-axis was the odds ratio estimates of the studies.

The funnel plot does not unequivocally imply publication bias. The basic premise of the funnel plot is that the precision of a study's estimate will increase as the number of participants increases. As a result, the plot should look like an inverted funnel, with a wide dispersion of odds ratio estimates among studies with relatively small numbers and a much narrower range for larger studies. If one section of the plot is missing studies then there is a gap in the literature and it raises the possibility that publication bias might be present. According to Felson (173), this is commonly the area representing small studies that suggest a negative association and for studies of any size which do not have significant findings in either direction (seen by a vertical gap in the funnel plot). However, Terrin et al (177) argue that distorted funnel plots may also imply other biases, such as reporting bias, or true heterogeneity and that interpreting these tests as a final means of evaluating publication bias is a mistake. The author of this thesis acknowledges

this controversy and intends on using funnel plots simply as a means of identifying potential publication bias to be considered in future research.

4.0. RESULTS

4.1. Glioma Total Sample – Characteristics of the Cases and the Controls

4.1.1. *Demographics of the Cases and Controls*

73 subjects in the glioma case group had to be removed from all analyses because their reported number of siblings was missing. A further 16 cases were excluded due to missing values for the total number of first degree relatives with cancer. This meant that the final glioma case group had a total of 1089 participants, 587 (53.9%) of which were males and 502 (46.1%) females. The mean age of the cases was 50.2 years, with a median age of 51.0 years. The ages ranged from 20 to 77 years of age.

57 glioma controls were excluded since the number of siblings they had was missing and an additional 8 controls were removed because it was not known how many first-degree relatives that they had with cancer. This meant that the control group consisted of 1922 participants, made up of 1000 (52.0%) males and 922 (48.0%) females. The controls were slightly older than the cases on average, with a mean age of 52.7 years and the median age being 54.0. The youngest control was 21 and the oldest was 79 years of age. Since the matching strategy employed in the selection of the controls meant that the case and control samples are not independent, the two-sample t-test to evaluate differences between the two groups is inappropriate for age, sex, and study centre.

As can be seen from table 5, Melbourne contributed the greatest number of cases to the analysis (31.7%), with Grenoble representing the study centre with the lowest proportion of included cases (5.3%). This was not seen in the controls, as the largest proportion of control subjects were recruited at the Adelaide and Heidelberg centres

Table 5. Frequencies of glioma cases and controls: data from eight study centres.

Variable	Case n = 1089	Control n = 1922	Total n = 3011
	n (%)	n (%)	n (%)
Age Group			
20-24	20 (1.8)	17 (0.9)	37 (1.2)
25-29	77 (7.1)	97 (5.0)	174 (5.8)
30-34	89 (8.2)	121 (6.3)	210 (7.0)
35-39	97 (8.9)	154 (8.0)	251 (8.3)
40-44	110 (10.1)	162 (8.4)	272 (9.0)
45-49	107 (9.8)	202 (10.5)	309 (10.3)
50-54	111 (10.2)	223 (11.6)	334 (11.1)
55-59	128 (11.8)	233 (12.1)	361 (12.0)
60-64	144 (13.2)	255 (13.3)	399 (13.2)
65-69	159 (14.6)	274 (14.3)	433 (14.4)
70+	47 (4.3)	184 (9.6)	231 (7.7)
Study Centre			
Adelaide	108 (9.9)	415 (21.6)	523 (17.4)
Grenoble	58 (5.3)	119 (6.2)	177 (5.9)
Heidelberg	115 (10.6)	416 (21.6)	531 (17.6)
Los Angeles	92 (8.4)	91 (4.7)	183 (6.1)
Melbourne	345 (31.7)	359 (18.7)	704 (23.4)
Stockholm	150 (13.8)	153 (8.0)	303 (10.0)
Toronto	147 (13.5)	218 (11.3)	365 (12.1)
Winnipeg	74 (6.8)	151 (7.9)	225 (7.5)
Number of First-degree Relatives			
2	11 (1.0)	16 (0.8)	27 (0.9)
3-4	137 (12.6)	261 (13.6)	398 (13.2)
5-7	495 (45.5)	846 (44.0)	1341 (44.5)
8-10	291 (26.7)	513 (26.7)	804 (26.7)
More than 10	155 (14.2)	286 (14.9)	441 (14.7)
Type of Interview			
Direct	690 (63.4)	1791 (93.2)	2481 (82.4)
Assisted/Part Proxy/Proxy	399 (36.6)	131 (6.8)	530 (17.6)
Quality of Interview			
Reliable	504 (46.3)	597 (31.1)	1101 (36.6)
Very Good	442 (40.6)	1215 (63.2)	1657 (55.0)
Questionable	114 (10.5)	85 (4.4)	199 (6.6)
Unsatisfactory	17 (1.5)	18 (0.4)	35 (1.2)
Unknown	12 (1.1)	7 (0.9)	19 (0.6)
Education			
University/College Degree	149 (13.7)	287 (14.9)	436 (14.5)
Some University/College – No Degree	130 (11.9)	190 (9.9)	320 (10.6)
Technical Training, Apprenticeship, Or Adult Evening Classes	349 (32.0)	685 (35.7)	1034 (34.3)
High School Graduate	77 (7.1)	103 (5.4)	180 (6.0)
Some High School	136 (12.5)	191 (9.9)	327 (10.9)
7-9 Years of Schooling	199 (18.3)	408 (21.2)	607 (20.2)
Less Than 7 Years of Schooling	49 (4.5)	58 (3.0)	107 (3.5)

(21.6% each) and the least number of controls coming from Los Angeles (4.7%), though it is noted that the Los Angeles centre only included female subjects.

On average, the glioma cases reported having 2.2 children, ranging from a low of 0 to a high of 9 offspring. This was similar to the controls, who had 2.3 children on average. The lowest reported number of children was again 0, while the highest was 13. There was not a significant difference in the number of children for the cases and controls as determined by a two-sample t-test ($p = 0.56$). For the number of siblings, cases reported having an average of 3.2, with the lowest number being 0 and the highest number of siblings being 16. The controls also had 3.2 siblings on average, and the range of values was from 0 to 19. Again, no difference existed in the number of siblings between the cases and the controls ($p = 0.81$). The average number of first-degree relatives reported by cases was 7.3 people. The range was from 2 to 22, though it should be clear that the 2 comes from the number added *post hoc* by the authors to account for the parents of the participant. The average number of first-degree relatives reported by controls was also 7.3 people, with a range of 2 to 24. There was no significant difference ($p = 0.93$) between the number of relatives at risk of cancer between the cases and controls.

A highly significant difference did exist between the number of cases and controls whose interview type consisted of either assisted, part proxy, or complete proxy responses. A significantly higher proportion of cases ($p < 0.0001$) required help from either the interviewer or a proxy respondent in completing the questionnaire. Of the 530 participants that did not answer all questions directly, 350 were completed entirely by proxy, 27 partially by proxy, and 153 required the assistance of the interviewer.

Heidelberg (90.2%), Los Angeles (97.3%), and Toronto (97.8%) all were able to get direct responses from more than 90 percent of their participants. At only 64.4 percent, Winnipeg had the lowest percentage of participants providing direct responses out of all of the study centres. Grenoble had the largest proportion of assisted responses (18.1%), Stockholm the most part proxy respondents (4.3%), and the Winnipeg centre had the greatest percentage of proxy responses (32.9%).

For the quality of the interview, which was a measure of the level of understanding of the questionnaire by the participant as interpreted by the study interviewers, there was a statistically significant difference ($p = 0.03$) between the cases and the controls. More cases than controls were deemed to have given reliable responses (46.3% versus 31.1%, respectively), but cases were also more likely to give questionable answers (10.5% versus 4.4%). Controls were significantly more likely than cases to have been deemed to have a very good understanding of the questionnaire (63.2% versus 40.6%). Overall, the understanding of the questionnaire tended to be very high, with 91.6% of the included participants considered to have provided either reliable or very good responses. Only 1.2% of the population gave what was thought of as unsatisfactory responses.

As previously mentioned, the socioeconomic status of the cases and controls were projected based on the reported educational history of the participants. There were no statistically significant differences found between the cases and the controls based on the seven-point scale that was developed for the education level. 60.5% of the controls reported some education after high school, falling in either the “University/College Degree”, “University/College – No Degree”, or “Technical Training, Apprenticeship, or

Adult Evening Classes” category. This was greater than the percentage of cases (57.6%), but this difference was not found to be significant ($p = 0.56$).

4.1.2. Results of Analysis of Covariates

Table 6 outlines the trends associated with varying family sizes and the socio-economic status of the glioma cases and controls. The odds ratios reported pertain to the odds of a respondent being a case, thus a point estimate of less than 1.0 implies a lowered odds of glioma, whereas an estimate of greater than 1.0 suggests elevated odds of glioma. The referent groups are as follows: two for the number of first degree relatives and less than 7 years of schooling for the estimation of socio-economic status.

It is clear that as the number of first degree relatives increases, the risk of glioma does not significantly change for this data. The p-value for the trend was nearly 1.00 (0.99) and the Wald chi-square value was 0.20 with 4 degrees of freedom. The only point estimate that was not 1.0 was for those individuals who had more than 10 first degree relatives. The point estimate was 1.1, suggesting a slightly elevated risk of being a case with the largest family size, but this was not significant ($p = 0.71$).

The seven point scale used by the author to estimate socio-economic status of the participants depends on their secondary and tertiary education levels. The lowest education level (less than 7 years of schooling) was associated with the greatest risk of glioma. For all of the increasing levels of education, the risk of glioma significantly decreased (p -value for trend = 0.03). It can be seen that the highest category for socio-economic status (university/college degree) led to the greatest reduction in glioma risk, with a point estimate of 0.5.

Table 6. Odds ratios, 95 percent confidence intervals (CI), and trend statistics for glioma cases and controls (adjusted for age, sex, and study centre): data from eight study centres.

CHARACTERISTIC	ODDS RATIO	95% CI
Number of first degree relatives		
• 2 (0 siblings and 0 children)	1.0	-
• 3-4	1.0	0.9-1.3
• 5-7	1.0	0.8-1.3
• 8-10	1.0	0.8-1.3
• More than 10	1.1	0.9-1.3
P-value for trend		0.99
Socio-economic status (estimated by reported education level)		
• Less than 7 years of schooling	1.0	-
• 7-9 years of schooling	0.6	0.4-0.9
• Some high school	0.8	0.5-1.2
• High school graduate	0.6	0.4-1.0
• Technical training, apprenticeship, or adult evening classes	0.6	0.4-0.9
• Some university/college-no degree	0.6	0.4-1.0
• University/college degree	0.5	0.3-0.8
P-value for trend		0.03

4.1.3. Unconditional Model-based Analysis

Estimates of the adjusted odds ratios and 95% confidence intervals for the various forms of cancer using unconditional logistic regression are presented in table 7. Model one includes study centre, sex, and five-year age group as the covariates. Melbourne was used as the referent group for study centre because it contributed the greatest portion of participants to the final analysis. Females were the referent group for sex since all of the study centres included female cases and controls, while the Los Angeles centre did not include male subjects. For five-year age groups, the youngest classification to be included in all centres, 25-29 years, was selected as the reference category.

Models two through five incorporated one additional independent variable at a time that was found to have a significant effect on the fit of the model (change in

likelihood ratio and Wald chi-square associated with a p-value of 0.05 or less). The second model included the three matching variables as well as adjusting for the number of first degree relatives, with the referent group being those with only two first degree relatives. It should be noted that the inclusion of this variable did not greatly increase the model fit statistics, but the results are reported here due to previous studies that found that not including family size may bias the results (155). Based on this analysis, it can be concluded that further results found using a simple dichotomous “yes/no” answer for the presence of a family history of cancer will not be biased by failing to acknowledge the actual number of first-degree relatives at risk.

The third and fourth models incorporated the effect of the type of interview (referent group = direct respondent) and the quality of interview (referent group = reliable respondent), respectively. Socioeconomic status of the individual was included in the fifth model and those classified as having seven years or less of schooling were used as the reference group. Whether or not someone had continued their education after high school was evaluated but was not found to greatly contribute to the overall fit of the model, thus this variable was not included. The final model was constructed by forcing in the three matching variables and then introducing the remaining variables one at a time. The decision on whether or not to retain a variable in the model was decided upon using the various model statistics outlined in appendix B. Table 8 describes the effect of the addition of the three matching variables, the type of interview variable, and the quality of interview variable on the risk of being a glioma case if they reported having a first degree relative with any form of cancer. The inclusion of each of these produced the final model used in the analysis of the pooled glioma cases and controls. Number of first

degree relatives and socioeconomic status did not significantly influence the fit of the model after the inclusion of interview type and quality, so these variables were dropped from the model.

Of the included variables in the final model, logit plots to assess linearity were only applicable for age and interview quality. Sex and interview type could not be assessed because they each only consist of two exposure levels. Measuring linearity in the study centre variable would be meaningless because it is not nominal data. Linearity was evaluated in the natural log because logistic regression measures in a multiplicative scale, not an additive scale. Neither age nor interview quality displayed a lack of linearity, suggesting that including these variables in the model without transformation is acceptable (figures not shown).

Table 7. Associations between glioma in adults and cancers reported in first-degree family members¹: pooled data from eight study centres.

Type of Cancer	Cases (%) ²	Controls (%) ²	Crude OR (95% CI) ³	Adjusted OR (95% CI) Wald Chi-square and p-value
Any type				
None reported	796 (68.4) ⁴	1229 (62.1) ⁴	1.0	1.0 Model 1 ⁵ : 0.8 (0.7-1.0) $\chi^2=4.1$ p=0.04 Model 2 ⁶ : 0.8 (0.7-1.0) $\chi^2=4.1$ p=0.04 Model 3 ⁷ : 0.9 (0.7-1.0) $\chi^2=2.7$ p=0.10 Model 4 ⁸ : 0.8 (0.7-1.0) $\chi^2=3.9$ p=0.05 Model 5 ⁹ : 0.8 (0.7-1.0) $\chi^2=3.8$ p=0.05 Model 6 ¹⁰ : 0.9 (0.7-1.0) $\chi^2=2.9$ p=0.09
All first degree relatives	367 (31.6)	750 (37.9)	0.8 (0.6-0.9)	
Brain tumour				
No	1049 (96.3)	1844 (95.9)	1.0	1.0 Model 1: 0.9 (0.6-1.4) $\chi^2=0.3$ p=0.62 Model 2: 0.9 (0.6-1.4) $\chi^2=0.3$ p=0.61 Model 3: 1.0 (0.7-1.6) $\chi^2=0.0$ p=0.90 Model 4: 0.9 (0.6-1.3) $\chi^2=0.4$ p=0.51 Model 5: 0.9 (0.6-1.4) $\chi^2=0.2$ p=0.66 Model 6: 1.0 (0.6-1.5) $\chi^2=0.0$ p=0.93
All first degree relatives	40 (3.7)	78 (4.1)	0.9 (0.6-1.3)	

Table 7 (Cont). Associations between glioma in adults and cancers reported in first-degree family members¹: pooled data from eight study centres.

Any type except brain tumour				
No	740 (68.0)	1187 (61.8)	1.0	1.0 Model 1: 0.8 (0.7-1.0) $\chi^2=4.1$ p=0.04 Model 2: 0.8 (0.7-1.0) $\chi^2=4.1$ p=0.04
All first degree relatives	349 (32.0)	735 (38.2)	0.8 (0.7-0.9)	Model 3: 0.9 (0.7-1.0) $\chi^2=2.7$ p=0.10 Model 4: 0.8 (0.7-1.0) $\chi^2=3.9$ p=0.05 Model 5: 0.8 (0.7-1.0) $\chi^2=3.8$ p=0.05 Model 6: 0.9 (0.7-1.0) $\chi^2=2.9$ p=0.09
Any type in mother				
No	1023 (86.8)	1693 (85.2)	1.0	1.0 Model 1: 0.9 (0.7-1.1) $\chi^2=1.6$ p=0.21 Model 2: 0.9 (0.7-1.1) $\chi^2=1.6$ p=0.21
Yes	155 (13.2)	294 (14.8)	0.9 (0.7-1.1)	Model 3: 0.9 (0.7-1.2) $\chi^2=0.4$ p=0.52 Model 4: 0.9 (0.7-1.1) $\chi^2=1.5$ p=0.22 Model 5: 0.9 (0.7-1.1) $\chi^2=1.5$ p=0.23 Model 6: 0.9 (0.7-1.1) $\chi^2=0.5$ p=0.47
Any type in father				
No	1040 (88.3)	1718 (86.5)	1.0	1.0 Model 1: 0.8 (0.7-1.1) $\chi^2=2.0$ p=0.16 Model 2: 0.8 (0.7-1.1) $\chi^2=2.0$ p=0.16
Yes	138 (11.7)	269 (13.5)	0.8 (0.7-1.1)	Model 3: 0.9 (0.7-1.1) $\chi^2=1.5$ p=0.22 Model 4: 0.9 (0.7-1.1) $\chi^2=1.3$ p=0.25 Model 5: 0.9 (0.7-1.1) $\chi^2=1.4$ p=0.23 Model 6: 0.9 (0.7-1.1) $\chi^2=1.1$ p=0.31
Any type in siblings¹¹				
No	983 (89.0)	1718 (89.0)	1.0	1.0 Model 1: 1.2 (0.9-1.5) $\chi^2=1.5$ p=0.22 Model 2: 1.2 (0.9-1.5) $\chi^2=1.8$ p=0.18
Yes	122 (11.0)	212 (11.0)	1.0 (0.8-1.3)	Model 3: 1.2 (0.9-1.6) $\chi^2=1.4$ p=0.24 Model 4: 1.1 (0.9-1.5) $\chi^2=0.7$ p=0.40 Model 5: 1.2 (0.9-1.5) $\chi^2=1.3$ p=0.26 Model 6: 1.1 (0.8-1.5) $\chi^2=0.7$ p=0.41
Any type in children¹²				
No	1074 (99.6)	1789 (99.1)	1.0	1.0 Model 1: 0.5 (0.2-1.6) $\chi^2=1.2$ p=0.27 Model 2: 0.5 (0.2-1.6) $\chi^2=1.2$ p=0.27
Yes	4 (0.4)	17 (0.9)	0.4 ¹³ (0.1-1.2)	Model 3: 0.5 (0.1-1.7) $\chi^2=1.4$ p=0.24 Model 4: 0.6 (0.2-1.9) $\chi^2=0.7$ p=0.39 Model 5: 0.5 (0.2-1.6) $\chi^2=1.4$ p=0.24 Model 6: 0.5 (0.1-1.8) $\chi^2=1.1$ p=0.30
Lung ca. in parents				
No	1034 (87.9)	1707 (86.1)	1.0	1.0 Model 1: 0.9 (0.7-1.1) $\chi^2=1.7$ p=0.20 Model 2: 0.9 (0.7-1.1) $\chi^2=1.7$ p=0.20
Yes	142 (12.1)	275 (13.9)	0.9 (0.7-1.1)	Model 3: 0.9 (0.7-1.1) $\chi^2=1.5$ p=0.23 Model 4: 0.9 (0.7-1.1) $\chi^2=1.0$ p=0.31 Model 5: 0.9 (0.7-1.1) $\chi^2=1.2$ p=0.28 Model 6: 0.9 (0.7-1.1) $\chi^2=0.9$ p=0.33
Lung ca. in father				
No	1151 (98.0)	1941 (98.0)	1.0	1.0 Model 1: 0.9 (0.5-1.6) $\chi^2=0.0$ p=0.84 Model 2: 0.9 (0.5-1.6) $\chi^2=0.0$ p=0.84
Yes	24 (2.0)	39 (2.0)	1.0 (0.6-1.7)	Model 3: 0.9 (0.5-1.6) $\chi^2=0.3$ p=0.59 Model 4: 0.8 (0.5-1.5) $\chi^2=0.4$ p=0.53 Model 5: 1.0 (0.6-1.7) $\chi^2=0.0$ p=0.91 Model 6: 0.8 (0.4-1.5) $\chi^2=0.6$ p=0.43

Table 7 (Cont). Associations between glioma in adults and cancers reported in first-degree family members¹: pooled data from eight study centres.

Lung ca. in siblings¹¹				
No	1044 (94.5)	1828 (94.7)	1.0	1.0 Model 1: 1.2 (0.8-1.7) $\chi^2=1.1$ p=0.30 Model 2: 1.2 (0.9-1.7) $\chi^2=1.2$ p=0.27
Yes	61 (5.5)	102 (5.3)	1.0 (0.8-1.5)	Model 3: 1.3 (0.9-1.9) $\chi^2=1.6$ p=0.21 Model 4: 1.2 (0.8-1.7) $\chi^2=0.6$ p=0.43 Model 5: 1.2 (0.8-1.7) $\chi^2=0.9$ p=0.36 Model 6: 1.2 (0.8-1.8) $\chi^2=0.9$ p=0.33
Breast ca. in mother				
No	1146 (97.3)	1920 (96.6)	1.0	1.0 Model 1: 0.7 (0.5-1.2) $\chi^2=1.8$ p=0.18 Model 2: 0.7 (0.5-1.2) $\chi^2=1.8$ p=0.18
Yes	32 (2.7)	67 (3.4)	0.8 (0.5-1.2)	Model 3: 0.8 (0.4-1.3) $\chi^2=1.1$ p=0.29 Model 4: 0.8 (0.5-1.2) $\chi^2=1.2$ p=0.28 Model 5: 0.7 (0.5-1.2) $\chi^2=1.5$ p=0.21 Model 6: 0.8 (0.5-1.3) $\chi^2=0.9$ p=0.35
Breast ca. in sister¹¹				
No	1030 (98.1)	1765 (98.3)	1.0	1.0 Model 1: 1.5 (0.8-2.7) $\chi^2=1.7$ p=0.19 Model 2: 1.5 (0.8-2.7) $\chi^2=1.7$ p=0.19
Yes	20 (1.9)	31 (1.7)	1.1 (0.6-1.9)	Model 3: 1.2 (0.6-2.4) $\chi^2=0.2$ p=0.67 Model 4: 1.5 (0.8-2.8) $\chi^2=1.6$ p=0.21 Model 5: 1.5 (0.8-2.7) $\chi^2=1.6$ p=0.21 Model 6: 1.2 (0.6-2.5) $\chi^2=0.2$ p=0.62
Lip, oral, or pharyngeal ca. in parents				
No	1172 (99.5)	1976 (99.4)	1.0	1.0 Model 1: 0.7 (0.2-2.1) $\chi^2=0.4$ p=0.55 Model 2: 0.7 (0.2-2.1) $\chi^2=0.4$ p=0.55
Yes	6 (0.5)	11 (0.6)	0.9 ¹⁴ (0.3-2.5)	Model 3: 0.9 (0.3-2.7) $\chi^2=0.1$ p=0.80 Model 4: 0.7 (0.2-2.2) $\chi^2=0.3$ p=0.56 Model 5: 0.7 (0.3-2.2) $\chi^2=0.3$ p=0.59 Model 6: 0.9 (0.3-2.8) $\chi^2=0.0$ p=0.83
Lip, oral, or pharyngeal ca. in siblings¹¹				
No	1049 (99.9)	1791 (99.7)	1.0	1.0 Model 1: 0.4 (0.0-3.7) $\chi^2=0.6$ p=0.44 Model 2: 0.4 (0.0-3.7) $\chi^2=0.6$ p=0.44
Yes	1 (0.1)	5 (0.3)	0.3 ¹⁵ (0.0-2.9)	Model 3: 0.4 (0.0-3.7) $\chi^2=0.6$ p=0.43 Model 4: 0.6 (0.1-5.2) $\chi^2=0.2$ p=0.62 Model 5: 0.4 (0.0-3.8) $\chi^2=0.6$ p=0.45 Model 6: 0.5 (0.1-4.5) $\chi^2=0.4$ p=0.53
Gastrointestinal ca. in parents				
No	1087 (92.4)	1829 (92.1)	1.0	1.0 Model 1: 1.0 (0.8-1.4) $\chi^2=0.0$ p=0.91 Model 2: 1.0 (0.8-1.4) $\chi^2=0.0$ p=0.91
Yes	89 (7.6)	156 (7.9)	1.0 (0.7-1.3)	Model 3: 1.2 (0.9-1.7) $\chi^2=1.1$ p=0.30 Model 4: 1.0 (0.8-1.4) $\chi^2=0.0$ p=0.86 Model 5: 1.0 (0.8-1.4) $\chi^2=0.0$ p=0.88 Model 6: 1.2 (0.9-1.7) $\chi^2=1.0$ p=0.31
Gastrointestinal ca. in siblings¹¹				
No	1022 (97.3)	1755 (97.7)	1.0	1.0 Model 1: 1.4 (0.9-2.4) $\chi^2=1.9$ p=0.16 Model 2: 1.5 (0.9-2.5) $\chi^2=2.1$ p=0.15
Yes	28 (2.7)	41 (2.3)	1.2 (0.7-1.9)	Model 3: 1.7 (1.0-3.0) $\chi^2=3.2$ p=0.07 Model 4: 1.6 (0.9-2.7) $\chi^2=2.6$ p=0.11 Model 5: 1.4 (0.8-2.4) $\chi^2=1.7$ p=0.19 Model 6: 1.8 (1.0-3.3) $\chi^2=3.5$ p=0.06

Table 7 (Cont). Associations between glioma in adults and cancers reported in first-degree family members¹: pooled data from eight study centres.

Genitourinary ca. in parents				
No	1135 (96.3)	1921 (96.7)	1.0	1.0 Model 1: 1.2 (0.8-1.8) $\chi^2=0.8$ p=0.37 Model 2: 1.2 (0.8-1.8) $\chi^2=0.8$ p=0.37
Yes	43 (3.7)	66 (3.3)	1.1 (0.7-1.6)	Model 3: 1.2 (0.8-1.9) $\chi^2=0.7$ p=0.39 Model 4: 1.2 (0.8-1.9) $\chi^2=0.9$ p=0.35 Model 5: 1.2 (0.8-1.8) $\chi^2=0.8$ p=0.37 Model 6: 1.2 (0.8-2.0) $\chi^2=0.7$ p=0.39
Genitourinary ca. in siblings¹¹				
No	1035 (98.6)	1766 (98.3)	1.0	1.0 Model 1: 1.1 (0.6-2.1) $\chi^2=0.1$ p=0.77 Model 2: 1.1 (0.6-2.1) $\chi^2=0.1$ p=0.77
Yes	15 (1.4)	30 (1.7)	0.9 (0.5-1.6)	Model 3: 1.2 (0.6-2.5) $\chi^2=0.2$ p=0.68 Model 4: 1.0 (0.5-2.0) $\chi^2=0.0$ p=0.98 Model 5: 1.1 (0.6-2.1) $\chi^2=0.1$ p=0.79 Model 6: 1.1 (0.5-2.3) $\chi^2=0.0$ p=0.88
Unspecified ca. in parents				
No	1166 (99.0)	1965 (98.9)	1.0	1.0 Model 1: 0.9 (0.4-1.8) $\chi^2=0.2$ p=0.68 Model 2: 0.9 (0.4-1.8) $\chi^2=0.2$ p=0.68
Yes	12 (1.0)	21 (1.1)	1.0 (0.5-2.0)	Model 3: 1.0 (0.4-2.3) $\chi^2=0.0$ p=0.95 Model 4: 0.8 (0.4-1.8) $\chi^2=0.3$ p=0.59 Model 5: 0.9 (0.4-1.9) $\chi^2=0.1$ p=0.71 Model 6: 0.9 (0.4-2.3) $\chi^2=0.0$ p=0.89
Unspecified ca. in siblings¹¹				
No	1044 (99.4)	1782 (99.2)	1.0	1.0 Model 1: 1.0 (0.4-2.7) $\chi^2=0.0$ p=0.98 Model 2: 1.0 (0.4-2.7) $\chi^2=0.0$ p=0.99
Yes	6 (0.6)	14 (0.8)	0.7 ¹⁶ (0.3-1.9)	Model 3: 0.8 (0.2-2.7) $\chi^2=0.1$ p=0.72 Model 4: 0.6 (0.2-1.7) $\chi^2=1.0$ p=0.32 Model 5: 1.1 (0.4-2.9) $\chi^2=0.0$ p=0.91 Model 6: 0.6 (0.2-2.1) $\chi^2=0.6$ p=0.43

¹ First-degree family members include mother, father, siblings, and children.

² Subjects with missing data excluded on a variable by variable basis.

³ Crude (unadjusted) odds ratio and 95% confidence intervals.

⁴ Values in parentheses indicate percentages.

⁵ Adjusted for study centre, sex, and five-year age group.

⁶ Adjusted for study centre, sex, five-year age group, and number of first-degree relatives.

⁷ Adjusted for study centre, sex, five-year age group, and interview type.

⁸ Adjusted for study centre, sex, five-year age group, and quality of interview.

⁹ Adjusted for study centre, sex, five-year age group, and socioeconomic status.

¹⁰ Adjusted for study centre, sex, five-year age group, interview type, and quality of interview.

¹¹ Excludes those respondents who reported having zero siblings.

¹² Excludes those respondents who reported having zero children.

¹³ Fisher's exact test value p=0.98.

¹⁴ Fisher's exact test value p=0.65.

¹⁵ Fisher's exact test value p=0.94.

¹⁶ Fisher's exact test value p=0.81.

Table 8. Model-fit statistics for glioma cases and controls: pooled data from eight study centres.

Model Number	Variables Included	R ² (Change in value)	c-statistic (Change in value)	Wald Chi-square (Change in value)	-2 Log Likelihood (Change in value)	Hosmer and Lemeshow Chi-square and p-value
1	Age, sex, study centre	0.07	0.66	208.36	3711.24	17.08 p=0.03
2	Age, sex, study centre, interview type	0.22 (+0.15)	0.78 (+0.12)	530.83 (+322.47)	3196.23 (-515.01)	12.58 p=0.13
3	Age, sex, study centre, interview type, interview quality	0.25 (+0.03)	0.80 (+0.02)	564.64 (+33.81)	3092.40 (-103.83)	16.50 p=0.04

4.1.4. Conditional Model-based Analysis

Five centres were included in the conditional logistic regression as a result of using individual matching strategies. The number of cases and controls contributed by each of these centres are outlined in table 9, after removing all of the individuals with missing data. An initial total of 719 glioma cases and 873 controls were found to be individually matched, or 1592 participants combined. However, due to the removal of observations, matched sets were disrupted, such that in some sets there was a case but no control, or vice versa. In these instances, both the case and the control were removed from further analysis. The author notes that the Grenoble and Winnipeg centres used a 2:1 control:case matching strategy. For these centres, matched sets were retained where only one of the controls was removed due to missing data.

Table 9: Participation rates for centres included in the conditional model-based analysis of glioma cases and controls.

Centre	# of Cases (% of total cases)	# of Controls (% of total controls)	Ratio of Controls to Cases	Total # of Participants (% of total)
Melbourne	345 (48.0)	359 (41.1)	1.04:1	704 (44.2)
Grenoble	58 (8.1)	119 (13.6)	2.05:1	177 (11.1)
Stockholm	150 (20.9)	153 (17.5)	1.02:1	303 (19.0)
Winnipeg	74 (10.3)	151 (17.3)	2.04:1	225 (14.1)
Los Angeles	92 (12.8)	91 (10.4)	0.99:1	183 (11.5)

As can be seen in table 9, the Melbourne study centre had the greatest number of cases and controls of all of the centres which used an individual matching strategy. The number of participants listed in the above table reflects those that were input into the SAS system for analysis, which is why the ratios of controls to cases are not exactly 2:1 or 1:1. The SAS system recognizes the response patterns and removes those strata which had only one case and no control, no case and one control, and no case and two controls as uninformative strata. Therefore, the true ratios of the included centres will be 2:1 or 1:1.

Table 10 compares the odds ratio and 95 percent confidence interval for each of the cancer exposure variables as estimated using conditional logistic regression and unconditional logistic regression, restricted to the five SEARCH study centres which used individual matching. The unconditional model took into account the effect of the study centre, with Melbourne serving as the reference; sex of the individual, using female

Table 10: Associations between glioma in adults and cancers reported in first degree family members: pooled conditional analysis of five study centres.

Type of cancer	Total # of included cases/controls	OR (95% CI)	Wald chi-square & p-value	OR (95% CI) estimated by unconditional model 1
Any type	Cases = 677 Controls = 805	1.1 (0.9-1.4)	$\chi^2=0.5$ p=0.47	1.1 (0.9-1.4)
Brain tumour	Cases = 677 Controls = 805	0.9 (0.5-1.5)	$\chi^2=0.2$ p=0.65	0.9 (0.5-1.5)
Any type except brain tumour	Cases = 677 Controls = 805	1.0 (0.8-1.3)	$\chi^2=0.1$ p=0.80	1.0 (0.8-1.3)
Any type in mother	Cases = 677 Controls = 805	1.1 (0.8-1.5)	$\chi^2=0.6$ p=0.44	1.1 (0.8-1.5)
Any type in father	Cases = 677 Controls = 805	0.9 (0.6-1.2)	$\chi^2=0.6$ p=0.43	0.9 (0.6-1.2)
Any type in siblings	Cases = 624 Controls = 724	1.3 (0.9-1.8)	$\chi^2=1.8$ p=0.18	1.4 (1.0-1.9)
Any type in children	Cases = 597 Controls = 683	0.2 (0.0-1.5)	$\chi^2=2.5$ p=0.11	0.2 (0.0-1.9)
Lung ca. in parents	Cases = 672 Controls = 797	0.9 (0.7-1.2)	$\chi^2=0.3$ p=0.56	0.9 (0.6-1.2)
Lung ca. in father	Cases = 672 Controls = 797	1.1 (0.5-2.3)	$\chi^2=0.1$ p=0.76	1.0 (0.5-2.1)
Lung ca. in siblings	Cases = 624 Controls = 724	1.5 (0.9-2.4)	$\chi^2=2.3$ p=0.13	1.5 (0.9-2.3)
Breast ca. in mother	Cases = 677 Controls = 805	0.9 (0.5-1.6)	$\chi^2=0.1$ p=0.71	0.9 (0.5-1.5)
Breast ca. in sister	Cases = 624 Controls = 724	1.1 (0.5-2.7)	$\chi^2=0.1$ p=0.82	1.4 (0.6-3.1)
Lip, oral, or pharyngeal ca. in parents	Cases = 677 Controls = 805	1.4 (0.3-7.2)	$\chi^2=0.2$ p=0.68	1.4 (0.3-7.2)
Lip, oral, or pharyngeal ca. in siblings ¹	Cases = 624 Controls = 724	0.0 (0.0-999.9)	$\chi^2=0.0$ p=0.99	0.0 (0.0-999.9)
Gastrointestinal ca. in parents	Cases = 675 Controls = 802	1.0 (0.7-1.4)	$\chi^2=0.0$ p=0.85	1.0 (0.7-1.4)
Gastrointestinal ca. in siblings	Cases = 624 Controls = 724	1.1 (0.6-2.2)	$\chi^2=0.1$ p=0.77	1.1 (0.6-2.2)
Genitourinary ca. in parents	Cases = 677 Controls = 805	1.2 (0.7-2.0)	$\chi^2=0.5$ p=0.50	1.2 (0.7-2.0)
Genitourinary ca. in siblings	Cases = 624 Controls = 724	0.8 (0.3-1.9)	$\chi^2=0.3$ p=0.55	0.9 (0.4-2.1)
Unspecified ca. in parents	Cases = 676 Controls = 804	1.0 (0.4-2.4)	$\chi^2=0.0$ p=0.94	0.9 (0.4-2.3)
Unspecified ca. in siblings	Cases = 624 Controls = 724	1.9 (0.5-6.7)	$\chi^2=0.9$ p=0.34	2.1 (0.6-7.8)

¹ There was a possible quasi-complete separation of data points; therefore, the maximum likelihood estimate does not exist (either no cases or no controls included).

as the referent sex; and five-year age group, with those falling in the 25-29 group being the referent category. The Wald chi-square and p-values reported are for the conditional based analysis. The purpose of this comparison was to evaluate whether it was appropriate to include those centres which used individual matching in the pooled unconditional analysis. Looking at the comparative results, it is clear that including all eight centres in the unconditional analysis is appropriate.

All but six of the point estimates of the odds of being a glioma cases were the exact same for the 20 different cancer exposures. Of these six, only two had a difference of 0.1, which was actually an inflated difference in each instance as a result of rounding. In no instance did a point estimate in either the conditional or unconditional regression analysis fall outside of the confidence interval predicted by the other modeling strategy. For any type of cancer in siblings, the 95 percent confidence interval did not border 1.0 when conditional regression was used (0.9-1.8), but did when unconditional regression was the method of prediction (1.0-1.9). However, this difference was very slight and due to rounding. The increased glioma risk associated with this exposure did not achieve statistical significance using unconditional logistic regression at the 95 percent confidence level ($p = 0.09$), which means that the confidence interval did in fact cross 1.0.

4.1.5. Overview of Family History of Cancer Analysis

Only two of the 20 different exposure variables investigated in the pooled unconditional analysis, any type of cancer in first degree relatives and any type of cancer excluding brain tumours, were found to have significant unadjusted odds ratios.

Interestingly, having a first degree relative with any form of cancer lowers the risk of being a glioma case for the SEARCH study dataset. Also, when one excludes those first degree relatives with brain tumours, having a relative with cancer significantly decreases the risk of developing glioma in the adults of this study. However, failure to account for the sex, five-year age group, and study centre in the analysis would be incorrect due to the matching strategy employed in the SEARCH study, as previously mentioned.

After adjusting for the matching variables and the family size, type of interview, quality of interview, and socioeconomic status in models one through six, having a first degree relative with any type of cancer and having a first degree relative with any type of cancer excluding brain tumours remained the only two exposures that were significantly associated with a change in risk of glioma development at the $p = 0.05$ significance level. The presence of gastrointestinal cancer in siblings approached statistical significance, particularly when the final model was applied to the data, but did not reach the 0.05 level of significance that was set *a priori* ($p = 0.06$).

4.1.6. Any Type of Cancer

For each of the six models that were run, having a first degree relative with any form of cancer was associated with a decreased risk of adult glioma. These findings were fairly consistent from model to model, with estimates ranging from 0.8 to 0.9. However, for two of the models (model three adjusted for sex, age, study centre, and interview type and model six adjusted for sex, age, study centre, interview type, and interview quality) the findings were not statistically significant. As well, every one of the 95% confidence intervals bordered 1.0. Taking this into account and the fact that the best fitted model,

the sixth model, suggested that the decreased odds was not statistically significant, the finding that there is an association between reduced risk of developing glioma and having a first degree relative with cancer is highly questionable for this dataset.

4.1.7. Any Type of Cancer Excluding Brain Tumours

The decreased risk of glioma in the SEARCH study dataset associated with a first degree relative having any form of cancer except for a brain tumour was fairly consistent from model to model in the unconditional analysis (range of OR: 0.8-0.9). Four of the six models achieved statistical significance, though each of the upper confidence limits bordered 1.0. The initial model, which adjusted for the matching covariates age, sex, and study centre, found a statistically significant reduced risk, but when the model which was found to have the best fit was applied, that which adjusted for age, sex, study centre, interview type, and interview quality, the point estimate changed from 0.8 to 0.9 and the lowered risk was no longer significant ($p = 0.09$). Based on these findings, there is a suggestion that having a first degree relative with any form of cancer other than a brain tumour may decrease ones risk of having glioma, but there is no conclusive evidence from this data.

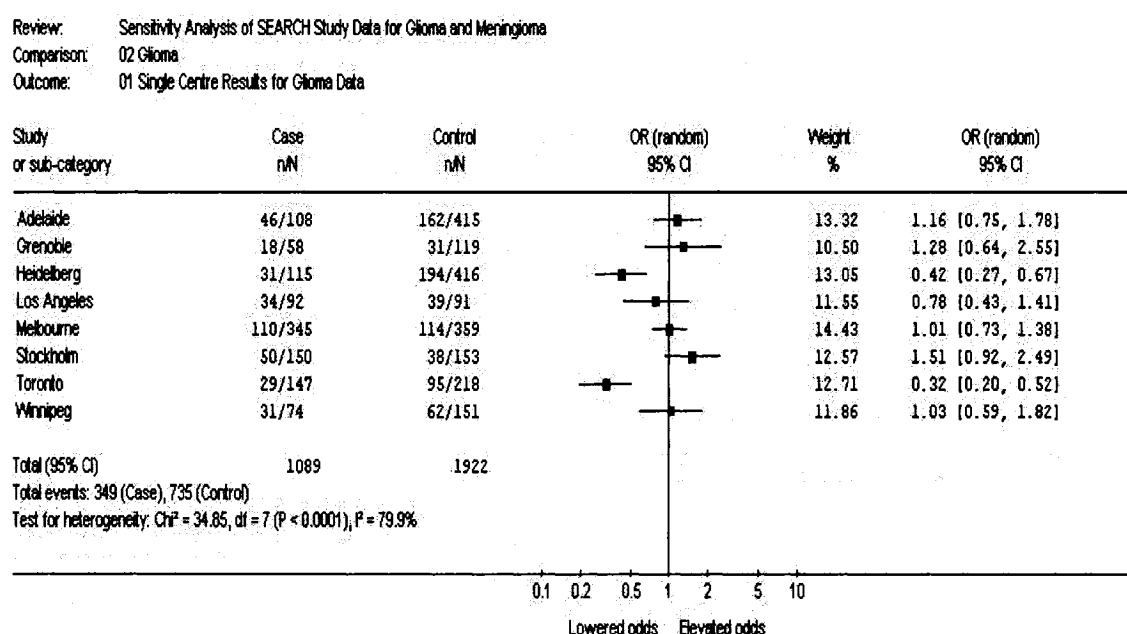
4.1.8. Sensitivity Analysis

4.1.8.a. Centre-specific Results

In order to assess the appropriateness of pooling the data pertaining to the glioma cases and controls from each of the eight SEARCH study centres, the heterogeneity of centre-specific results for the association between glioma and a family history of any

form of cancer was evaluated using the RevMan statistical package. Figure 1 is a forest plot showing the odds ratio and 95 percent confidence interval for each of the study centres, the overall odds ratio, and the tests for heterogeneity amongst the centres. A random effects model was used to generate the odds ratios, with the study centre serving as the random effect.

Figure 1: Forest plot of centre-specific odds ratios for glioma cases and controls: exposure variable is any form of cancer in a first degree relative.



A number of observations can be made regarding figure 1. Two of the eight study centres, Heidelberg and Toronto, were found to produce significantly reduced odds of glioma for those who reported having a first degree relative with cancer. Their respective point estimates and 95 percent confidence intervals were 0.4 (0.3-0.7) and 0.3 (0.2-0.5). The six remaining centres seemed to produce fairly homogeneous results, with all of their confidence intervals crossing 1.0. As was to be expected, the centre with the largest number of study participants, Melbourne, produced the tightest confidence interval, while

the study centre which had the lowest weight in the cumulative analysis, Grenoble, had the widest intervals. Important comments must be made about the heterogeneity statistics presented in figure 1.

There were a number of instances where there was a complete lack of overlap between the predicted confidence intervals from each of the different study centres. Toronto had no overlap with the Stockholm, Adelaide, Grenoble, Melbourne, and Winnipeg study centres, as well as the overall predicted interval. As a result, the test for heterogeneity amongst the centres produced an I^2 value of 79.9%. This finding suggests that it is inappropriate to consider evaluating the pooled data for the association between adult glioma and a family history of any cancer amongst the SEARCH study participants since the findings are not consistent from centre to centre.

Each of the eight study centres was removed from the pooled analysis one at a time in order to evaluate the impact that it had on the cumulative point estimate for having a first degree relative with any form of cancer. The author also removed both the Heidelberg and Toronto centres at the same time. The results can be seen in table 11. The removal of a single centre never significantly improved the level of heterogeneity between the different sites, though removing Toronto from the pooled data did produce the greatest drop in the I^2 statistic, suggesting that it had the greatest influence on the heterogeneity that was present. It is interesting to note also that only the removal of Toronto moved the point estimate for the risk of adult glioma to 1.0 when considering the deletion of single centres. When both Heidelberg and Toronto were removed, the inverse association of a family history of cancer completely disappeared and the point estimate

moved to 1.1. Also, the heterogeneity found between centres was no longer an issue, as the I^2 value dropped to nil.

Table 11: Results of the cumulative association of a first degree relative with cancer amongst glioma cases and controls: effect of the removal of individual centre data.

Study Centre Dropped	Cumulative Odds Ratio (95 % CI)	Two-sided Test for Overall Effect (p-value)	Chi-square Test for Heterogeneity (p-value)	I^2 Value
None	0.8 (0.6-1.2)	Z = 0.95 (0.34)	34.85 (< 0.01)	79.9%
Adelaide	0.8 (0.5-1.2)	Z = 1.06 (0.29)	32.22 (<0.01)	81.4%
Grenoble	0.8 (0.5-1.2)	Z = 1.12 (0.26)	33.30 (<0.01)	82.0%
Heidelberg	0.9 (0.6-1.3)	Z = 0.43 (0.67)	24.87 (<0.01)	75.9%
Los Angeles	0.8 (0.6-1.3)	Z = 0.80 (0.42)	34.80 (<0.01)	82.8%
Melbourne	0.8 (0.5-1.3)	Z = 0.91 (0.36)	33.03 (<0.01)	81.8%
Stockholm	0.8 (0.5-1.1)	Z = 1.33 (0.18)	28.74 (<0.01)	79.1%
Toronto	1.0 (0.7-1.3)	Z = 0.30 (0.77)	17.72 (<0.01)	66.1%
Winnipeg	0.8 (0.5-1.2)	Z = 0.98 (0.33)	34.24 (<0.01)	82.5%
Heidelberg & Toronto	1.1 (0.9-1.3)	Z = 0.91 (0.36)	3.42 (0.64)	0%

The author notes that the significant level of heterogeneity seen in the Heidelberg and Toronto centres may not have been restricted to the “any cancer in any relative” exposure variable and may have contributed to varying odds ratios found in the unconditional logistic regression performed on the other exposure variables discussed in section 4.1.3. To assess this, tests for centre heterogeneity were performed for each of the 20 different cancer exposures, for which results can be found in table 12.

Table 12: Test for heterogeneity amongst eight study centres assessing the association between cancer in first degree relatives and glioma in adults.

Cancer Exposure Variable	Cumulative Odds Ratio (95 % CI)	Two-sided Test for Overall Effect (p-value)	Chi-square Test for Heterogeneity (p-value)	I² Value
Any Cancer	0.8 (0.6-1.2)	Z = 0.95 (0.34)	34.85 (< 0.01)	79.9%
Brain Tumour	0.9 (0.6-1.4)	Z = 0.46 (0.64)	4.18 (0.76)	0%
Any Cancer Except Brain Tumour	0.9 (0.6-1.3)	Z = 0.77 (0.44)	35.60 (<0.01)	80.3%
Any in Mother	0.9 (0.6-1.2)	Z = 0.75 (0.45)	15.49 (0.03)	54.8%
Any in Father	0.8 (0.7-1.1)	Z = 1.34 (0.18)	3.40 (0.85)	0%
Any in Siblings	1.0 (0.7-1.6)	Z = 0.06 (0.95)	17.30 (0.02)	59.5%
Any in Children	0.7 (0.3-1.9)	Z = 0.71 (0.48)	4.67 (0.46)	0%
Lung in Parents	0.9 (0.7-1.1)	Z = 1.24 (0.21)	2.82 (0.90)	0%
Lung in Father	1.1 (0.6-1.9)	Z = 0.22 (0.83)	3.73 (0.81)	0%
Lung in Siblings	1.1 (0.8-1.6)	Z = 0.51 (0.61)	7.85 (0.35)	10.8%
Breast in Mother	0.8 (0.4-1.4)	Z = 0.91 (0.36)	8.36 (0.21)	28.2%
Breast in Sister	1.5 (0.8-3.0)	Z = 1.18 (0.24)	6.36 (0.38)	5.6%
Lip, Oral, or Pharyngeal in Parents	0.9 (0.3-2.5)	Z = 0.25 (0.80)	3.07 (0.55)	0%
Lip, Oral, or Pharyngeal in Siblings	0.4 (0.1-2.7)	Z = 0.88 (0.38)	0.01 (0.91)	0%

Table 12 (Cont): Test for heterogeneity amongst eight study centres assessing the association between cancer in first degree relatives and glioma in adults.

Gastrointestinal in Parents	1.0 (0.7-1.3)	Z = 0.03 (0.98)	1.80 (0.94)	0%
Gastrointestinal in Siblings	1.4 (0.8-2.3)	Z = 1.27 (0.20)	3.03 (0.81)	0%
Genitourinary in Parents	1.2 (0.8-1.8)	Z = 0.80 (0.42)	2.38 (0.88)	0%
Genitourinary in Siblings	1.0 (0.5-2.1)	Z = 0.13 (0.90)	5.40 (0.49)	0%
Unspecified in Parents	0.9 (0.4-2.0)	Z = 0.29 (0.77)	1.69 (0.79)	0%
Unspecified in Siblings	1.2 (0.4-3.6)	Z = 0.35 (0.72)	3.31 (0.65)	0%

Four of the 20 different forms of cancer exposures were found to have significant levels of heterogeneity amongst the centre-specific results. These variables were: any cancer amongst all first degree relatives; any cancer except brain tumours amongst all first degree relatives; any form of cancer amongst mothers; and, any form of cancer amongst siblings. Random effect modeling, using study centre as the random effect, did not find statistically significant associations between any of these exposures and adult glioma for this dataset. The forest plots for each of these variables can be seen in figures 1-4. As was the case for the variable which considered any form of cancer amongst all first degree relatives, the Toronto study centre had a much lower predicted odds ratio and 95 percent confidence interval than all of the other centres, excluding Heidelberg. The Heidelberg centre did have the lowest point estimate for any cancer amongst siblings, but for any cancer in mother its predicted value was much closer to the cumulative odds ratio, falling within the confidence intervals of five of the other six study centres.

Figure 2: Forest plot of centre-specific odds ratios for glioma cases and controls: exposure variable is any form of cancer except brain tumour in a first degree relative.

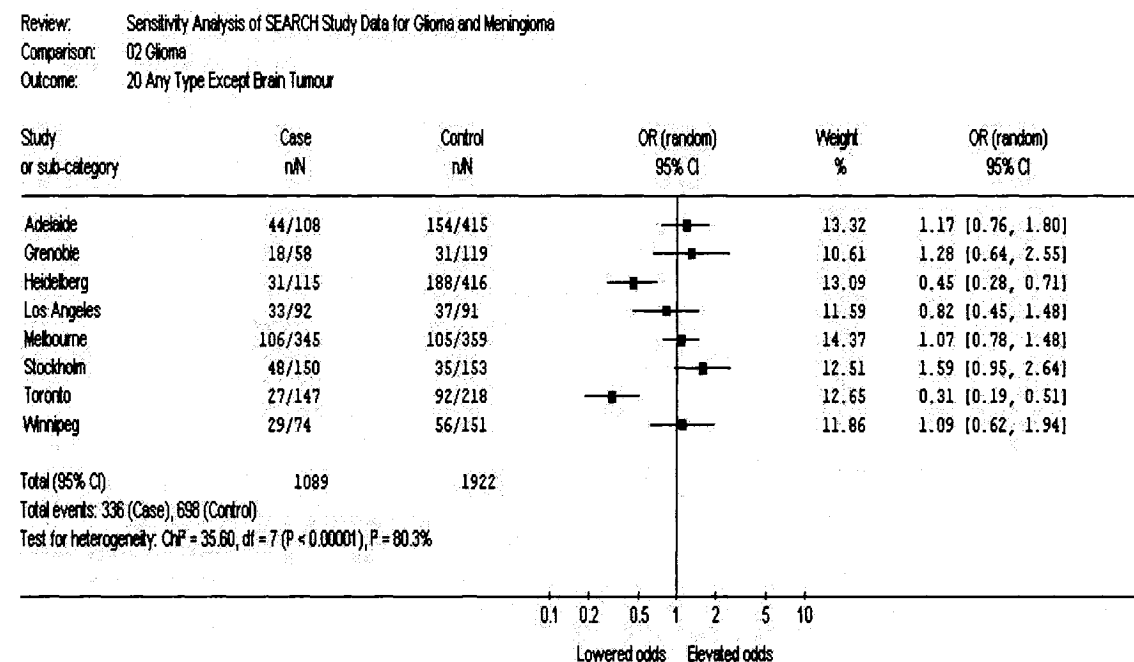


Figure 3: Forest plot of centre-specific and pooled odds ratios for glioma cases and controls: exposure variable is any form of cancer in mothers.

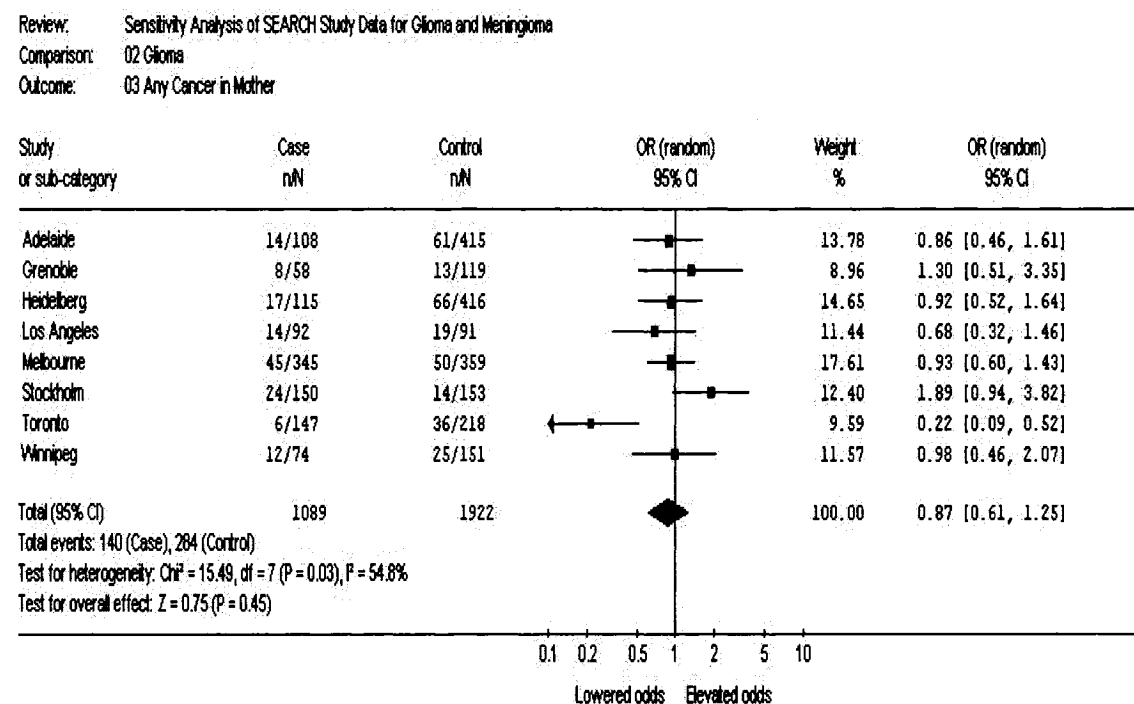
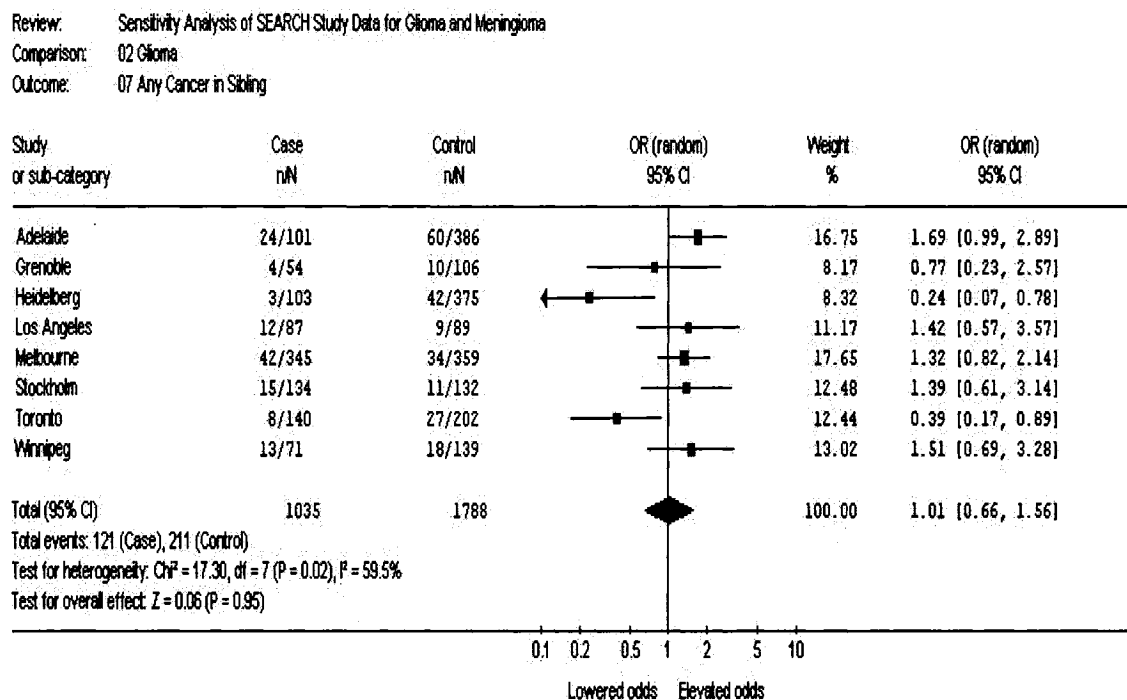


Figure 4: Forrest plot of centre-specific and pooled odds ratios for glioma cases and controls: exposure variable is any form of cancer in siblings.



As previously mentioned, the unconditional logistic regression reported in section 4.1.3. dealt with pooled results from all of the SEARCH study centres. Since it was found that the assumed homogeneity of results amongst the centres was violated for some of the exposure variables, centre-specific unconditional analysis was run. The first model was meant to include only the matching variables. Since the effect of study centre was being studied, only age and sex were controlled for, with 25-29 year olds and females serving as the respective referent categories. The second model run was the one that was found to have the best fit in the pooled analysis. It took into account a participant's age, sex, type of interview, and quality of interview. The particular reference groups were 25-29 year olds, females, direct interviews, and reliable interview responses. Table 13 lists the centre specific odds ratios and 95 percent confidence intervals, Wald chi-square values, and p-values for both of these models.

For both of the models, the Heidelberg and Toronto centres continued to have statistically significant reduced odds of glioma associated with any cancer in a first degree relative, though the Wald chi-square values were reduced for both centres in the second model. The Stockholm centre approached statistical significance, suggesting an elevated risk of glioma, but did not reach the $p = 0.05$ level. This trend was also found when all relatives with any form of cancer except brain tumours were considered. For those participants that reported having a mother with cancer, the results from the Toronto centre differed greatly from the other seven centres. No significant associations were reported for the Heidelberg centre for this exposure. The greatest disparity occurred between the Toronto and Stockholm centres. Finally, for any cancer in siblings, the Heidelberg centre found a significantly reduced odds ratio when age and sex were controlled for, but this significance did not exist when the type and quality of interview were also controlled for. No other centre, including Toronto, found a significant association with a history of cancer reported amongst siblings. The Adelaide, Grenoble, Los Angeles, Melbourne, and Winnipeg centres all suggested a lack of an association and never neared statistical significance for any of the four forms of cancer history.

Table 13: Centre-specific results of unconditional logistic regression for adult glioma.

Cancer Exposure Variable	Model 1: Adjusted for Sex & Five-year Age Group – OR (95% CI), χ^2, p-value	Model 2: Adjusted for Sex, Age, Type of Interview, & Interview Quality – OR (95% CI), χ^2, p-value
Any Cancer	Adelaide: 1.1 (0.7-1.7) $\chi^2=0.1$ $p=0.70$ Grenoble: 1.7 (0.8-3.4) $\chi^2=1.6$ $p=0.21$ Heidelberg: 0.4 (0.3-0.7) $\chi^2=12.3$ $p<0.01$ Los Angeles: 0.7 (0.3-1.3) $\chi^2=1.3$ $p=0.26$ Melbourne: 1.0 (0.8-1.4) $\chi^2=0.1$ $p=0.81$ Stockholm: 1.5 (0.9-2.5) $\chi^2=2.3$ $p=0.13$ Toronto: 0.3 (0.2-0.6) $\chi^2=14.6$ $p<0.01$ Winnipeg: 1.1 (0.6-1.9) $\chi^2=0.1$ $p=0.80$	Adelaide: 0.9 (0.5-1.5) $\chi^2=0.3$ $p=0.61$ Grenoble: 1.3 (0.6-2.9) $\chi^2=0.3$ $p=0.59$ Heidelberg: 0.5 (0.3-0.8) $\chi^2=8.0$ $p<0.01$ Los Angeles: 0.6 (0.3-1.3) $\chi^2=1.6$ $p=0.20$ Melbourne: 1.1 (0.7-1.7) $\chi^2=0.3$ $p=0.59$ Stockholm: 1.6 (0.9-2.9) $\chi^2=2.7$ $p=0.10$ Toronto: 0.4 (0.2-0.7) $\chi^2=11.3$ $p<0.01$ Winnipeg: 1.3 (0.7-2.5) $\chi^2=0.8$ $p=0.38$

Table 13 (Cont): Centre-specific results of unconditional logistic regression for adult glioma.

Any Cancer Except Brain Tumour	Adelaide: 1.1 (0.7-1.8) $\chi^2=0.3$ $p=0.60$ Grenoble: 1.6 (0.8-3.4) $\chi^2=1.5$ $p=0.23$ Heidelberg: 0.5 (0.3-0.7) $\chi^2=10.6$ $p<0.01$ Los Angeles: 0.7 (0.4-1.3) $\chi^2=1.2$ $p=0.27$ Melbourne: 1.1 (0.8-1.5) $\chi^2=0.2$ $p=0.66$ Stockholm: 1.6 (0.9-2.8) $\chi^2=3.2$ $p=0.07$ Toronto: 0.3 (0.2-0.5) $\chi^2=17.0$ $p<0.01$ Winnipeg: 1.2 (0.6-2.2) $\chi^2=0.3$ $p=0.58$	Adelaide: 0.9 (0.5-1.5) $\chi^2=0.2$ $p=0.64$ Grenoble: 1.3 (0.6-2.9) $\chi^2=0.3$ $p=0.56$ Heidelberg: 0.5 (0.3-0.8) $\chi^2=6.9$ $p=0.01$ Los Angeles: 0.6 (0.3-1.3) $\chi^2=1.6$ $p=0.21$ Melbourne: 1.2 (0.7-1.8) $\chi^2=0.5$ $p=0.49$ Stockholm: 1.7 (0.9-3.2) $\chi^2=3.1$ $p=0.08$ Toronto: 0.3 (0.2-0.6) $\chi^2=13.7$ $p<0.01$ Winnipeg: 1.6 (0.8-3.2) $\chi^2=1.9$ $p=0.17$
Any Cancer in Mother	Adelaide: 0.8 (0.4-1.5) $\chi^2=0.4$ $p=0.53$ Grenoble: 1.5 (0.6-4.1) $\chi^2=0.7$ $p=0.41$ Heidelberg: 0.9 (0.5-1.7) $\chi^2=0.0$ $p=0.85$ Los Angeles: 0.7 (0.3-1.6) $\chi^2=0.8$ $p=0.36$ Melbourne: 0.9 (0.6-1.4) $\chi^2=0.2$ $p=0.65$ Stockholm: 1.9 (0.9-3.9) $\chi^2=3.1$ $p=0.08$ Toronto: 0.2 (0.1-0.5) $\chi^2=11.0$ $p<0.01$ Winnipeg: 1.0 (0.4-2.1) $\chi^2=0.0$ $p=0.92$	Adelaide: 0.9 (0.4-1.9) $\chi^2=0.1$ $p=0.71$ Grenoble: 1.4 (0.5-4.1) $\chi^2=0.3$ $p=0.59$ Heidelberg: 1.1 (0.6-2.0) $\chi^2=0.0$ $p=0.86$ Los Angeles: 0.7 (0.3-1.6) $\chi^2=0.7$ $p=0.41$ Melbourne: 0.8 (0.5-1.5) $\chi^2=0.5$ $p=0.48$ Stockholm: 2.1 (0.9-4.6) $\chi^2=3.1$ $p=0.08$ Toronto: 0.2 (0.1-0.7) $\chi^2=7.9$ $p<0.01$ Winnipeg: 1.4 (0.6-3.3) $\chi^2=0.5$ $p=0.47$
Any Cancer in Siblings	Adelaide: 1.5 (0.9-2.7) $\chi^2=2.2$ $p=0.14$ Grenoble: 0.9 (0.2-3.3) $\chi^2=0.0$ $p=0.84$ Heidelberg: 0.2 (0.1-0.8) $\chi^2=5.3$ $p=0.02$ Los Angeles: 1.5 (0.5-4.5) $\chi^2=0.6$ $p=0.46$ Melbourne: 1.5 (0.9-2.4) $\chi^2=2.2$ $p=0.13$ Stockholm: 1.3 (0.6-3.1) $\chi^2=0.4$ $p=0.53$ Toronto: 0.6 (0.3-1.5) $\chi^2=1.0$ $p=0.31$ Winnipeg: 1.7 (0.7-4.0) $\chi^2=1.6$ $p=0.21$	Adelaide: 1.5 (0.7-3.1) $\chi^2=1.0$ $p=0.31$ Grenoble: 0.8 (0.2-3.3) $\chi^2=0.1$ $p=0.74$ Heidelberg: 0.3 (0.1-1.0) $\chi^2=3.6$ $p=0.06$ Los Angeles: 1.7 (0.5-5.1) $\chi^2=0.8$ $p=0.38$ Melbourne: 1.6 (0.8-3.2) $\chi^2=1.9$ $p=0.17$ Stockholm: 1.5 (0.5-4.0) $\chi^2=0.5$ $p=0.47$ Toronto: 0.7 (0.3-1.8) $\chi^2=0.6$ $p=0.45$ Winnipeg: 1.7 (0.7-4.4) $\chi^2=1.3$ $p=0.25$

4.1.8.b. Type of Interview Results

All 1089 adult glioma cases and 1922 controls from the eight SEARCH study centres were included in looking for a difference in the odds ratios associated with a family history of cancer for those who required assistance in completing the interview via a proxy, compared to those who did not. 780 cases (71.6%) were categorized as either completing the interview directly or with some assistance from the interviewer, while 309 cases (28.4%) needed some form of proxy response. Of the 1922 glioma controls, 1854 (96.5%) did not require a proxy, and only 68 (3.5%) did.

The impact of the type of interview on the risk of glioma was evaluated using unconditional logistic regression for the pooled data, controlling for the study centre, sex, and five-year age group of the participant. The respondents who did not have need of a proxy were used as the referent group. This covariate had a highly significant impact on glioma risk, with a point estimate for the proxy respondents of 18.7 (95% CI = 13.6-25.7,

$p < 0.01$), but the risk of glioma associated with a family history of any form of cancer did not achieve statistical significance. The odds ratio was found to be 0.9 (0.7-1.0) with a p-value of 0.11. This odds ratio is slightly elevated compared to that found when only age, sex, and study centre were controlled for (OR = 0.8, 95% CI = 0.7-1.0).

4.1.8.c. Age-specific Results

In order to assess the impact of age of the respondent on the association of a family history of cancer and glioma in adults similar to that which was done by Hill (11), cases and controls were separated into two groups: those who were under the age of 50 at the time of diagnosis or interview, and those over 50 years of age. 500 of the 1089 glioma cases (45.9%) were less than 50 years old when they were diagnosed, compared to just 753 of the 1922 controls (39.2%) at their time of interview.

The unconditional pooled logistic regression of the glioma dataset produced a non-significantly lowered risk of glioma associated with being 50 years of age or older, with a variable-specific odds ratio of 0.9 (95% CI = 0.8-1.0, $p = 0.11$). However, there was significantly lowered risk of being a glioma case associated with having a family history of cancer when the sex, study centre, and age were controlled for using this particular age covariate. The point estimate was 0.8, with a 95 percent confidence interval of 0.7-1.0 ($p = 0.02$). This is similar to the findings of the logistic model which adjusted for age, sex, and five-year age group, using 25-29 year olds as referent (OR = 0.8, 95% CI = 0.7-1.0, $p = 0.04$).

4.1.8.d. Socioeconomic Status Results

The final sensitivity analysis performed on the glioma dataset looked at the possible effect of a university or college education on the association of reported cancer in first degree relatives and glioma development in adults. Cases and controls were placed in one of two groups: those who answered that they had attended university or college, regardless of whether they had completed a degree, and those who had not, including individuals who had completed some form of adult evening classes, apprenticeship, or technical training. Of the 1089 cases, 279 (25.6%) had attended university or college, compared to 477 of the 1922 controls (24.8%).

Much like the regression analysis in section 4.1.3., in which a significantly lowered risk of glioma was found in the model which controlled for age, sex, study centre, and socioeconomic status of the individual (based on the seven-point scale set *a priori*), modeling this dataset whilst adjusting for age, sex, study centre, and previous tertiary education produced a significantly lowered odds ratio. The point estimate for having a family member with cancer associated with adult-onset glioma was 0.8 (95% CI = 0.7-1.0, $p = 0.05$), numbers which were identical to those found with model 5 in 4.1.3. However, it is noted that having no university or college experience was associated with a greater risk of glioma and this difference was significant, with a point estimate of 1.2 and a 95 percent confidence interval of 1.0-1.5 ($p = 0.05$).

4.2. Meningioma Total Sample – Characteristics of the Cases and the Controls

4.2.1. Demographics of the Cases and Controls

There was an original total of 1454 participants included in the meningioma analysis, 331 cases and 1123 controls. One case and six controls had to be excluded from further analysis because the information pertaining to the number of siblings was missing. A further 23 cases and 28 controls were not eligible for inclusion since it was not possible to determine the number of first-degree relatives with cancer as a result of missing information. This left a total of 1402 participants in the meningioma analysis, 307 cases and 1095 controls.

Of the 307 included meningioma cases, 86 (28.0%) were males, 221 (72.0%) were females. The mean age of the cases was 55.1 years old and the median was 56.0 years of age. The youngest of the included meningioma cases was 24 years old, with the oldest person being 78.

The final meningioma control group included 1095 participants, 472 (43.1%) of which were male, 623 (56.9%) were female. The controls included in the meningioma analysis had a mean age that was just slightly older than that of the cases, at 55.7 years of age. The median age was 57.0 years. Age values ranged from a low of 24 to a high of 79 years old. As was the case in the glioma analysis, the similarity between the ages of the cases and controls was introduced artificially by the matching strategy employed by each of the SEARCH study centres.

Table 14. Frequencies of meningioma cases and controls: data from six study centres.

Variable	Case n = 307	Control n = 1095	Total n = 1402
	n (%)	n (%)	n (%)
Age Group			
20-24	1 (0.3)	2 (0.2)	3 (0.2)
25-29	5 (1.6)	11 (1.0)	16 (1.1)
30-34	8 (2.6)	24 (2.2)	32 (2.3)
35-39	19 (6.2)	80 (7.3)	99 (7.1)
40-44	28 (9.1)	97 (8.9)	125 (8.9)
45-49	43 (14.0)	140 (12.8)	183 (13.0)
50-54	35 (11.4)	125 (11.4)	160 (11.4)
55-59	43 (14.0)	153 (14.0)	196 (14.0)
60-64	47 (15.3)	168 (15.3)	215 (15.3)
65-69	44 (14.3)	151 (13.8)	195 (13.9)
70+	34 (11.1)	144 (13.1)	178 (12.7)
Study Centre			
Adelaide	60 (19.5)	369 (33.7)	429 (30.6)
Grenoble	52 (16.9)	105 (9.6)	157 (11.2)
Heidelberg	77 (25.1)	379 (34.6)	456 (32.5)
Stockholm	68 (22.2)	71 (6.5)	139 (9.9)
Toronto	21 (6.8)	112 (10.2)	133 (9.5)
Winnipeg	29 (9.4)	59 (5.4)	88 (6.3)
Number of First-degree Relatives			
2	105 (34.2)	533 (48.7)	638 (45.5)
3-4	26 (8.5)	73 (6.7)	99 (7.1)
5-7	82 (26.7)	251 (22.9)	333 (23.8)
8-10	57 (18.6)	149 (13.6)	206 (14.7)
More than 10	37 (12.0)	89 (8.1)	126 (9.0)
Type of Interview			
Direct	270 (88.0)	1029 (94.0)	1299 (92.6)
Assisted/Part Proxy/Proxy	37 (12.0)	66 (6.0)	103 (7.4)
Quality of Interview			
Reliable	124 (40.4)	361 (33.0)	485 (34.6)
Very Good	148 (48.2)	663 (60.6)	811 (57.8)
Questionable	23 (7.5)	62 (5.7)	85 (6.1)
Unsatisfactory	9 (2.9)	9 (0.8)	18 (1.3)
Unknown	3 (1.0)	0 (0.0)	3 (0.2)
Education			
University/College Degree	20 (6.9)	126 (11.7)	146 (10.7)
Some University/College – No Degree	18 (6.2)	77 (7.2)	95 (7.0)
Technical Training, Apprenticeship, Or Adult Evening Classes	113 (39.0)	413 (38.4)	526 (38.5)
High School Graduate	16 (5.5)	40 (3.7)	56 (4.1)
Some High School	30 (10.3)	104 (9.7)	134 (9.8)
7-9 Years of Schooling	77 (26.6)	280 (26.0)	357 (26.2)
Less Than 7 Years of Schooling	16 (5.5)	35 (3.3)	51 (3.7)

As can be seen in Table 14, for both the cases and the controls, the 60-64 age group contributed the greatest proportion of eligible study participants, with 215 people, or 15.3% of the total population, falling in that category. 77 of the cases (25.1%) and 379 of the controls (34.6%) were recruited at the Heidelberg centre, making it the largest contributor of all six study centres for both cases and controls. The Toronto study centre contributed the fewest number of cases ($n = 21$), while the smallest amount of controls was recruited in Winnipeg ($n = 59$).

On average, the meningioma cases reported having 2.6 children, ranging from a low of 0 to a high of 9 offspring. Similar values were found in the controls, with an average of 2.5 children and a range of 0 to 10 children. The slightly higher mean number of children reported by the controls was not significantly different from the cases, as determined by a t-test ($p = 0.37$). 3.4 siblings were reported by the cases on average. The lowest observation was 0 and the highest was 15. Controls reported a lower number of siblings on average at 3.1, with a range of 0 to 19, but this difference was not significant ($p = 0.19$). The 307 included cases reported an average of 7.9 first degree relatives, with a range of two to 21 people by one person. It is noted that, for the 105 cases who were classified as having two first degree relatives, this number came as a result of the *post hoc* addition by the author to account for the participants' parents. All of these cases reported having no live births and no siblings. The mean number of first degree family members reported by the 1095 included controls was 7.6 relatives. There was a range of values from a low of two to a high of 20 reported by two controls. The reported difference between the family members at risk of cancer between the cases and controls did not approach significance as determined by a pooled t-test ($p = 0.27$).

The proportion of cases and controls and the type of interview conducted, separated by those which were entirely direct responses from the participant and those that required some form of assistance (assisted, part proxy, or proxy) was found to contribute a significant difference ($p < 0.001$). A significantly greater percentage of cases required assistance or proxy respondents compared to the controls. 270 of the 307 meningioma cases gave direct responses, whereas 1029 of the 1095 meningioma controls completed the interview by themselves. 22 cases gave assisted responses, six were answered partially by proxy, and nine of the cases were accounted for by proxy respondents. For the controls, 39 were assisted, nine were part proxy, and 18 were completed by a proxy. Only two of the study centres, Adelaide (86.7%) and Stockholm (83.8%), had less than 90 percent of their included participants complete the questionnaire directly. Toronto and Adelaide both reported no proxy or part proxy interviewers, with all of their cases and controls answering either directly or with assistance from the interviewer. At 7.4 percent, Stockholm had the greatest proportion of individuals requiring proxy respondents.

It is evident from table 14 that a greater proportion of the cases were deemed by the interviewers to have given reliable responses than the controls (40.4% and 33.0%, respectively). However, a larger percentage of the controls were considered to have a very good understanding of what was asked of them compared to the cases (60.6% versus 48.2%, respectively). When the reliable and very good respondents were combined and the respondents who were classified as questionable, unsatisfactory, or unknown were grouped together, a significant difference existed between the cases and controls. The controls were significantly more likely ($p = 0.004$) than the cases to give reliable or very

good responses. Overall, the quality of the interview was excellent, with 92.4% of the total meningioma sample being considered reliable or very good. Only 1.3% of the group gave replies that were deemed unsatisfactory by the study interviewer.

The highest level of education was used as a surrogate for the socioeconomic status of the SEARCH study participants. Overall, the controls tended to be slightly more educated than the cases. For the included meningioma cases, 52.1% reported some form of tertiary education (6.9% university/college with degree, 6.2% without degree, and 39.0% with technical training, apprenticeship, or adult evening classes), while 57.3% of the controls received post-secondary education (11.7%, 7.2%, and 38.4%). However, the difference between the cases and controls reporting tertiary training was not significant ($p = 0.11$).

4.2.2. Results of Analysis of Covariates

Trend analysis was conducted on the variables relating to number of first degree relatives and the socioeconomic status of the individual as they relate to the odds of being a meningioma case. Table 15 details the odds ratios and 95 percent confidence intervals for each of the values associated with these variables. The referent groups for each of the variables are two first degree relatives (no siblings and no children reported) and less than seven years of schooling.

Looking at the point estimates for the number of first degree relatives, it seems that having siblings and children increases the odds of being a meningioma case in this population as each estimate is greater than 1.0 compared to those individuals with no children and no siblings. However, the p-value for the trend is not close to approaching

significance ($p = 0.78$) and each of the associated 95 percent confidence intervals cross 1.0, which means that the difference is not significant for any of the strata.

Table 15. Odds ratios, 95 percent confidence intervals (CI), and trend statistics for meningioma cases and controls (adjusted for age, sex, and study centre): data from six study centres.

CHARACTERISTIC	ODDS RATIO	95% CI
Number of first degree relatives		
• 2 (0 siblings and 0 children)	1.0	-
• 3-4	1.2	0.6-1.6
• 5-7	1.2	0.8-1.5
• 8-10	1.1	0.5-1.5
• More than 10	1.2	0.5-1.6
P-value for trend	0.78	
Socio-economic status (estimated by reported education level)		
• Less than 7 years of schooling	1.0	-
• 7-9 years of schooling	0.5	0.2-0.9
• Some high school	0.4	0.2-1.0
• High school graduate	0.6	0.3-1.6
• Technical training, apprenticeship, or adult evening classes	0.5	0.3-1.0
• Some university/college-no degree	0.3	0.1-0.6
• University/college degree	0.2	0.1-0.6
P-value for trend	0.01	

As was seen in the glioma analysis, the lowest socioeconomic status as estimated by the education level was associated with the greatest risk of being a meningioma case. Compared to the reference category of less than seven years of schooling, all six other strata had point estimates of less than 1.0, ranging in value from 0.3 for some university or college with no degree to 0.6 for high school graduates. Four of the six strata were associated with significantly decreased risk of meningioma for this population compared to the referent group. These were: seven to nine years of schooling ($p = 0.02$), some high school ($p = 0.04$), some university or college with no degree ($p < 0.01$), and a completed

university or college degree ($p < 0.01$). Overall, the trend of decreased odds associated with increasing socioeconomic status was found to be significant ($p = 0.01$).

4.2.3. Unconditional Model-based Analysis

Table 16 provides estimates of the unadjusted and adjusted odds ratios and their respective 95 percent confidence intervals for each of the various forms of cancers, as determined using unconditional logistic regression. The unadjusted estimates should not be interpreted as appropriate estimates since they do not take into account the matching done by the study centres on the age and sex of the cases and controls. Rather, they are listed so as to show the impact of the adjustment for age, sex, and study centre, which were the three covariates that were included in model one. For this model, and all of the others used in the unconditional analysis, Heidelberg was used as the referent category for study centre, since it contributed the greatest number of both cases and controls, females were the referent sex, and the youngest age category to be included in all six centres, 25-29, served as the reference for the five-year age group of the meningioma subjects.

Table 16. Associations between meningioma in adults and cancers reported in first-degree family members¹: pooled data from six study centres.

Type of Cancer	Cases (%) ²	Controls (%) ²	Crude OR (95% CI) ³	Adjusted OR (95% CI) Wald Chi-square and p-value
Any type				
None reported	182 (59.3) ⁴	609 (55.6) ⁴	1.0	1.0 Model 1 ⁵ : 0.9 (0.7-1.2) $\chi^2=0.6$ p=0.44 Model 2 ⁶ : 0.9 (0.7-1.2) $\chi^2=0.6$ p=0.42 Model 3 ⁷ : 0.9 (0.7-1.2) $\chi^2=0.5$ p=0.47 Model 4 ⁸ : 0.9 (0.7-1.2) $\chi^2=0.2$ p=0.62 Model 5 ⁹ : 0.9 (0.7-1.2) $\chi^2=0.2$ p=0.69
All first degree relatives	125 (40.7)	486 (44.4)	0.9 (0.7-1.1)	
Brain tumour				
No	294 (95.8)	1054 (96.3)	1.0	1.0 Model 1: 1.2 (0.6-2.4) $\chi^2=0.4$ p=0.52 Model 2: 1.2 (0.6-2.4) $\chi^2=0.3$ p=0.57 Model 3: 1.3 (0.6-2.5) $\chi^2=0.4$ p=0.52 Model 4: 1.3 (0.7-2.6) $\chi^2=0.5$ p=0.46 Model 5: 1.2 (0.6-2.4) $\chi^2=0.2$ p=0.63
All first degree relatives	13 (4.2)	41 (3.7)	1.1 (0.6-2.2)	
Any type except brain tumour				
No	191 (37.8)	632 (57.7)	1.0	1.0 Model 1: 0.8 (0.6-1.1) $\chi^2=1.4$ p=0.24 Model 2: 0.8 (0.6-1.1) $\chi^2=1.4$ p=0.24 Model 3: 0.9 (0.6-1.1) $\chi^2=1.2$ p=0.27 Model 4: 0.9 (0.7-1.2) $\chi^2=0.8$ p=0.36 Model 5: 0.9 (0.7-1.2) $\chi^2=0.7$ p=0.41
All first degree relatives	116 (37.8)	463 (42.3)	0.8 (0.6-1.1)	
Any type in mother				
No	260 (84.7)	907 (82.8)	1.0	1.0 Model 1: 0.9 (0.6-1.2) $\chi^2=0.7$ p=0.39 Model 2: 0.9 (0.6-1.2) $\chi^2=0.6$ p=0.43 Model 3: 0.9 (0.6-1.2) $\chi^2=0.6$ p=0.43 Model 4: 0.9 (0.6-1.2) $\chi^2=0.5$ p=0.48 Model 5: 0.9 (0.6-1.2) $\chi^2=0.7$ p=0.41
Yes	47 (15.3)	188 (17.2)	0.9 (0.6-1.2)	
Any type in father				
No	256 (83.4)	925 (84.5)	1.0	1.0 Model 1: 1.1 (0.7-1.5) $\chi^2=0.1$ p=0.77 Model 2: 1.1 (0.7-1.5) $\chi^2=0.1$ p=0.73 Model 3: 1.1 (0.7-1.5) $\chi^2=0.1$ p=0.74 Model 4: 1.0 (0.7-1.5) $\chi^2=0.0$ p=0.85 Model 5: 1.1 (0.7-1.6) $\chi^2=0.2$ p=0.66
Yes	51 (16.6)	170 (15.5)	1.1 (0.8-1.5)	
Any type in siblings¹⁰				
No	231 (84.0)	860 (85.7)	1.0	1.0 Model 1: 1.2 (0.8-1.8) $\chi^2=1.1$ p=0.29 Model 2: 1.2 (0.8-1.8) $\chi^2=1.1$ p=0.29 Model 3: 1.2 (0.8-1.9) $\chi^2=1.2$ p=0.28 Model 4: 1.3 (0.9-2.0) $\chi^2=2.0$ p=0.16 Model 5: 1.3 (0.8-1.9) $\chi^2=1.2$ p=0.27
Yes	44 (16.0)	143 (14.3)	1.1 (0.8-1.7)	
Any type in children^{11, 12}				
No	197 (98.5)	541 (98.9)	1.0	1.0 Model 1: 1.9 (0.5-7.7) $\chi^2=0.8$ p=0.38 Model 2: 1.9 (0.4-7.6) $\chi^2=0.7$ p=0.39 Model 3: 1.4 (0.3-6.2) $\chi^2=0.2$ p=0.66 Model 4: 1.9 (0.4-7.9) $\chi^2=0.7$ p=0.40 Model 5: 1.6 (0.4-6.7) $\chi^2=0.4$ p=0.52
Yes	3 (1.5)	6 (1.1)	1.4 ¹³ (0.3-5.5)	

Table 16 (Cont). Associations between meningioma in adults and cancers reported in first-degree family members¹: pooled data from six study centres.

Lung ca. in parents				
No	292 (95.1)	1059 (96.7)	1.0	1.0 Model 1: 1.6 (0.9-3.1) $\chi^2=2.3$ p=0.13 Model 2: 1.7 (0.9-3.2) $\chi^2=2.6$ p=0.11 Model 3: 1.6 (0.8-3.1) $\chi^2=2.1$ p=0.15 Model 4: 1.6 (0.8-3.1) $\chi^2=2.0$ p=0.16 Model 5: 1.6 (0.8-3.1) $\chi^2=2.0$ p=0.16
Yes	15 (4.9)	36 (3.3)	1.5 (0.8-2.8)	
Lung ca. in father				
No	294 (95.8)	1068 (97.5)	1.0	1.0 Model 1: 2.0 (1.0-4.0) $\chi^2=3.5$ p=0.06 Model 2: 2.0 (1.0-4.0) $\chi^2=3.6$ p=0.06 Model 3: 1.9 (0.9-3.8) $\chi^2=3.0$ p=0.08 Model 4: 1.9 (0.9-3.9) $\chi^2=3.3$ p=0.07 Model 5: 1.9 (0.9-4.0) $\chi^2=3.2$ p=0.07
Yes	13 (4.2)	27 (2.5)	1.7 (0.9-3.4)	
Lung ca. in siblings¹⁰				
No	271 (98.5)	990 (98.7)	1.0	1.0 Model 1: 0.8 (0.2-2.7) $\chi^2=0.1$ p=0.75 Model 2: 0.7 (0.2-2.5) $\chi^2=0.2$ p=0.64 Model 3: 0.9 (0.3-3.0) $\chi^2=0.0$ p=0.87 Model 4: 0.9 (0.3-2.9) $\chi^2=0.0$ p=0.83 Model 5: 1.3 (0.4-4.4) $\chi^2=0.1$ p=0.70
Yes	4 (1.5)	13 (1.3)	1.1 ¹⁴ (0.4-3.5)	
Breast ca. in mother				
No	303 (98.7)	1064 (97.2)	1.0	1.0 Model 1: 0.5 (0.2-1.4) $\chi^2=1.7$ p=0.20 Model 2: 0.5 (0.2-1.5) $\chi^2=1.6$ p=0.21 Model 3: 0.5 (0.2-1.5) $\chi^2=1.6$ p=0.21 Model 4: 0.5 (0.2-1.6) $\chi^2=1.3$ p=0.26 Model 5: 0.5 (0.2-1.6) $\chi^2=1.3$ p=0.26
Yes	4 (1.3)	31 (2.8)	0.5 ¹⁵ (0.2-1.3)	
Breast ca. in sister¹⁰				
No	273 (99.3)	979 (97.6)	1.0	1.0 Model 1: 0.3 (0.1-1.4) $\chi^2=2.3$ p=0.13 Model 2: 0.3 (0.1-1.3) $\chi^2=2.7$ p=0.10 Model 3: 0.3 (0.1-1.4) $\chi^2=2.2$ p=0.13 Model 4: 0.3 (0.1-1.5) $\chi^2=2.0$ p=0.16 Model 5: 0.3 (0.1-1.4) $\chi^2=2.3$ p=0.13
Yes	2 (0.7)	24 (2.4)	0.3 ¹⁶ (0.1-1.3)	
Lip, oral, or pharyngeal ca. in parents				
No	306 (99.7)	1086 (99.2)	1.0	1.0 Model 1: 0.2 (0.0-1.9) $\chi^2=1.8$ p=0.18 Model 2: 0.2 (0.0-1.9) $\chi^2=1.9$ p=0.17 Model 3: 0.2 (0.0-2.0) $\chi^2=1.7$ p=0.19 Model 4: 0.3 (0.0-2.2) $\chi^2=1.6$ p=0.21 Model 5: 0.2 (0.0-2.2) $\chi^2=1.6$ p=0.21
Yes	1 (0.3)	9 (0.8)	0.4 ¹⁷ (0.1-3.1)	
Lip, oral, or pharyngeal ca. in siblings¹⁰				
No	274 (99.6)	1000 (99.7)	1.0	1.0 Model 1: 1.2 (0.1-12.8) $\chi^2=0.0$ p=0.90 Model 2: 1.2 (0.1-13.4) $\chi^2=0.0$ p=0.86 Model 3: 1.4 (0.1-15.1) $\chi^2=0.1$ p=0.79 Model 4: 1.5 (0.1-15.7) $\chi^2=0.1$ p=0.75 Model 5: 1.2 (0.1-13.6) $\chi^2=0.0$ p=0.86
Yes	1 (0.4)	3 (0.3)	1.2 ¹⁸ (0.1-11.7)	

Table 15 (Cont). Associations between meningioma in adults and cancers reported in first-degree family members¹: pooled data from six study centres.

Gastrointestinal ca. in parents				
No	272 (88.6)	994 (90.8)	1.0	1.0 Model 1: 1.1 (0.7-1.7) $\chi^2=0.1$ p=0.70 Model 2: 1.1 (0.7-1.7) $\chi^2=0.2$ p=0.66 Model 3: 1.1 (0.7-1.7) $\chi^2=0.2$ p=0.69 Model 4: 1.1 (0.7-1.6) $\chi^2=0.1$ p=0.80 Model 5: 1.0 (0.7-1.6) $\chi^2=0.0$ p=0.85
Yes	35 (11.4)	101 (9.2)	1.3 (0.8-1.9)	
Gastrointestinal ca. in siblings¹⁰				
No	269 (97.8)	981 (97.8)	1.0	1.0 Model 1: 0.9 (0.3-2.3) $\chi^2=0.1$ p=0.78 Model 2: 0.8 (0.3-2.2) $\chi^2=0.1$ p=0.71 Model 3: 0.8 (0.3-2.1) $\chi^2=0.3$ p=0.61 Model 4: 1.1 (0.4-2.9) $\chi^2=0.0$ p=0.87 Model 5: 1.0 (0.3-2.8) $\chi^2=0.0$ p=0.94
Yes	6 (2.2)	22 (2.2)	1.0 ¹⁹ (0.4-2.5)	
Genitourinary ca. in parents				
No	290 (94.5)	1056 (96.4)	1.0	1.0 Model 1: 1.4 (0.7-2.5) $\chi^2=0.9$ p=0.35 Model 2: 1.4 (0.7-2.6) $\chi^2=1.0$ p=0.32 Model 3: 1.4 (0.7-2.6) $\chi^2=1.1$ p=0.29 Model 4: 1.4 (0.8-2.7) $\chi^2=1.2$ p=0.28 Model 5: 1.6 (0.8-3.1) $\chi^2=2.0$ p=0.16
Yes	17 (5.5)	39 (3.6)	1.6 (0.9-2.8)	
Genitourinary ca. in siblings¹⁰				
No	270 (98.2)	983 (98.0)	1.0	1.0 Model 1: 0.7 (0.2-2.0) $\chi^2=0.4$ p=0.52 Model 2: 0.7 (0.2-2.0) $\chi^2=0.5$ p=0.47 Model 3: 0.7 (0.2-2.1) $\chi^2=0.4$ p=0.55 Model 4: 0.8 (0.3-2.2) $\chi^2=0.2$ p=0.62 Model 5: 0.6 (0.2-2.0) $\chi^2=0.6$ p=0.42
Yes	5 (1.8)	20 (2.0)	0.9 ²⁰ (0.3-2.4)	
Unspecified ca. in parents				
No	302 (98.4)	1041 (95.1)	1.0	1.0 Model 1: 0.4 (0.2-1.1) $\chi^2=3.2$ p=0.07 Model 2: 0.4 (0.2-1.1) $\chi^2=3.3$ p=0.07 Model 3: 0.4 (0.2-1.1) $\chi^2=3.3$ p=0.07 Model 4: 0.4 (0.2-1.1) $\chi^2=3.2$ p=0.07 Model 5: 0.4 (0.2-1.1) $\chi^2=3.1$ p=0.08
Yes	5 (1.6)	54 (4.9)	0.3 ²¹ (0.1-0.8)	
Unspecified ca. in siblings¹⁰				
No	271 (98.5)	979 (97.6)	1.0	1.0 Model 1: 0.9 (0.3-2.7) $\chi^2=0.0$ p=0.83 Model 2: 0.8 (0.3-2.5) $\chi^2=0.1$ p=0.75 Model 3: 0.9 (0.3-2.8) $\chi^2=0.0$ p=0.90 Model 4: 0.9 (0.3-2.6) $\chi^2=0.1$ p=0.80 Model 5: 0.9 (0.3-2.8) $\chi^2=0.0$ p=0.90
Yes	4 (1.5)	24 (2.4)	0.6 ²² (0.2-1.8)	

¹ First-degree family members include mother, father, siblings, and children.

² Subjects with missing data excluded on a variable by variable basis.

³ Crude (unadjusted) odds ratio and 95% confidence intervals.

⁴ Values in parentheses indicate percentages.

⁵ Adjusted for study centre, sex, and five-year age group.

⁶ Adjusted for study centre, sex, five-year age group, and number of first-degree relatives.

⁷ Adjusted for study centre, sex, five-year age group, and interview type.

⁸ Adjusted for study centre, sex, five-year age group, and quality of interview.

⁹ Adjusted for study centre, sex, five-year age group, and socioeconomic status.

¹⁰ Excludes those respondents who reported having zero siblings.

¹¹ Excludes those respondents who reported having zero children.

¹² Reference for five-year age group was 25-29 since there were no observations in the 20-24 group.

¹³ Fisher's two-sided exact test value p=0.71.

¹⁵ Fisher's two-sided exact test value p=0.15.

¹⁷ Fisher's two-sided exact test value p=0.70.

¹⁹ Fisher's two-sided exact test value p=1.00.

²¹ Fisher's two-sided exact test value p<0.01.

¹⁴ Fisher's two-sided exact test value p=0.77.

¹⁶ Fisher's two-sided exact test value p=0.09.

¹⁸ Fisher's two-sided exact test value p=1.00.

²⁰ Fisher's two-sided exact test value p=1.00.

²² Fisher's two-sided exact test value p=0.49.

The second unconditional logistic regression model used for assessing the association of meningioma and a family history of cancer included the three matching variables from model one, as well as incorporating the effect of the reported number of first degree relatives at risk. The referent group for this variable was those who reported having only two first degree relatives, a number added *post hoc* by the author to account for the mother and father, meaning that those in the referent group reported having no siblings and no children. As was seen in the analysis of the glioma cases and controls, adjusting for the size of the family at risk did not significantly improve the model fit statistics ($p = 0.78$ for the family size variable with four degrees of freedom). The reason for its inclusion in the results section of this paper is because of the findings of a previous study which suggests that failing to account for family size may induce biased findings (155). However, since this variable introduces such a small impact on the fit of the model, utilizing the dichotomous “yes or no” for the presence of a family history of cancer is acceptable. Doing so simplifies the meaning of the adjustments made by the final model.

The third model introduced the type of interview variable, using “direct” as the referent category. All of those interviews which required assistance, part proxy, or proxy responses were not included in this group. The type of interview was found to be highly significant for the fit of the model when included with the age, sex, and study centre matching variables ($p = 0.0004$ with one degree of freedom). Those subjects which required some form of assistance in completing the interview were found to be significantly more likely to be cases ($OR = 2.3$, $95\% CI = 1.5-3.7$).

The perceived quality of the interview, according to the SEARCH member who administered the interview, was introduced as a covariate into the fourth unconditional logistic regression model. Those individuals that were deemed as providing reliable responses were treated as the referent group, being compared with meningioma cases and controls that provided very good, questionable, unknown, or unsatisfactory responses. The Wald chi square value for the quality of interview variable, with four degrees of freedom, was 20.2, making it highly statistically significant in terms of model fit ($p = 0.0005$).

For the fifth model the socioeconomic status of the individual, as determined by their highest level of reported education, was found to significantly contribute to the fit of the model when included with the three matching covariates ($p = 0.01$ with six degrees of freedom). The lowest educational experience (less than seven years of school) was used as the referent category. It is noted that there was a restriction on the number of cases and controls that were eligible for inclusion in this model. Three cases and three controls were eliminated since they were missing the number of years of school completed. Another 14 meningioma cases and 17 controls were not included because they did not indicate the highest level of tertiary education received.

The author also assessed the impact of a post-secondary education. Those individuals who did not indicate that they had any post-secondary educational experience served as the referent group. When included with the matching variables age, sex, and study centre, an education after high school did not significantly influence the odds of being a case for this data set ($p = 0.22$). Therefore, a model was not created using this variable.

Table 17 highlights the changes in model fit statistics from the inclusion of the three matching variables and all subsequent additions regarding the risk of being a meningioma case based on whether or not they reported having a first degree relative with any form of cancer. The model did not achieve statistical significance when age, sex, and study centre were adjusted for. The adjusted odds ratio for having a first degree relative with cancer was near 1.0 (0.9) and the 95 percent confidence interval crossed 1.0 (0.7-1.2). While the Hosmer and Lemeshow goodness-of-fit test did not attain statistical significance ($p=0.11$), its value was not that far from the $p = 0.05$ level, implying that the model's estimates barely fit the data at an acceptable level. The second step introduced the type of interview, with direct responses being the referent category. The inclusion of the interview type variable made negligible changes to the fit of the model based on the R^2 , c-statistic, Wald chi-square, and -2 log likelihood values, though it did move the Hosmer and Lemeshow goodness-of-fit test much further away from statistical significance ($p = 0.62$). Based on these observations, interview type was dropped from further consideration in the model.

The third step in building the final model introduced the quality of the interview using "reliable" as the referent. While it led to a better model fit than the inclusion of interview quality, as evidenced by the larger change in the Wald chi square and -2 log likelihood values, it did not improve the fit of the model as compared to only including age, sex, and study centre. The Hosmer and Lemeshow goodness-of-fit test again moved further away from significance, but there was little improvement in the R^2 and c-statistic values. Therefore, the perceived quality of the interview was not included as a variable in the final model for the meningioma analysis.

Finally, the socioeconomic status of the cases and controls was evaluated for its impact on the fit of the unconditional logistic regression model. As can be seen in table 16, adding this variable did little to improve the fit of the model and again the Hosmer and Lemeshow statistic moved further away from significance. This meant that including an adjustment for the education level of a participant did not greatly improve the predictive ability of the model, so this variable was also dropped from consideration.

Table 17. Model-fit statistics for meningioma cases and controls: pooled data from six study centres.

Model Number	Variables Included	R ² (Change in value)	c-statistic (Change in value)	Wald Chi-square (Change in value)	-2 Log Likelihood (Change in value)	Hosmer and Lemeshow Chi-square and p-value
1	Age, sex, study centre	0.08	0.70	108.37	1360.41	12.98 p=0.11
2	Age, sex, study centre, interview type	0.09 (+0.01)	0.70 (+0.00)	116.89 (+8.52)	1348.76 (-11.65)	6.29 p=0.62
3	Age, sex, study centre, interview quality	0.09 (+0.01)	0.71 (+0.01)	118.37 (+10.00)	1336.15 (-24.26)	9.58 p=0.30
4	Age, sex, study centre, socioeconomic status	0.09 (+0.01)	0.70 (+0.00)	112.88 (+4.51)	1288.44 (-71.97)	7.53 P=0.48

The final model used only included the age, sex, and study centre of the cases and controls, all of which were mandatory inclusions since they were artificially influenced by the methodology of the SEARCH study. The final model had 17 degrees of freedom; five from the study centre variable, 10 from the different age groups, one from the sex of the individual, and one from the various cancer in first degree relatives exposure variables that were assessed in this dataset. The only variable that was applicable for a

logit plot to assess linearity was the five-year age group of the participant (figure not shown). Linearity was assessed in the natural log and was found to satisfy the assumption of linearity, meaning that no transformation of the age variable was necessary.

4.2.4. Conditional Model-based Analysis

The only SEARCH study centres that collected meningioma data and used individual matching were the Grenoble, Stockholm, and Winnipeg centres. A total of 384 participants, 149 cases and 235 controls, were initially eligible for inclusion in the conditional logistic regression analysis, however a further nine cases and 17 controls had to be removed because their matched pair had been eliminated due to missing data. Therefore, the conditional model-based analysis included a total of 358 participants, 140 cases and 218 controls, from three study centres. It should be noted that both the Grenoble and the Winnipeg centres employed a 2:1 control:case matching strategy. For these centres, if one of the controls was removed because of missing data the paired case was not removed as long as one matched control remained eligible.

Table 18: Participation rates for centres included in the conditional model-based analysis of meningioma cases and controls.

Centre	# of Cases (% of total cases)	# of Controls (% of total controls)	Ratio of Controls to Cases	Total # of Participants (% of total)
Grenoble	51 (36.4)	105 (46.9)	2.06:1	156 (42.9)
Stockholm	60 (42.9)	60 (26.8)	1.00:1	120 (33.0)
Winnipeg	29 (20.7)	59 (26.3)	2.03:1	88 (24.2)

The Grenoble study centre had the greatest number of participants, as well as the most controls, but it was the Stockholm centre which contributed the greatest amount of the meningioma cases to the conditional logistic regression analysis. As was the case in the glioma analysis, the ratio of controls to cases listed in table 18 reflects those that were eligible for inclusion. The SAS system automatically removed the strata that did not have at least one case and one control.

The results of the conditional logistic regression of the SEARCH study meningioma data for the Grenoble, Stockholm, and Winnipeg study centres are shown in table 19 below. The odds ratios and corresponding 95 percent confidence intervals generated by this conditional analysis are compared to those found for the same participants using unconditional logistic regression which controlled for the three matching variables age, sex, and study centre. Overall, the results of the conditional logistic regression nearly mirrored those found using unconditional regression, suggesting that it is appropriate to pool the data from all of the SEARCH study centres in the unconditional analysis, regardless if the matching strategy employed was individual or frequency. All of the point estimates found in the conditional regression were contained in the 95 percent confidence intervals generated by the unconditional regression, and vice versa. Differences in the point estimates were found for eight of the exposure variables, of which only one had a difference of greater than 0.2. The risk of meningioma associated with having a sibling with gastrointestinal cancer was 1.4 when conditional analysis methods were employed, but this estimate jumped to 2.2 when unconditional modeling was performed. However, these estimates were based on very low numbers of cases ($n = 4$) and controls ($n = 3$) reporting that they had a

Table 19: Associations between meningioma in adults and cancers reported in first degree family members: pooled conditional analysis of three study centres.

Type of cancer	Total # of included cases/controls	OR (95% CI)	Wald chi-square & p-value	OR (95% CI) estimated by unconditional model 1
Any type	Cases = 140 Controls = 218	1.1 (0.7-1.7)	$\chi^2=0.3$ p=0.56	1.1 (0.7-1.8)
Brain tumour	Cases = 140 Controls = 218	1.2 (0.4-3.6)	$\chi^2=0.1$ p=0.71	1.3 (0.4-4.2)
Any type except brain tumour	Cases=140 Controls = 218	1.1 (0.7-1.7)	$\chi^2=0.2$ p=0.63	1.1 (0.7-1.8)
Any type in mother	Cases = 140 Controls = 218	1.0 (0.6-1.8)	$\chi^2=0.0$ p=0.89	1.0 (0.5-1.8)
Any type in father	Cases = 140 Controls = 218	1.2 (0.7-2.1)	$\chi^2=0.4$ p=0.51	1.2 (0.7-2.2)
Any type in siblings	Cases = 115 Controls = 176	1.8 (0.9-3.7)	$\chi^2=2.5$ p=0.11	2.0 (1.0-4.0)
Any type in children ¹	Cases = 85 Controls = 119	0.0 (0.0-999.9)	$\chi^2=0.0$ p=0.99	0.0 (0.0-999.9)
Lung ca. in parents	Cases = 140 Controls = 218	0.8 (0.2-2.9)	$\chi^2=0.1$ p=0.75	0.8 (0.2-3.0)
Lung ca. in father	Cases = 140 Controls = 218	0.6 (0.2-2.5)	$\chi^2=0.4$ p=0.51	0.7 (0.2-2.6)
Lung ca. in siblings	Cases = 115 Controls = 176	0.5 (0.1-2.5)	$\chi^2=0.8$ p=0.38	0.6 (0.1-3.3)
Breast ca. in mother	Cases = 140 Controls = 218	0.6 (0.1-3.1)	$\chi^2=0.4$ p=0.52	0.6 (0.1-3.7)
Breast ca. in sister	Cases = 115 Controls = 176	0.3 (0.0-2.7)	$\chi^2=1.1$ p=0.28	0.3 (0.0-3.1)
Lip, oral, or pharyngeal ca. in parents ¹	Cases = 140 Controls = 218	0.0 (0.0-999.9)	$\chi^2=0.0$ p=0.99	0.0 (0.0-999.9)
Lip, oral, or pharyngeal ca. in siblings ¹	Cases = 115 Controls = 176	0.0 (0.0-999.9)	$\chi^2=0.0$ p=0.99	0.0 (0.0-999.9)
Gastrointestinal ca. in parents	Cases = 140 Controls = 218	1.4 (0.7-2.7)	$\chi^2=1.0$ p=0.31	1.4 (0.7-2.6)
Gastrointestinal ca. in siblings	Cases = 115 Controls = 176	1.4 (0.3-7.2)	$\chi^2=0.2$ p=0.68	2.2 (0.5-8.7)
Genitourinary ca. in parents	Cases = 140 Controls = 218	1.4 (0.6-3.4)	$\chi^2=0.6$ p=0.45	1.3 (0.5-3.4)
Genitourinary ca. in siblings	Cases = 115 Controls = 176	0.7 (0.2-3.0)	$\chi^2=0.2$ p=0.63	0.8 (0.2-3.5)
Unspecified ca. in parents ¹	Cases = 140 Controls = 218	0.0 (0.0-999.9)	$\chi^2=0.0$ p=0.99	0.0 (0.0-999.9)
Unspecified ca. in siblings	Cases = 115 Controls = 176	2.0 (0.1-32.0)	$\chi^2=0.2$ p=0.62	2.1 (0.1-36.3)

¹ There was a possible quasi-complete separation of data points; therefore, the maximum likelihood estimate does not exist (either no cases or no controls included).

sibling with gastrointestinal cancer and the confidence intervals were fairly wide (0.3-7.2 for conditional, 0.5-8.7 for unconditional).

Four of the 20 exposure variables did not include either a case or a control with the particular exposure, making it unfeasible to attain an odds ratio and corresponding 95 percent confidence interval for being a meningioma case. These exposure variables were: any type of cancer in children, which had only one case that reported cancer in a child and no controls that did so; lip, oral, or pharyngeal cancer in parents, since there were no cases with an affirmative response for this exposure; lip, oral, or pharyngeal cancer in siblings, again due to no cases with the exposure; and unspecified cancer in parents, which despite having three controls that reported having a parent with an unspecified cancer, included no exposed cases.

4.2.5. Overview of Family History of Cancer Analysis

As a result of the smaller number of participants in the adult meningioma analysis as compared to the glioma data, none of the odds ratios for the 20 cancer exposure variables achieved statistical significance at the $p = 0.05$ level set *a priori* for any of the five models constructed for the unconditional logistic regression analysis and the 95 percent confidence intervals were much wider than those found in the glioma analysis. Only two of the cancer exposures in first degree relatives produced p-values of less than 0.10, lung cancer in father and unspecified cancer in parents. Having lung cancer in parents or breast cancer in a sister approached a p-value of 0.10 for the first, and best fitting, model but did not quite reach that level.

4.2.6. Lung Cancer in Father

The general trend amongst the five models used in assessing the association between reporting lung cancer in one's father and the odds of being a meningioma case in this dataset were elevated odds, ranging from 1.9 to 2.0. For two of the models (model 1 and model 2) the lower limit of the confidence intervals bounded 1.0, but the result was not statistically significant ($p = 0.06$ for each). Though 4.2 percent of the cases did report having a father with lung cancer, as compared to just 2.5 percent of the controls, these findings are based on only 13 cases and 27 controls with this exposure.

4.2.7. Unspecified Cancer in Parents

The SEARCH study data pertaining to adult meningioma cases and controls suggests that having a parent with an unspecified form of cancer may lower one's risk of meningioma. This is seen in the general trend found using unconditional logistic regression of point estimates of less than 1.0, which was 0.4 for each of the five fitted models. However, since this estimate was based on only five meningioma cases that reported having a parent with unspecified cancer, the upper limit of the confidence intervals stretched past 1.0, to 1.1 for each. Still, one has to consider that the results for the adjusted odds ratios were all nearly significant ($p = 0.07-0.08$), suggesting that with a larger number of observations a significantly lowered risk of meningioma might exist.

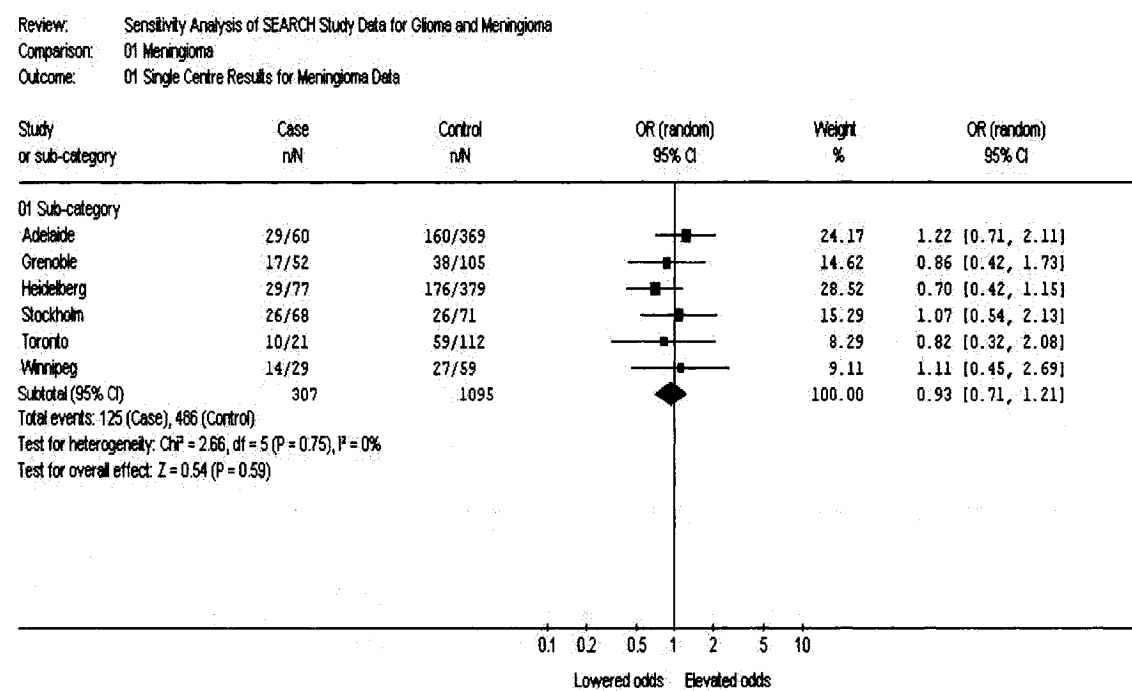
4.2.8. Sensitivity Analysis

4.2.8.a. Centre-specific Results

Centre-specific results were generated for each of the six study centres included in the meningioma data analysis pertaining to the risk of meningioma associated with having any first degree relative with any form of cancer. The results generated using the RevMan statistical package are shown below in figure 5.

The size of the square located at the centre-specific point estimate is directly proportional to the amount of information that centre contributes to the overall estimate of the effect, with those centres which had the greater numbers of participants having the largest squares. Thus, the Heidelberg centre has the largest square and the study centre located in Winnipeg has the smallest.

Figure 5: Forest plot of centre-specific and pooled odds ratios for meningioma cases and controls: exposure variable is any form of cancer in a first degree relative.



It can be seen that all of the point estimates fall close to 1.0, with Heidelberg having the lowest point estimate at 0.70 and Adelaide having the highest odds ratio estimate at 1.22. There is some disagreement in the results of these two centres, as the point estimate of the Heidelberg centre falls outside of the lower confidence limit for Adelaide (0.71) and the point estimate of the Adelaide centre is higher than the upper limit predicted according to the Heidelberg data (1.15). However, overlap does exist between the confidence intervals generated by both of these centres. The point estimate based on the overall results of all six study centres is the diamond located at the bottom of the graph. One can clearly see that there is no significant change in the risk of developing a meningioma associated with a general family history of cancer for this dataset since the diamond crosses the vertical line established at 1.00. This is confirmed by the two-sided test for overall effect, which was not found to be statistically significant ($p = 0.59$).

The I^2 value of 0 percent meant that the findings for the meningioma data were highly consistent across each of the six study centres. Each of the specific cancer exposure variables was evaluated and it was found that in no instances was the assumption of homogeneity amongst the centres violated (data not shown). In a further attempt to justify the pooling of data from each of the study centres, each location was dropped from the pooled analysis of the association between meningioma and a family history of cancer one centre at a time to assess the impact on the overall association (forest plots not shown).

Table 20: Results of the cumulative association of a first degree relative with cancer amongst meningioma cases and controls: effect of the removal of individual centre data.

Study Centre Dropped	Cumulative Odds Ratio (95 % CI)	Two-sided Test for Overall Effect (p-value)	Chi-square Test for Heterogeneity (p-value)	I² Value
None	0.9 (0.7-1.2)	Z = 0.54 (0.59)	2.66 (0.75)	0%
Adelaide	0.9 (0.6-1.2)	Z = 1.03 (0.30)	1.38 (0.85)	0%
Grenoble	0.9 (0.7-1.3)	Z = 0.41 (0.68)	2.60 (0.63)	0%
Heidelberg	1.0 (0.8-1.4)	Z = 0.25 (0.80)	0.91 (0.92)	0%
Stockholm	0.9 (0.7-1.2)	Z = 0.67 (0.50)	2.46 (0.65)	0%
Toronto	0.9 (0.7-1.2)	Z = 0.44 (0.66)	2.58 (0.63)	0%
Winnipeg	0.9 (0.7-1.2)	Z = 0.64 (0.52)	2.49 (0.65)	0%

As can be seen in table 20, the removal of each of the centres from the cumulative analysis had no significant impact on the overall association. As was to be expected, the largest change to the point estimate and 95 percent confidence interval came with the removal of the Heidelberg study centre, which was responsible for contributing the greatest number of study participants. This large removal also resulted in the lowest z-score for the overall effect and the p-value with the least statistical significance. The I² value always remained at 0 percent, regardless of which centre was dropped, meaning that the assumption of homogeneity amongst the centres was never violated.

4.2.8.b. Type of Interview Results

A total of 307 adult meningioma cases and 1095 controls were included in the sensitivity analyses of the SEARCH study data regarding the type of interview. 292 of the cases (95.1%) and 1068 of the controls (97.5%) answered all of their interview questions either directly or with some assistance from the interviewer, but with no responses coming from a proxy. The remaining 15 cases (4.9%) and 27 (2.5%) of the controls included either partial or complete responses from a proxy, most commonly a spouse.

Unconditional logistic regression was performed on the pooled dataset, with adjustments made for the sex and age of the participant, the study centre, and the type of interview reported. The respective referent groups were females, 25-29 year olds, the Heidelberg centre, and those respondents who did not require a proxy. For this dataset, the type of interview did not have a significant influence on the odds ratio of being a case. The point estimate for those needing either a proxy or part proxy compared to direct and assisted participants was elevated (OR = 1.8, 95% CI = 0.9-3.7), but was not statistically significant ($p = 0.10$). The odds associated with having any first degree relative with cancer was not significant either (OR = 0.9, 95% CI = 0.7-1.2, $p = 0.41$), which was similar to the findings for the model which was adjusted only for age, sex, and study centre (OR = 0.9, 95% CI = 0.7-1.2, $p = 0.44$).

4.2.8.c. Age-specific Results

Following the methods employed by Hill et al (154), participants in the SEARCH study meningioma analysis were sub-divided into two groups based on age – those between 20 and 49, and those who were 50 years of age or older at the time of diagnosis for the cases and interview for the controls. The proportions in each of the two groups were fairly similar between the cases and controls. 104 of the 307 adult meningioma cases (33.9%) were in the younger age category, a slightly higher percentage compared to 354 of the 1095 meningioma controls (32.3%).

In the unconditional logistic regression model analysis of the association between a family history of cancer and meningioma in adults, adjusted for sex, study centre, and age, the effect on the pooled odds ratio introduced by a participant being 50 years or older was not significant. The covariate-specific odds ratio was found to be 0.9, with a 95 percent confidence interval of 0.7-1.2 ($p = 0.51$). The risk of meningioma for those reporting a first degree relative with cancer in this model was 0.9 (95% CI = 0.7-1.2, $p = 0.48$), a result similar to that found in the unconditional model which adjusted for sex, study centre, and five-year age group of the participant (OR = 0.9, 95% CI = 0.7-1.2, $p = 0.44$).

4.2.8.d. Socioeconomic Status Results

Due to missing information pertaining to the highest education level attained and the number of years of school completed, sensitivity analysis concerning socioeconomic status was only possible for 290 meningioma cases and 1075 controls. Included individuals were grouped together such that those who had some university or college

experience were in one set and those without tertiary education were in another. To be in the former did not require the completion of a degree or diploma. Only 38 cases (13.1%) reported having any university or college-level education, a percentage much lower than that found in the meningioma controls (203 controls, 18.9%). When tertiary education was incorporated into a pooled unconditional logistic regression which also adjusted for the age, sex, and study centre of the participant, cases were significantly more likely to have not attended university or college (OR = 2.0, 95% CI = 1.3-3.1, $p < 0.01$). However, the inclusion of this modified method of accounting for one's socioeconomic status did not considerably change the risk of adult-onset meningioma in this dataset as predicted by the first model in section 4.2.3., which only adjusted for the age, sex, and study centre. The point estimate produced by this new model was 0.9, with a 95 percent confidence interval of 0.7-1.2, numbers that were the exact same as those found in model 1 of 4.2.3., as well as the fifth model which adjusted for the age, sex, study centre, and socioeconomic status as determined by the seven-point scale.

4.3. Results of the Systematic Review

4.3.1. Results of the Search of the Literature

The initial literature search was conducted in Medline, Embase, and PubMed on July 11, 2005, using the search strategies found in appendices C-E. Both Medline and Embase were searched using the OVID interface and for PubMed the NCBI search interface was used. These searches yielded a total of 4492 references, 1475 of which came from Medline, 2045 from Embase, and 972 from PubMed. 1562 duplicates were

found using the SRS program. Their removal meant that a total of 2930 articles were assessed for inclusion in this systematic review.

All 2930 abstracts were screened by one reviewer (Mr. Tomson), with 293 randomly selected abstracts assessed by a second reviewer (Dr. Little). In order to quantify the level of agreement between the two reviewers, Cohen kappa scores were calculated and found to be 0.67, which is considered to represent “substantial agreement” (178). Of the 293 articles that were evaluated by both reviewers, 286 were excluded by Dr. Little and 275 were excluded by Mr. Tomson. There were a total of 17 disagreements between them. These conflicts were resolved without the need of a third party. The final number of articles that were passed on to the next level of screening was 219, 7.47% of the original sample. The remaining 2711 studies (92.53%) were excluded from further consideration in the review.

On February 1, 2006, an updated search of the three electronic databases was performed, covering the time of the initial search through the end of January, 2006 using the same search strategies as the original search. The Medline search yielded an additional 38 articles, of which seven were passed on so that the entire article could be assessed. The final search of the Embase search engine produced 43 abstracts. Five of these were considered to be potentially relevant, but only one had not already been retrieved via the Medline search. Finally, the updated search of PubMed generated 43 new articles, of which seven were deemed eligible for strict screening, but none of which could not be found in either Medline or Embase.

For the more refined screening, a total of 227 full text articles were retrieved and further assessed, 219 coming from the initial search and eight from the final search of the

literature. Included among these were 82 review papers. These were passed on to the more refined screening level so that their included references could be scanned for relevance; however, the reviews themselves were not eligible for inclusion. As can be seen in table 21, a total of 186 articles were excluded following completion of the second screening level. The reason for exclusion is based on the first question that produced a “no” response during the full text review. Therefore, “publication was not a case-control study” is listed as the most common reason for exclusion simply because it was the first question about an article that was considered. A detailed flow chart of the included and excluded studies can be found in appendix F. The two articles that were excluded due to their language were both written in Japanese (179,180). Attempts were made by the author to obtain the necessary information from the corresponding authors to facilitate their inclusion in the review, but no response was received. As before, a random 10% sample was selected and reviewed by a second reviewer (Dr. Little). There was complete inter-observer agreement about the 22 selected studies (Cohen kappa score = 1.00).

Table 21 – Papers excluded from the systematic review at the more refined screening level.

REASON FOR EXCLUSION	NUMBER EXCLUDED
Publication was not a case-control study	131
The exposure of interest is not a genetic polymorphism	26
Duplicate	13
The publication did not include any cases or controls that were 18 years of age or older	8
Publication does not involve cases with brain tumours	4
It was not possible to estimate the overall magnitude of effect of the genetic polymorphism in terms of an odds ratio	2
It was not possible to extract the necessary information due to the language of publication	2

4.3.2. Included Studies

Based on the study eligibility criteria outlined in the methods section 3.2.3, a total of 41 studies were deemed acceptable for inclusion in this review. All 41 studies were written in English, peer-reviewed, and as can be seen in table 22, published in 21 different journals, with *Cancer Epidemiology, Biomarkers & Prevention* contributing nine included studies, the most of any journal. Table 22 also outlines some descriptive characteristics of each individual study. Great variety exists amongst the polymorphisms that have been studied for potential associations with brain tumours in adults. A list of the different genes examined and their functions can be found in appendix H. Table 22 also reveals that there is a great deal of geographical variation concerning the regions that the participants have been selected from, the size of the study, and the use of matching and the particular matching variables. Further adding to the inconsistency of the data is the variability that can be found within each of the studies, such as fluctuating numbers of included cases and controls for each of the different polymorphisms evaluated.

Polymorphisms were found on 46 different genes included amongst the 41 case-control studies. The *glutathione S-transferase (GST)* genes *M*, *T*, and *P* were evaluated by the most studies ($n = 10$), while the *cytochrome P* gene and the *excision repair cross-complementation* genes were each included in five separate studies. Four articles were found involving polymorphisms within the *p53* gene. All of the other genes were limited to one ($n = 34$) or two studies ($n = 3$). The results of the data syntheses are presented in figures 6-16. In the absence of statistical heterogeneity, overall point estimates and confidence intervals are represented as diamonds. When there is heterogeneity, overall estimates are not presented on the forest plots.

Table 22. Study characteristics of included studies evaluating the association of genetic polymorphisms and brain tumours in adults.

Study	Year of Publication	Journal	Polymorphism(s) Studied	Population Selected From	Cases (n)	Controls (n)	Matching	Matching Variables
Wundrack	1994	<i>Acta Neuropathologica</i>	Cytochrome P450 on the CYP2D6 gene	Cases = Germany Controls = England & Scotland	31	720	None	None
Elexpuru-Camiruaga	1995	<i>Cancer Research</i>	(i) GSTM1 Null (ii) GSTT1 Null (iii) CYP2D6	UK	156-158	412-577	None	None
Koopman	1995	<i>British Journal of Cancer</i>	6 SNPs on the WAF1/CIP1 gene	Cases = USA, Switzerland, Germany Controls = Germany	158	157	None	None
Hand	1996	<i>Carcinogenesis</i>	(i) GSTM3 AA (ii) GSTM1 Null (iii) GSTT1 Null	Cases = UK Controls = Not stated	89	211-300	None	None
Kelsey	1997	<i>Pharmacogenetics</i>	(i) CYP2D6 (ii) GSTT1 Null	USA	156-158	154-158	Frequency	Age (5 yrs), race, sex
Platten	1997	<i>Journal of Neuropathology & Experimental Neurology</i>	SNP on the TSC2 gene	Cases = Germany, Switzerland Controls = Not stated	244	381	None	None
Rothberg	1997	<i>Molecular Carcinogenesis</i>	Deletion on the RB gene	USA	18	185	None	None
Wiencke	1997	<i>Carcinogenesis</i>	GSTM1 Null	USA	156-158	157	Frequency	Age (5 yrs), sex

Table 22 (Cont). Study characteristics of included studies evaluating the association of genetic polymorphisms and brain tumours in adults.

Study	Year of Publication	Journal	Polymorphism(s) Studied	Population Selected From	Cases (n)	Controls (n)	Matching	Matching Variables
Trizna	1998	<i>Cancer Epidemiology, Biomarkers & Prevention</i>	(i) <i>GSTM1</i> Null (ii) <i>GSTT1</i> Null (iii) <i>NAT2</i> acetylase (iv) <i>CYP1A1</i>	USA	90	90	Frequency	Age (5 yrs), race, sex
Chen	2000	<i>Cancer Epidemiology, Biomarkers & Prevention</i>	SNP on the <i>ERCC1</i> gene	USA	122	159	Frequency	Age, race, sex
Kondratieva	2000	<i>Journal of Experimental & Clinical Cancer Research</i>	(i) SNP on the <i>L-MYC</i> gene (ii) <i>GSTM1</i> Null	Cases = Russia Controls = Not stated	54-57	102-103	None	None
Nishimori	2000	<i>Journal of Neuro-oncology</i>	SNP on the <i>PCAF</i> gene	Cases = Japan Controls = Not stated	37	31	None	None
Zhou	2000	<i>Journal of Medical Genetics</i>	2 SNPs on the <i>PPARγ</i> gene	USA & Germany	27-44	60-80	Not specified	Race
Caggana	2001	<i>Cancer Epidemiology, Biomarkers & Prevention</i>	8 SNPs on the <i>ERCC2</i> gene	USA	114-148	137-148	Frequency	Age, race, sex
Peters	2001	<i>Cancer Epidemiology, Biomarkers & Prevention</i>	(i) <i>NAT2</i> gene (ii) <i>NQO1</i> gene	USA	156-157	155-163	Frequency	Age (5 yrs), race, sex
Reis	2001	<i>Acta Neuropathologica</i>	SNP on the <i>hBUB3</i> gene	Cases = Switzerland Controls = Not stated	22	60	None	None
Vega	2001	<i>Cancer</i>	Rare <i>HRAS1</i> alleles	Cases = Spain Controls = Not stated	84	109	None	None

Table 22 (Cont). Study characteristics of included studies evaluating the association of genetic polymorphisms and brain tumours in adults.

Study	Year of Publication	Journal	Polymorphism(s) Studied	Population Selected From	Cases (n)	Controls (n)	Matching	Matching Variables
Biros	2002	<i>Physiological Research</i>	2 SNPs on the <i>p53</i> gene	Slovakia	60	183	Not specified	Age
Ezer	2002	<i>Journal of Neuro-oncology</i>	(i) <i>GSTM1 Null</i> (ii) <i>GSTT1 Null</i> (iii) 2 SNPs on the <i>GSTP1</i> gene	USA	220-221	782-1473	None	None
Sasaki	2002	<i>Cancer Research</i>	2 deletions and 3 SNPs on the <i>DMBT1</i> gene	Not stated	98-99	64	None	None
Baeza	2003	<i>Oncogene</i>	4 SNPs on the <i>AXIN1</i> gene	Cases = Switzerland Controls = Not stated	39	86	None	None
De Roos	2003	<i>Cancer Epidemiology, Biomarkers & Prevention</i>	(i) <i>GSTM1 Null</i> (ii) 2 SNPs on the <i>GSTP1</i> gene (iii) <i>GSTT1 Null</i> (iv) 2 separate polymorphisms of the <i>CYP2E1</i> gene	USA	615-647	545-576	Frequency	Hospital, age, race, sex, proximity of home to hospital
Inoue	2003	<i>Neurological research</i>	2 polymorphic alleles on the <i>MGMT</i> gene	Japan	58	225	None	None
Leone	2003	<i>BMC Cancer</i>	SNP on the <i>RAD54L</i> gene	Spain & Ecuador	70	236	None	None
Bhowmick	2004	<i>Cancer Research</i>	SNP on the <i>EGF</i> gene	USA	42	78	None	None

Table 22 (Cont.). Study characteristics of included studies evaluating the association of genetic polymorphisms and brain tumours in adults.

Study	Year of Publication	Journal	Polymorphism(s) Studied	Population Selected From	Cases (n)	Controls (n)	Matching	Matching Variables
Sciacca	2004	<i>Clinical Cancer Research</i>	SNP on the following genes: (i) <i>F2</i> (ii) <i>F5</i> (iii) <i>MTHFR</i> (iv) <i>VEGF</i> (v) <i>PAI-1</i> Deletion on the <i>PLAT</i> gene	Italy	250	270	Not specified	Age, sex
Wang	2004	<i>Cancer Research</i>	SNPs on the following genes: (i) <i>XRCC1</i> (ii) <i>XRCC3</i> (iii) <i>RAD51</i> (iv) <i>p53</i> (v) <i>XRCC7</i>	USA	309	342	Frequency	Age (5 yrs), race, sex
Wrensch	2004	<i>Cancer Epidemiology, Biomarkers & Prevention</i>	(i) <i>GSTM1 Null</i> (ii) <i>GSTT1 Null</i> (iii) 2 SNPs on the <i>GSTP</i> gene	USA	447-452	491-504	Frequency	Age, race, sex
De Bustos	2005	<i>Journal of Medical Genetics</i>	SNP on the <i>PDGFRα</i> promoter	Sweden	137	91	None	None
Degerli	2005	<i>Clinical Biochemistry</i>	Delta-32 allele on the <i>CCR5</i> gene	Turkey	20	267	None	None
Pinarbasi	2005	<i>Cancer Genetics & Cytogenetics</i>	(i) <i>GSTM1 Null</i> (ii) <i>GSTT1 Null</i> (iii) <i>GSTP</i>	Turkey	75	153	Frequency	Age, sex

Table 22 (Cont). Study characteristics of included studies evaluating the association of genetic polymorphisms and brain tumours in adults.

Study	Year of Publication	Journal	Polymorphism(s) Studied	Population Selected From	Cases (n)	Controls (n)	Matching	Matching Variables
Sadetzki	2005	<i>Cancer Epidemiology, Biomarkers & Prevention</i>	SNPs on: (i) <i>NF2</i> (ii) <i>Ki-ras</i> (iii) <i>p16</i> (iv) <i>Cyclin D1</i> (v) <i>PTEN</i> (vi) <i>E-cadherin</i> (vii) <i>TGFB1</i> (viii) <i>TGFBR2</i> (ix) <i>ERCC2</i> (x) <i>XRCC1</i> (xi) <i>XRCC3</i> (xii) <i>XRCC5</i>	Asia, Africa, & Europe	131-216	121-220	Frequency	Year of birth (<1944, 1944-49, >1949), sex, continent of origin
Yang	2005	<i>Cancer</i>	SNPs on: (i) <i>ERCC2</i> (exon 6 & exon 22) (ii) <i>RAI</i> (iii) <i>ASE-1</i> (iv) <i>ERCC1</i> (v) <i>GLTSCR1</i> (vi) <i>LIG</i>	Cases = USA, Brazil, Greece, Hungary, Mexico, Peru, Saudi Arabia, Spain, & Yugoslavia	137-141	104-108	None	None
				Controls = USA				
Parhar	2005	<i>Molecular Brain Research</i>	<i>p53</i> codon 72 polymorphism	USA	92	117	None	None

Table 22 (Cont). Study characteristics of included studies evaluating the association of genetic polymorphisms and brain tumours in adults.

Study	Year of Publication	Journal	Polymorphism(s) Studied	Population Selected From	Cases (n)	Controls (n)	Matching	Matching Variables
Schwartzbaum	2005	<i>Cancer Research</i>	(i) 2 SNPs on <i>IL-4RA</i> (ii) 2 SNPs on <i>IL-13</i> (iii) SNP on <i>ADAM33</i> (iv) SNP on <i>COX-2</i>	Sweden	105-110	399-503	Frequency	Age, sex, geographic location
Tang	2005	<i>Cancer Epidemiology, Biomarkers & Prevention</i>	(i) 8 SNPs on the <i>HLA</i> gene (ii) SNP on the <i>MICA</i> gene (iii) SNP on the <i>TNFB</i> gene	USA	153-155	154-157	Frequency	Age (1 yr), sex, ethnicity
Wrensch	2005	<i>Neuro-oncology</i>	(i) SNP on the <i>ERCC1</i> gene (ii) 2 SNPs on the <i>ERCC2</i> gene	USA	419-450	494-519	Frequency	Age, race, sex
Malmer	2005	<i>Cancer Epidemiology, Biomarkers & Prevention</i>	3 SNPs on the <i>p53</i> gene	Sweden	347-354	349-364	Frequency	Age, sex, geographic location
McCready	2005	<i>International Journal of Cancer</i>	SNP on the <i>MMP-1</i> promoter	Not stated	81	57	None	None
Miller	2005	<i>Neuroepidemiology</i>	SNP on the <i>MDR-1</i> gene	USA	458	528	Frequency	Age, sex, ethnicity
Rajaraman	2005	<i>Environmental Health Perspectives</i>	SNP on the <i>ALAD</i> gene	USA	506	505	Frequency	Hospital, age (10 yrs), sex, ethnicity, proximity to hospital

4.3.3. Results of Studies Involving Glutathione S-Transferase Genes

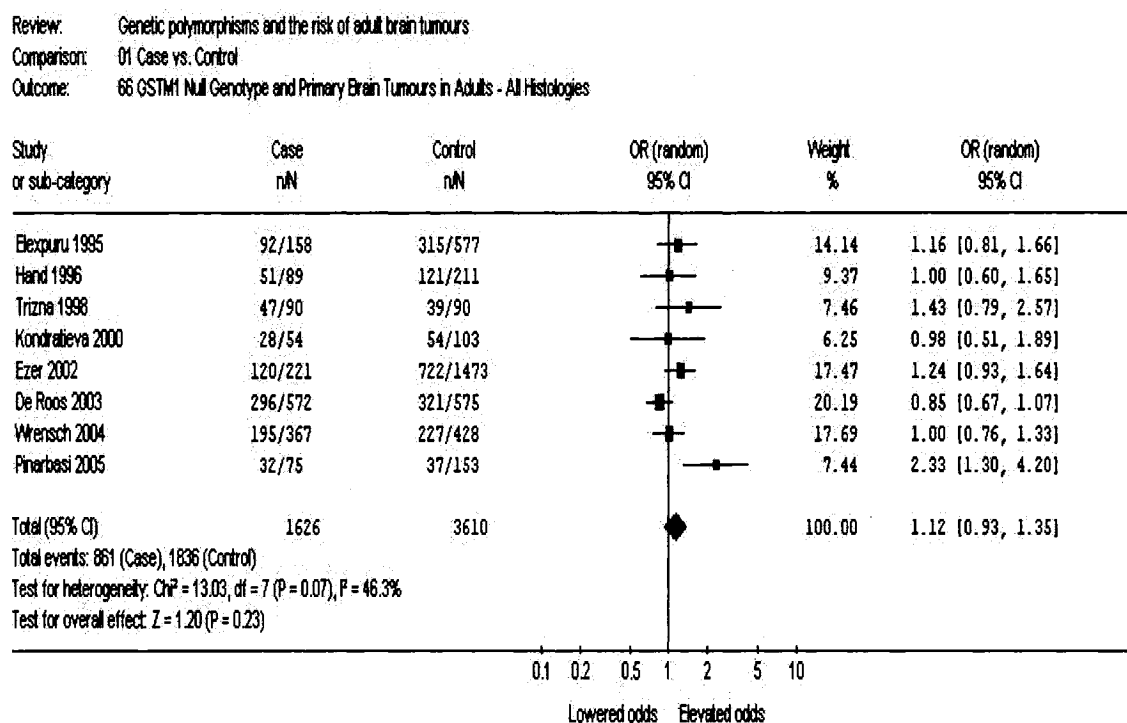
The primary function of *GSTs* is to catalyze the conjugation of glutathione to carcinogens in the body (181). This helps protect cells from the harmful reactive electrophiles and is the first step in the elimination of potentially harmful carcinogenic compounds. There are seven classes of cytosolic *GSTs*, each with unique roles in the metabolism process, but the focus of the 10 articles included in this review is limited to three specific *GST* genes – *GSTM1*, *GSTT1*, and *GSTP1*. Variants of both *GSTM1* and *GSTT1* are deletions called *M1-* and *T1-null*, since persons homozygous for the variants lack any enzymatic function for that gene. Two SNPs in particular are the focus of the research involving *GSTP1*. The first occurs on codon 105 and results in the production of valine in place of isoleucine. The second variant is on codon 114 and instead of valine, alanine is formed. The gene products of each of these SNPs are enzymes which have altered activities, affinity for electrophilic substrates, and heat stability (182). One paper also evaluated the association between variants of the *GSTM3* gene and astrocytomas in adults (183).

Of the 10 included case-control studies, nine looked at *GSTM1*; eight assessed polymorphisms in *GSTT1*; four publications evaluated the SNP on codon 105 in *GSTP1*, with the *Val/Val* genotype being considered the variant; and three studies focused on the SNP on codon 114 in *GSTP1*, with both heterozygotes and individual homozygous for valine serving as the variant cases and controls. Forest plots were used to graphically assess the results of each study.

4.3.3.a. *GSTM1* Null Genotype

Figure 6 is the forest plot of the eight included case-control studies in the quantitative data synthesis of the association between the *GSTM1* null genotype and primary brain tumours in adults. The analysis includes a total of 5236 subjects, 1626 cases and 3610 controls, of which 861 of the cases and 1836 of the controls were found to have the variant genotype.

Figure 6: Odds of primary brain tumours in adults associated with *GSTM1* null genotype: pooled results from eight case-control studies.



Only one of the studies found a significant change in the risk of brain tumours associated with the *GSTM1* null polymorphism. The Pinarbasi et al study (184), a hospital-based case-control evaluation conducted using Turkish participants, found a more than two-fold increase in the odds of primary brain tumours, a significant change

(OR = 2.33, 95% CI = 1.30-4.20). The remaining point estimates were all fairly homogeneous. In fact, the removal of the significant findings of Pinarbasi reduced the I^2 value to zero percent.

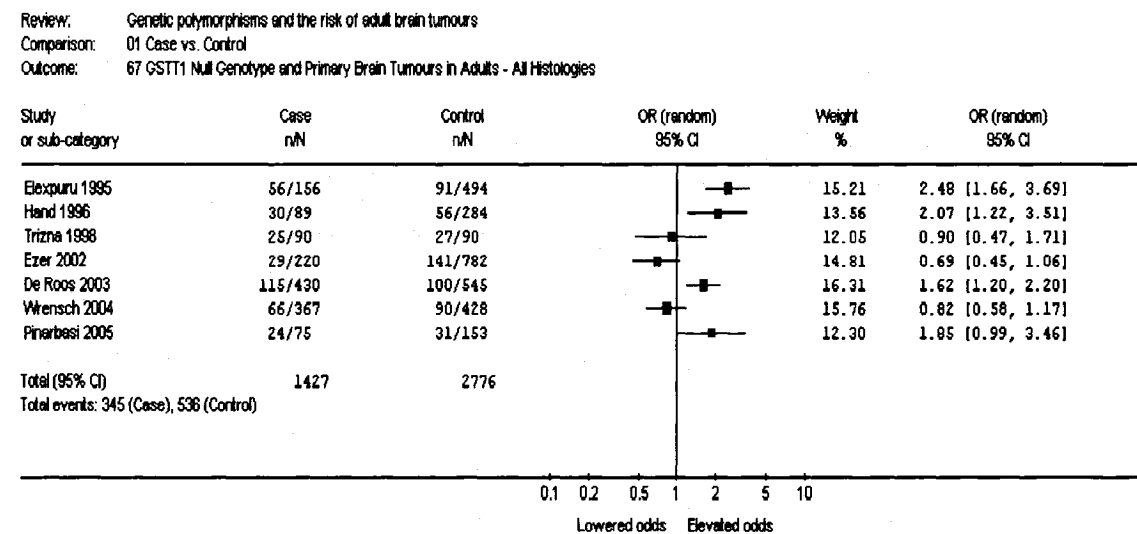
Overall, there was a slight increase in the risk of PBTs amongst adults with the *GSTM1* null genotype, though this was not statistically significant (OR = 1.12, 95% CI = 0.93-1.35, $p = 0.23$). Due to the large number of participants included in the data synthesis, the cell values for both the exposed and non-exposed cases and controls were all great in size. This allowed for tight confidence intervals, which crossed the odds value of 1.0, suggesting that there is no association between this SNP and adult brain tumours based on this data. It should be noted that a ninth study was found that evaluated this association (185); however, the data used by this study was encapsulated in the larger Wrensch study (186) so including it would have meant double-counting.

4.3.3.b. *GSTT1* Null Genotype

Seven studies were deemed eligible for inclusion in the quantitative synthesis, contributing 1427 cases and 2776 controls. The *GSTT1* null genotype was present in 345 of the tumour cases and 536 of the controls. As seen in figure 7, the results varied greatly from study to study, as indicated by the I^2 value of 81.4%. This inconsistency means that it is inappropriate to interpret the overall point estimate produced by the data synthesis because the individual study results are not suggesting the same association, or lack thereof. Four of the seven case-control studies produced a point estimate of greater than 1.0, including two with more than a two-fold increase in odds, while the other four studies all suggested that the presence of the *GSTT1* null genotype may lower one's odds

of a primary brain tumour. The Elexpuru-Camiruaga (187), Hand (183), and De Roos (188) papers all attained statistical significance, with each reporting an elevated odds. None of the four studies which found odds ratios of less than 1.0 were significant findings. Again, an eighth study (189) had to be dropped because it was a subset of the Wrensch study.

Figure 7: Odds of primary brain tumours in adults associated with *GSTT1* null genotype: results from seven case-control studies.



A number of methodological issues were considered for each of the studies to determine if the observed heterogeneity was true. All of the studies which found elevated risk of brain tumours used hospital-based controls. However, the Wrensch study was the only one to use true population-based controls, since Trizna utilized healthy blood donors and Ezer utilized controls from the literature. The use of matching did influence the risk since studies employing frequency matching were found on either side, as were studies which did not use any form of matching. No trend was observed concerning the histology of the tumours found in the cases. The Trizna, Ezer, and de Roos papers were the only ones who made any mention of quality control measures taken, but as can be

seen in figure 7, their results were not similar. It would seem that based on these studies, the heterogeneity observed is not influenced by the methodologies of the different studies, but rather is due to true differences in the study results.

4.3.3.c. *GSTP* Ile105Val Val/Val Genotype

The homozygous SNP found at codon 105 on the *GSTP* gene, which results in the production of valine in place of isoleucine, was only assessed in three eligible case-control studies for its potential association with adult brain tumours. The results of Ezer et al (182), De Roos et al (188), and Wrensch et al (186) contributed a total of 1171 cases (126 homozygous variants) and 2704 controls (286 variants). The results were found to be inconsistent from study to study ($I^2 = 82.6\%$), so a pooled odds ratio was not found.

Ezer found significantly lowered odds of tumour associated with the variant genotype (OR = 0.43, 95% CI = 0.22-0.82, $p = 0.01$), though caution should be taken with this result since it is based on only 10 cases homozygous for the SNP and the control population was formed from those described in previous literature (182). The findings of Wrensch supported the notion of lowered risk (OR = 0.74, 95% CI = 0.48-1.16), but was not a statistically significant difference. Contrary to this, de Roos' findings suggested an increased risk of brain tumour associated with the Val/Val genotype, but was not significant (OR = 1.35, 95% CI = 0.98-2.01, $p = 0.10$). All three studies used American participants and the de Roos and Wrensch studies used frequency matching, though the matching variables did differ.

4.3.3.d. *GSTP* Ala114Val Ala/Val or Val/Val Genotype

The evaluation of the association of the polymorphic valine phenotype at codon 114 on the *GSTP* gene and PBTs was restricted to the same three studies which looked at the SNP on codon 105 in section 4.3.3.c. Again, there was a lack of homogeneity between the individual study findings ($I^2 = 95.2\%$). The studies by De Roos and Wrensch produced similar results, with odds ratios that were very close to 1.0 (1.03 and 1.08, respectively). However, the Ezer paper found a very significant elevation of the risk of PBTs associated with the polymorphism (OR = 14.92, 95% CI = 6.95-32.03). Only 9 of the 898 controls were found to have the variant allele, compared to 29 of the 221 cases. Again, caution should be taken in interpreting these results since the control population came from other published studies that were not the author's own. Overall, there were 171 variant cases out of 1162 total patients with a tumour, compared to 155 of the 1902 controls with a variant allele.

4.3.4. Results of the Studies Involving Glutathione-S Transferase Genes by Histology

Each of the polymorphisms on the *GSTM1*, *GSTT1*, and *GSTP* genes were evaluated separately for four different histological sub-types of primary brain tumours in adults: glioma, astrocytoma, oligodendroglioma, and meningioma. The results are presented below. Table 23 summarizes the percentage of cases and controls from each study that were genotypic variants, subdivided by the classification of primary brain tumour.

Table 23: Distribution of *GSTM1*, *GSTT1*, *GSTP1 Ile105Val*, and *GSTP1 Ala114Val* genotypes among cases and controls by type of brain tumour: results from 10 studies.

Type of Tumour	First Author	% <i>GSTM1</i> Null		% <i>GSTT1</i> Null		% <i>I105V</i> Val/Val		% <i>A114V</i> Ala/Val or Val/Val	
		Ca.	Co.	Ca.	Co.	Ca.	Co.	Ca.	Co.
Glioma	Kelsey	-	-	17.2	19.6	-	-	-	-
	Wiencke	48.9	49.7	-	-	-	-	-	-
	Trizna	52.2	43.3	27.8	30.0	-	-	-	-
	Kondratieva	51.9	52.4	-	-	-	-	-	-
	De Roos	52.6	55.8	19.9	18.4	16.9	10.4	14.6	13.5
	Wrensch	53.1	53.0	17.9	21.0	8.9	22.6	16.2	15.9
	Pinarbasi	48.4	24.2	32.3	20.3	3.2 ¹	10.7 ¹	-	-
Astrocytoma	Elexpuru-Camiruaga	59.6	54.6	32.1	18.4	-	-	-	-
	Hand	57.3	57.3	33.7	19.7	-	-	-	-
	Kelsey	-	-	11.4	19.6	-	-	-	-
	Wiencke	54.3	49.7	-	-	-	-	-	-
	Ezer	48.0	49.0	16.3	18.0	5.1	10.0	9.2	1.0
	De Roos	54.6	55.8	19.6	18.4	22.2	10.4	16.4	13.5
	Wrensch	54.8	53.0	11.3	21.0	8.1	22.6	19.4	15.9
Oligodendro-Glioma	Kelsey	-	-	43.8	19.6	-	-	-	-
	Wiencke	66.7	49.7	-	-	-	-	-	-
	Ezer	60.5	49.0	11.6	18.0	2.3	10.0	11.6	1.0
	De Roos	32.6	55.8	26.7	18.4	8.9	10.4	25.5	13.5
	Wrensch	52.1	53.0	20.2	21.0	11.7	22.6	14.9	15.9
Meningioma	Elexpuru-Camiruaga	55.1	54.6	44.7	18.4	-	-	-	-
	De Roos	49.7	55.8	23.9	18.4	7.1	10.4	12.4	13.5
	Pinarbasi	47.8	24.2	26.1	20.3	8.7 ¹	10.7 ¹	-	-

¹ Only information available combined Val/Val and Ile/Val genotypes.

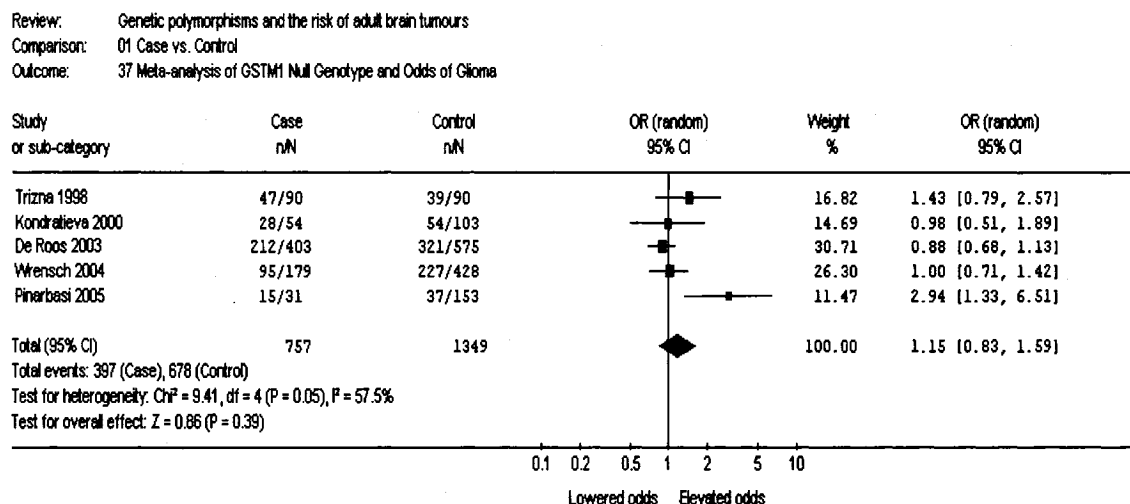
4.3.4.a. *GSTM1* Null Genotype and Glioma

Figure 8 presents a forest plot of the results of five separate case-control studies evaluating the association between adult glioma and the *GSTM1* null genotype. The pooled analysis is based on 2106 subjects (757 cases, 1349 controls) and yields a non-significant point estimate of 1.15 (95% CI = 0.83-1.59, $p = 0.39$). Only one of the five individual studies, Pinarbasi et al (184), reported a significant change in the risk of glioma associated with the polymorphism. The study by Pinarbasi et al found an elevated

glioma risk (OR = 2.94, 95% CI = 1.33-6.51), but it should be noted that this study included the fewest number of participants and there was no information provided about the hospital-based controls except for that they had no previous cancer diagnosis and radio- or chemotherapy. Three investigations found a slight reduction in risk associated with the *GSTM* null genotype, one suggested a modest increase in risk, and one study found no difference in risk between the cases and controls.

The test for heterogeneity amongst the studies bordered statistical significance ($I^2 = 57.5\%$), suggesting that there was some degree of disparity across the studies. This inconsistency is largely attributed to the Pinarbasi study, since removing these results from the analysis yields an I^2 value of 0%. The Kondratieva et al study (190) was included in the analysis, though it made no mention of the ages of the participants. The author tried to contact the corresponding author, but no response was received. The result of removing this study from the pooled analysis did not significantly alter the point estimate (OR = 1.14, 95% CI = 0.84-1.55, $p = 0.41$), though its removal did produce an I^2 value of 62.7%, implying a lack of consistency amongst the remaining studies.

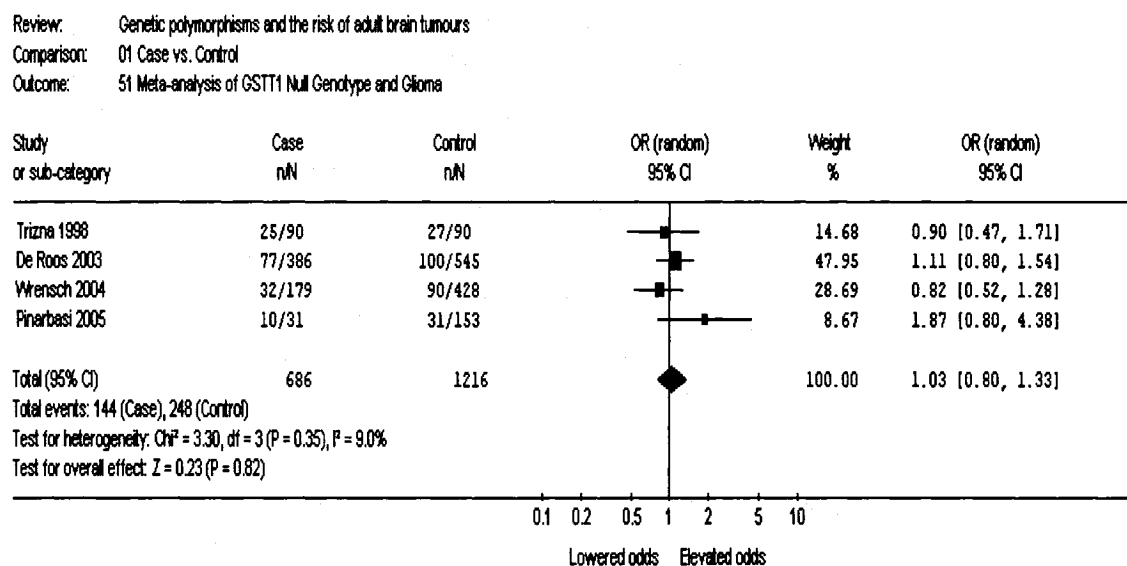
Figure 8: Odds of glioma in adults associated with *GSTM1* null genotype: pooled results from five case-control studies.



4.3.4.b. *GSTT1* Null Genotype and Glioma

Four separate case-control studies evaluated the potential association between glioma in adults and the *GSTT1* null genetic polymorphism. As seen in figure 9, the pooled analysis of 686 cases and 1216 controls produced an odds ratio of 1.03, with a 95% confidence interval of 0.80-1.33. No individual study found a significant difference amongst the cases and the controls, and all but one study produced a point estimate within +/- 0.15 of 1.00. As was the case with the *GSTM1* null polymorphism, the Pinarbasi et al study (184) produced the most elevated odds ratio (OR = 1.87, 95% CI = 0.80-4.38).

Figure 9: Odds of glioma in adults associated with *GSTT1* null genotype: pooled results from four case-control studies.



Examining the forest plot, it is clear that the results appear to be fairly consistent across all of the studies, supported by the I^2 test statistic value of 9.0%. The point estimate for the Pinarbasi study does exceed the upper confidence limits of the other four studies; however, all of the other point estimates are contained within the 95 percent

confidence interval of the Pinarbasi data. Since the Pinarbasi study has a low cell value for the number of cases with the polymorphism and includes the fewest number of participants, it carries little weight in determining the overall point estimate.

4.3.4.c. *GSTP* Ile105Val Val/Val Genotype and Glioma

There were three separate studies which evaluated the association between glioma and the SNP causing valine to be produced in place of isoleucine on codon 105 of the *GSTP* gene. De Roos et al (188) conducted a case-control study in the United States using hospital-based controls and found a significantly elevated odds of glioma amongst those with the Val/Val genotype compared to those with either Ile/Ile or Ile/Val genotypes (OR = 1.75, 95% CI = 1.20-2.55). All of the controls were admitted to the hospital for non-neoplastic conditions and their discharge diagnoses are clearly reported. This significantly increased risk of adult glioma is in contrast to the findings reported by Wrensch et al (186), who found a lowered point estimate for glioma, though it did not reach statistical significance (OR = 1.10, 95% CI = 0.36-1.17). The Wrensch study used randomly selected population-based controls and all included subjects were from the United States. In the data synthesis of these two studies, the overall odds ratio was found to be 1.10, with a 95 percent confidence interval of 0.42-2.89 ($p = 0.85$).

The third article to look at glioma and the *GSTP* Ile105Val SNP was the Pinarbasi et al study (184). However, instead of comparing those homozygous for valine at codon 105 to the Ile/Ile and Ile/Val genotypes, Pinarbasi grouped together all participants that were found to have at least one allele which had the SNP (Ile/Val and Val/Val genotypes). Using hospital-based controls in Turkey, Pinarbasi found lowered odds of

glioma (OR = 0.28, 95% CI = 0.03-1.62), but this was based on only one glioma case with the variant genotype and eight variant controls.

4.3.4.d. *GSTP* Ala114Val Ala/Val or Val/Val Genotype and Glioma

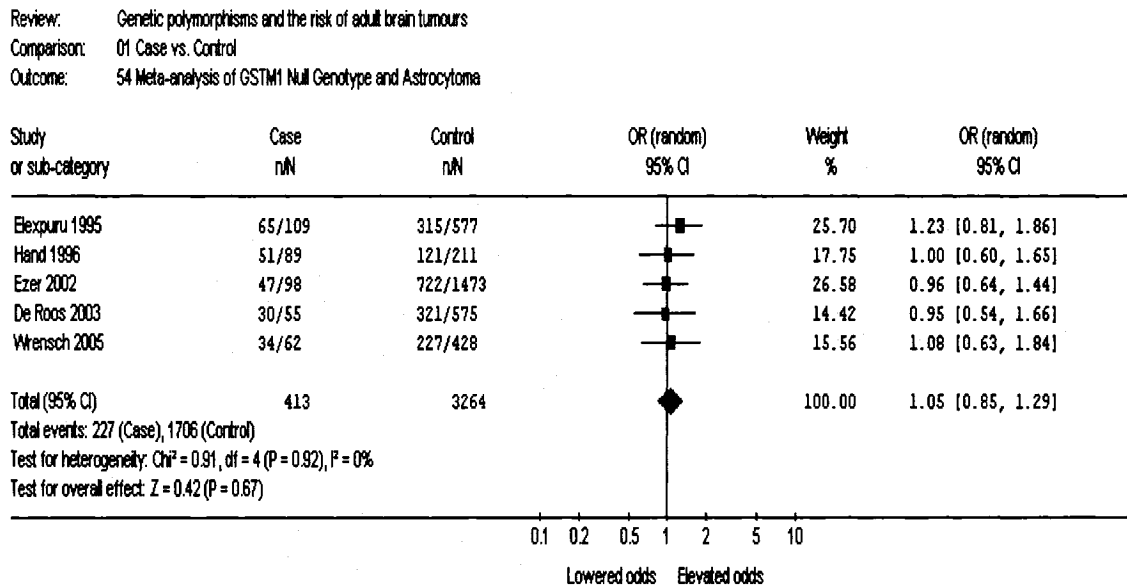
There were only two eligible studies found which compared the odds of adult glioma associated with the presence of the variant codon 114 on the *GSTP* gene which produces in place of alanine. The results of De Roos et al (188) and Wrensch et al (186) were very similar to each other ($I^2 = 0\%$). The point estimate produced by De Roos was slightly higher than Wrensch, at 1.09 and 1.02 (95% CIs = 0.76-1.57 and 0.64-1.65, respectively). Neither result was statistically significant. In the synthesis of the two reports, the overall odds of glioma associated with the SNP was 1.07 (95% CI = 0.80-1.42, $p = 0.67$).

4.3.4.e. *GSTM1* Null Genotype and Astrocytoma

Five case-control studies were found which assessed the possible association of the *GSTM1* null genotype and astrocytoma in adults. Figure 10 presents the findings of each of these studies and the results of the quantitative data synthesis of the 413 included cases and 3264 controls, of which 227 cases and 1706 controls were found to have the polymorphic genotype. There was little variation in the results from study to study. Each of the point estimates was within ± 0.23 of 1.00 and the I^2 value was 0%. Also, the point estimate for each of the investigations was contained within the confidence interval of every other study. Two studies found a very slight decrease in odds (182,188), two suggested a possible elevation of odds (186,187), while the Hand et al paper (183) found

no change in the odds of astrocytoma associated with the *GSTM1* null genotype. Overall, the point estimate was found to be slightly elevated (OR = 1.05, 95% CI = 0.85-1.29), but this increase was not statistically significant ($p = 0.67$).

Figure 10: Odds of astrocytoma in adults associated with *GSTM1* null genotype: pooled results from five case-control studies.



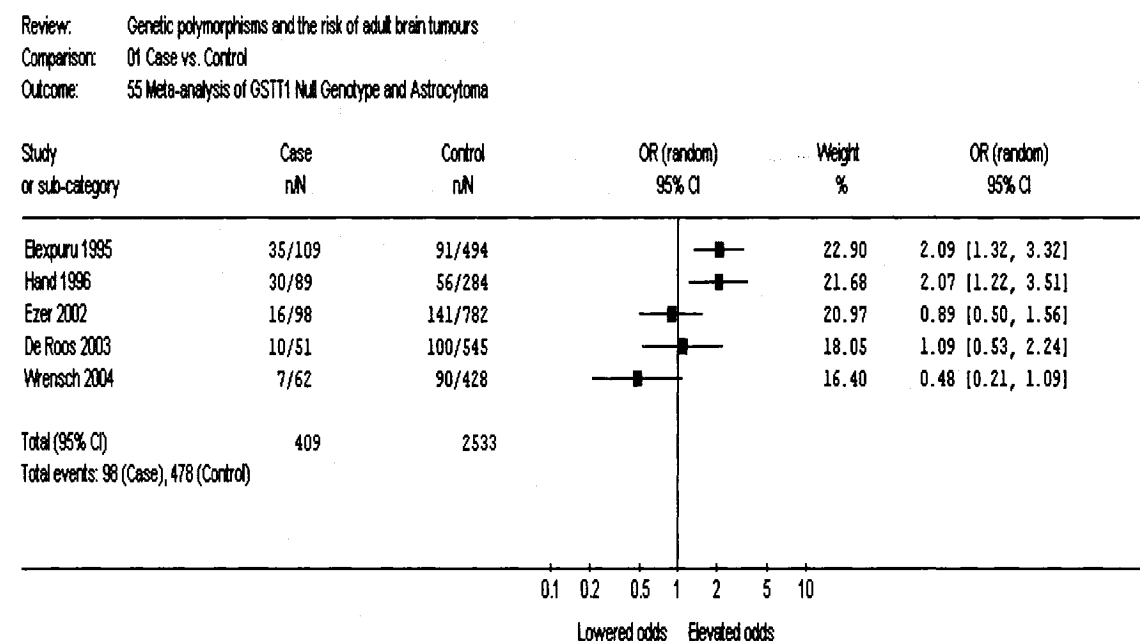
4.3.4.f. *GSTT1* Null Genotype and Astrocytoma

Five case-control studies, comprising 409 cases and 2533 controls, were identified which looked at the genetic polymorphism on the *GSTT1* gene and its possible association with astrocytoma in adults. The forest plots of each of these five studies are shown in figure 11. Unlike the consistency found in the association of *GSTT1* null and glioma, the results found for those cases with astrocytoma were highly inconsistent. The I^2 test statistic was 72.9%, suggesting great variability amongst the studies.

The two earliest published studies, by Elxepuru-Camiruaga et al (187) and Hand et al (183), both found a significant elevation in the risk of astrocytoma among those with the polymorphism. Elxepuru-Camiruaga's report was a hospital-based case-control study

restricted to UK whites and the authors found a more than two-fold increase in the risk of astrocytoma based on 109 cases and 494 eligible controls. Similarly, Hand et al used hospital-based controls in a study conducted amongst white UK participants and found a point estimate of greater than 2.0 (OR = 2.07, 95% CI = 1.22-3.51). The author notes that both of these studies represent the greatest weight in the quantitative synthesis of the five eligible investigations as a result of both their relatively large number of participants and the significantly elevated odds. Neither of these two studies discussed possible differences in population demographics between the cases and the controls, such as age or sex, and there was no mention of any quality control measures.

Figure 11: Odds of astrocytoma in adults associated with *GSTT1* null genotype: results from five case-control studies.



Only one of the remaining three studies reported a point estimate of greater than 1.0 (188). Each of the other case-control investigations produced smaller odds ratios, including the most recently published study by Wrensch et al (186), which approached

statistical significance (OR = 0.48, 95% CI = 0.21-1.09, $p = 0.08$). Despite the different findings, the Ezer, de Roos, and Wrensch studies were all completed in the United States. Both de Roos and Wrensch used frequency matching and no significant demographic differences between the cases and controls for any of the studies were mentioned. Due to the inconsistency across the studies, it was not appropriate to report the overall point estimate and 95 percent confidence interval.

4.3.4.g. *GSTP* Ile105Val Val/Val Genotype and Astrocytoma

Ezer et al (182), de Roos et al (188), and Wrensch et al (186) all examined the association between astrocytoma and the Val/Val genotype at codon 105 on the *GSTP* gene. There was little consistency in the results across the three studies ($I^2 = 80.8\%$). Both the Ezer and the Wrensch studies found lowered odds ratios (0.48 and 0.58, respectively), but each was limited to only five cases homozygous for the production of valine at codon 105 and the findings were not statistically significant. Interestingly, the findings of de Roos were significant at the $p = 0.05$ level, but these results suggested that having the variant genotype increased one's risk for adult astrocytoma (OR = 2.46, 95% CI = 1.23-4.93, $p = 0.01$). As mentioned in the previous section, all three studies were conducted in the United States. There were no restrictions based on ethnicity and all included participants were adults. No significant differences in demographic information between the cases and the controls were found. The heterogeneity found appears to be true heterogeneity in the results and not due to methodological differences.

4.3.4.h. *GSTP* Ala114Val Ala/Val or Val/Val Genotype and Astrocytoma

The same three papers which examined the SNP on codon 105 and astrocytoma also evaluated the association between either the Ala/Val or Val/Val genotype on codon 114 of the *GSTP* gene and astrocytoma in adults. Again, consistency in the results of the individual studies was not found ($I^2 = 86.2\%$). There was an issue with low cell values, as both the Ezer and de Roos papers contained only nine variant cases. The findings of de Roos and Wrensch closely mirrored one another, each producing a non-significant point estimate between 1.2-1.3. The Ezer paper however found an extremely significant elevated odds ratio for adult astrocytoma (OR = 9.99, 95% CI = 3.87-25.81, $p < 0.001$). As mentioned, this was based on only nine variant cases and only nine of the 898 controls had a variant allele as well. The author also notes that the Ezer study consisted of control data derived from previous literature, so caution should be taken in the interpretation of these results.

4.3.4.i. *GSTM1* Null Genotype and Oligodendroglioma

For the possible association between oligodendroglioma in adults and the *GSTM1* null genotype, only three studies were found (182,186,188). There was great variability amongst the individual results of the included studies ($I^2 = 80.4\%$). Only the finding of a lowered risk of oligodendroglioma by de Roos et al (188) was significant at the $p = 0.05$ level (OR = 0.38, 95% CI = 0.20-0.72), though Wrensch et al (186) did produce a non-significant point estimate of less than 1.0 (OR = 0.96, 95% CI = 0.62-1.51). The Ezer case-control investigation indicated a non-significant elevated risk of adult

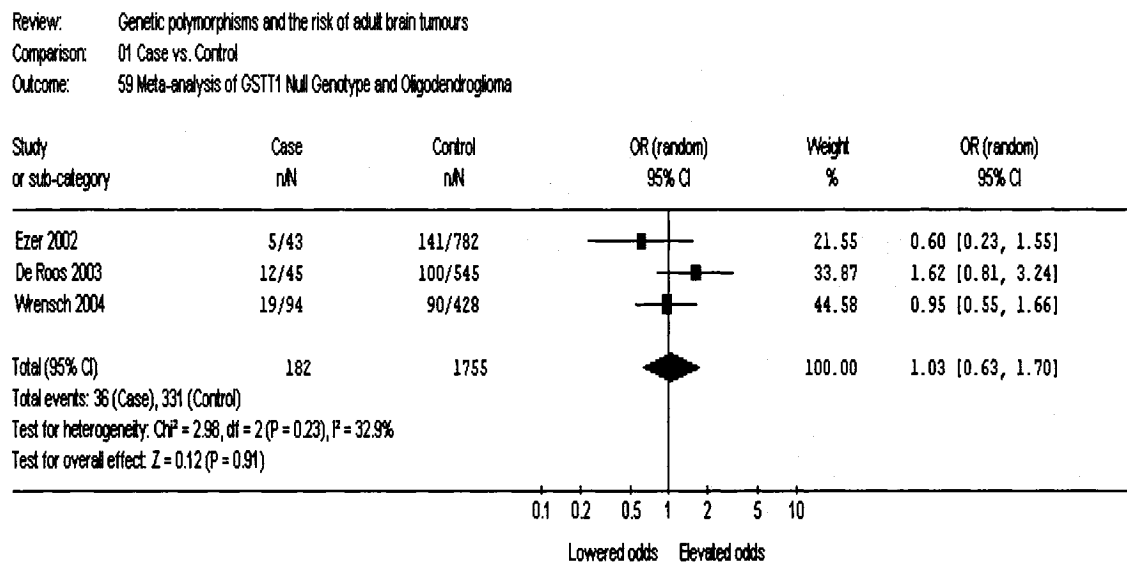
oligodendroglioma associated with the *GSTM1* null genetic polymorphism (OR = 1.59, 95% CI = 0.86-2.96). Wiencke et al (185) reported a more than two-fold increase in risk, but this finding was based on white participants included in the Wrensch study and consisted of only 10 cases with the polymorphism and 15 cases in total. The difference in the findings between the Wrensch study, which included all ethnicities in the San Francisco Bay Area adult glioma study, and the Wiencke study suggests that the association between the *GSTM1* null genotype and oligoastrocytoma may be influenced by ethnic differences. Further study which separates the included cases and controls by ethnicity is needed.

4.3.4.j. *GSTT1* Null Genotype and Oligodendroglioma

A total of three case-control studies were found that looked at the possible association between oligodendroglioma in adults and the *GSTT1* null polymorphism. As can be seen in figure 12, the overall point estimate suggests a slight increase in odds linked to the presence of the SNP, but this increase is not significant (OR = 1.03, 95% CI = 0.63-1.70). This is based on 182 oligodendroglioma cases, 36 of whom are genotypic variants, and 1755 adult controls, which includes 331 variants.

The results generated by each of the studies are not similar, with two papers suggesting a lowered risk of oligodendroglioma and one implying that one's odds are elevated with the presence of the *GSTT1* null polymorphism. However, the I^2 value of 32.9% suggests that the results are consistent enough for a quantitative data synthesis to be appropriate.

Figure 12: Odds of oligodendroglioma in adults associated with *GSTT1* null genotype: pooled results from three case-control studies.



4.3.4.k. *GSTP* Ile105Val Val/Val Genotype and Oligodendroglioma

There were only three eligible studies (182,186,188) to be assessed for the association of the Val/Val genotype on codon 105 of the *GSTP* gene and adult oligodendroglioma. Each found lowered odds of oligodendroglioma associated with the SNP at codon 105 and the I^2 statistic was 0%. Overall, the odds ratio was less than 1.0 at 0.78, but this was not found to be statistically significant (95% CI = 0.45-1.36). Included in these three studies were 182 cases and 2704 controls, however only 16 cases and 286 controls were found to be homozygous for the SNP. The findings of Ezer and de Roos were based on just one and four variant cases, respectively, and neither was statistically significant (Ezer: OR = 0.21, 95% CI = 0.03-1.57; de Roos: OR = 0.84, 95% CI = 0.29-2.43).

4.3.4.l. *GSTP* Ala114Val Ala/Val or Val/Val Genotypes and Oligodendroglioma

The case-control studies conducted by Ezer et al (182), de Roos et al (188), and Wrensch et al (186) also included an evaluation of the association between the Ala/Val and/or Val/Val genotypes at codon 114 of the *GSTP* gene and oligodendroglioma in adults. There was little consistency between the results of the included studies ($I^2 = 88.1\%$). The Wrensch study had the greatest number of variant cases, but this only represented 14 individuals. The Ezer case-control study had only five variant cases and nine controls with the SNP. Despite these low numbers of observed variants, Ezer did report a significant raise in odds, though the confidence intervals were extremely wide (OR = 13.00, 95% CI = 4.16-40.66). Supporting these findings, de Roos also reported a significant point estimate of greater than 1.0 (OR = 2.19, 95% CI = 1.09-4.40). Contrary to this, the most recently published study by Wrensch found decreased odds of oligodendroglioma associated with the polymorphism, but this result was not statistically significant (OR = 0.93, 95% CI = 0.50-1.73).

4.3.4.m. *GSTM1* Null Genotype and Meningioma

Only three studies were eligible for inclusion in the quantitative data synthesis of the association between the *GSTM1* null genotype and adult meningioma. The case-control reports of Elexpuru-Camiruaga (187), de Roos (188), and Pinarbasi (184) together contributed 241 cases and 1305 controls, of which 122 meningioma patients and 673 hospital-based controls were identified as having the variant genotype. Again, a great deal of disparity was found amongst the individual study results ($I^2 = 71.9\%$). The Pinarbasi study of Turkish individuals found a significant increased risk of meningioma

associated with the *GSTM1* null genotype (OR = 2.87, 95% CI = 1.17-7.05). This study used hospital-based controls that were frequency matched to cases by age and sex. No quality control measures were reported, but a significantly greater percentage of the cases smoked compared to the controls. The findings of Elexpuru-Camiruaga suggested very little change in risk associated with the SNP (OR = 1.02, 95% CI = 0.57-1.83). The controls for this study were also hospital-based, though no matching strategy was employed. All of the included participants were whites from the UK and there were no differences mentioned in demographic details, nor were quality control measures discussed. Finally, the results of de Roos propose that the presence of the SNP may lower one's risk of adult meningioma, but this difference was not significant (OR = 0.78, 95% CI = 0.55-1.10). The hospital-based controls were frequency matched to cases by age, sex, ethnicity, and the proximity of their home to the hospital. Based on these three studies, it is possible that geographic location may influence the potential association between *GSTM1* null and meningioma, but further study is required.

4.3.4.n. *GSTT1* Null Genotype and Meningioma

Similar to the analysis of *GSTM1* null genotype, the quantitative synthesis of the association of the *GSTT1* null genotype and adult meningioma was restricted to the findings of Elexpuru-Camiruaga et al (187), de Roos et al (188), and Pinarbasi et al (184). Taken together, a total of 229 cases (65 with the variant genotype) and 1192 controls (222 with the variant genotype) were eligible for inclusion in the analysis, ranging from a low of 176 participants in the Elexpuru-Camiruaga study to a high of 704 individuals in the de Roos hospital-based case-control study.

Each of the three studies all produced point estimates of greater than 1.0, ranging from 1.39 (95% CI = 0.51-3.82) in the Pinarbasi study to 3.58 in Elexpuru-Camiruaga (95% CI = 1.93-6.64). de Roos et al found an odds ratio of 1.40 (95% CI = 0.91-2.14). It is interesting to note that despite the common finding of elevated odds amongst the included investigations, there was still a significant amount of disparity between the three case-control studies ($I^2 = 68.6\%$). This is a result of the Elexpuru-Camiruaga study, whose point estimate is more than 2.5 times greater than the odds ratios of both of the other studies. The de Roos and Pinarbasi findings closely mirror one another ($I^2 = 0\%$), implying that the difference in the confidence intervals of these two studies is only due to their relative size.

4.3.4.o. *GSTP* Ile105Val Val/Val Genotype and Meningioma

It was not possible to conduct a data synthesis for the association of the homozygous variant Val/Val genotype at codon 105 on the *GSTP* gene and meningioma. Only two case-control studies were found that addressed the issue, and of these, only de Roos et al (188) considered the homozygous variants separate from the heterozygotes. The Pinarbasi et al case-control study (184) grouped all variants, whether homozygous or heterozygous, and compared the risk of meningioma to participants with the Ile/Ile genotype.

While both of the studies found a lowered risk of adult meningioma associated with the SNP, neither was statistically significant. De Roos found 12 variant cases amongst their 172 meningioma patients, and 59 of the 604 controls had the Val/Val genotype. This corresponds to an odds ratio of 0.69 (95% CI = 0.36-1.32). The point

estimate for Pinarbasi was 0.75 (95% CI = 0.32-1.78), based on eight of 75 cancer patients having at least one variant allele and 21 of the 153 controls.

4.3.4.p. GSTP Ala114Val Ala/Val or Val/Val Genotype and Meningioma

The hospital-based case-control study of American participants produced by de Roos et al (188) was the sole article retrieved that looked at the association of meningioma in adults with the variant Ala/Val or Val/Val genotypes at codon 114 on the *GSTP* gene. A total of 776 participants were included in the analysis, 172 cases and 604 controls, of which 21 meningioma cases had a variant allele and 78 of the controls. The odds ratio was slightly lower than 1.0 at 0.94, with a 95 percent confidence interval of 0.56-1.57.

4.3.5. *Results of Studies Involving Excision Repair Cross-complementation Genes*

The *excision repair cross-complementing (ERCC)* genes *ERCC1* and *ERCC2* both play an important role in the DNA repair process. Found on chromosome 19q13.3 near a putative glioma suppressor region, both *ERCC1* and *ERCC2* form products which are involved in the nucleotide excision repair complex (191). Mice cells lacking the *ERCC1* gene have shown high levels of genomic instability, lowered frequency of proper chromosome exchange, and a repair-deficient phenotype (192). It has been hypothesized that the product of the *ERCC1* gene is necessary for both the removal of DNA adducts and the re-joining of double-stranded breaks that may have been introduced as a result of exposure to ionizing radiation (192). If this is the case, then individuals who possess a deficient *ERCC1* genotype may be at an increased risk for developing brain tumours.

The subunit produced by *ERCC2* has a specific role in the repair of cells damaged by exposure to UV rays. Like *ERCC1*, *ERCC2* has also been hypothesized to be involved in repairing DNA damage induced by ionizing radiation due to its involvement in both transcription and nucleotide excision repair (193). One particular disease that has been associated with a deficient *ERCC2* gene is xeroderma pigmentosum (XP). XP individuals are at a greater risk of developing skin cancers since their ability to withstand UV-induced DNA damage is compromised (40). Previous studies of malignant brain tumour tissue have suggested a possible role for the helicase produced by *ERCC2* in glial cell tumorigenesis resulting from its role in correcting transcription-coupled DNA damage (40). It has also been postulated that polymorphisms in the *ERCC2* gene can lead to deficiencies in repairing DNA damage caused by other environmental factors, such as oxidative damage (193).

Five case-control studies regarding the association between genetic polymorphisms on the *ERCC* genes PBTs in adults were found that were deemed eligible for inclusion in this review. Of these, two looked solely at the *ERCC2* gene, one evaluated only *ERCC1*, and two studies considered the effect of polymorphisms on both genes. For the *ERCC1* gene, two different SNPs were considered: C8092A and N118N. The first is a result of an adenine in place of cytosine; the second is a cytosine in place of thymine. The analysis for the *ERCC2* gene included four SNPs: R156R, in which a cytosine is replaced with adenine; D312N, where adenine takes the place of guanine; D711D, which is a cytosine to thymine conversion; and K751Q, where an adenine is replaced with cytosine.

4.3.5.a. ERCC1 C8092 Polymorphism

Two studies were found which evaluated the association between the C8092 polymorphism on the *ERCC1* gene and PBTs in adults. The articles by Chen et al (192) and Wrensch et al (191) were both population-based case-control studies that were part of the San Francisco Bay Area adult glioma study, with the Chen study using the participants found between 1991-1995 and the Wrensch study combining the participants of the 1991-1995 series with the 1997-2000 series. The author notes that the eligible participants in the Chen paper were restricted to whites, whereas Wrensch included all ethnicities. Therefore, the Wrensch data encapsulates all of the Chen data and combining the two in a quantitative data synthesis would be incorrect.

Wrensch evaluated the risk of brain tumours associated with the polymorphism as both dominant (AA/AC vs. CC) and recessive (AA vs. AC/CC), with sensitivity analysis conducted that separated the cases into those with glioblastoma multiforme and those with non-glioblastoma multiforme. Chen stratified the cases by glioblastoma multiforme, astrocytoma, or oligoastrocytoma and evaluated the association based on the polymorphism being dominant (AA/AC vs. CC). The results for each are presented in table 24.

As seen in table 24, the only significant association found was between individuals either homozygous or heterozygous for the polymorphism and oligoastrocytoma in which a reduction in risk was reported. However, this finding is based on only five heterozygous cases and zero homozygous cases, so caution should be taken in interpreting these results.

Table 24: Results of case-control evaluation of the association of genetic polymorphisms on the *ERCC1* gene and primary brain tumours in adults: data from two studies.

Polymorphism	Tumour Type	First Author	Cases			Controls			Odds Ratio & 95% CI
			CC	AC	AA	CC	AC	AA	
C8092A	All	Wrensch	238	176	36	267	212	29	<u>Control=CC</u> 0.99 (0.76-1.28) <u>Control=AC/CC</u> 1.44 (0.86-2.42)
C8092A	GBM	Wrensch	115	84	21	267	212	29	<u>Control=CC</u> 0.97 (0.71-1.34) <u>Control=AC/CC</u> 1.67 (0.93-3.02)
C8092A	Non-GBM	Wrensch	123	92	15	267	212	29	<u>Control=CC</u> 1.00 (0.72-1.40) <u>Control=AC/CC</u> 1.10 (0.55-2.17)
C8092A	Astro-Cytoma	Chen	20	11	1	81	70	8	<u>Control=CC</u> 0.62 (0.29-1.36)
C8092A	Oligo-astro.	Chen	23	5	0	81	70	8	<u>Control=CC</u> 0.23 (0.08-0.62)

4.3.5.b. *ERCC1* N118N Polymorphism

There was only one eligible case-control study found which evaluated the possible association of the N118N SNP on *ERCC1* and adult brain tumours. Yang et al (194) conducted a population-based case-control study using American participants. The cases were divided into those with glioma, astrocytoma, and oligodendroglioma. However, no data was available regarding the number of individuals with each genotype. Only the percentage of each of the C and T alleles was given, making it impossible to calculate an odds ratio. An attempt was made to contact the author of the study, but no response was received. It is noted that there were no significant differences between the allelic distribution in any of the case groups and the controls.

4.3.5.c. ERCC2 R156R Polymorphism

Four studies looked at the association of the *ERCC2* R156R polymorphism and PBTs in adults. Yang et al (194) conducted a population-based case-control study, but did not provide the number of individual cases and controls with each genotype, so this data could not be included in a quantitative data synthesis. No statistically significant differences were found in the allelic distribution amongst the cases and the controls. The information obtained in the Caggana et al study (40) pertains to the first series of the San Francisco Bay Area adult glioma study, all of which is contained in the Wrensch et al paper (191), so data synthesis using these two papers is inappropriate. However, the authors do report elevated odds ratios associated with the polymorphism in white tumour patients, including significantly elevated point estimates for all PBT cases (OR = 2.1, 95% CI = 1.2-3.8) and for those with GBM (OR = 2.6, 95% CI = 1.3-5.5).

Sadetzki et al (193) considered the possible association between the R156R polymorphism and meningioma amongst Israeli adults. A total of 211 meningioma cases and 210 controls were included in the analysis. Odds ratios were found to be non-significantly elevated when the SNP was considered as dominant (AA/AC vs. CC: OR = 1.53, 95% CI = 0.94-2.48) and recessive (AA vs. AC/CC: OR = 1.06, 95% CI = 0.70-1.59).

The results of the San Francisco Bay Area adult glioma study presented in Wrensch evaluated the association of the SNP, as both dominant and recessive, in 419 cases and 519 healthy controls. Cases were further separated according to whether they had GBM (n = 203) or non-GBM tumours (n = 216). There were no significant findings found. Lowered odds ratios were associated with both dominant and recessive variants

for all cases taken together (OR = 0.88, 95% CI = 0.66-1.16 and OR = 0.98, 95% CI = 0.71-1.36, respectively), as well as for the dominant form in GBM cases (OR = 0.74, 95% CI = 0.53-1.05) and the recessive form in non-GBM cases (OR = 0.95, 95% CI = 0.63-1.42). The only slightly elevated odds ratios were associated with the dominant variant form in non-GBM cases (OR = 1.03, 95% CI = 0.73-1.47) and the recessive allele in cases with GBM (OR = 1.02, 95% CI = 0.68-1.53).

4.3.5.d. ERCC2 D312N Polymorphism

One case-control study was found which addressed the possible association between the D312N SNP on the *ERCC2* gene and adult brain tumours. Caggana et al (40) performed a case-control analysis of 135 cases and 137 population-based controls. All of the included participants were white Americans, and the analysis was restricted to the impact of the SNP as a dominant variant (AG/AA vs. GG). The histology of the cases was considered, with cases being separated into those with GBM (n = 51), astrocytoma (n = 29), and oligoastrocytoma (n = 19). All of the point estimates were below 1.0, but none reached statistical significance. However, the association between the D312N SNP and GBM approached significance (OR = 0.57, 95% CI = 0.30-1.09), as did the association with oligoastrocytoma (OR = 0.43, 95% CI = 0.18-1.02).

4.3.5.e. ERCC2 D711D Polymorphism

The published reports of Caggana et al (40) and Yang et al (194) both evaluated the association between PBTs in adults and the D711D SNP. However, a quantitative synthesis of the two studies findings is not possible because the Caggana paper looks at

individuals with GBM, astrocytoma, and oligoastrocytoma, whereas the Yang paper deals with oligodendroglioma cases only. Caggana includes 114 adult PBT cases, of which 45 have GBM, 24 have astrocytoma, and 19 have oligoastrocytoma. The estimate made in Yang is based on 40 cases and 109 controls. Both papers used the homozygous normal genotype (CC) as the referent category against those with either the CT or TT genotypes. The point estimate for all cases of PBTs in the Caggana study was 0.78, with a 95 percent confidence interval of 0.48-1.28. This trend of lowered risk associated with the D711D polymorphism was seen across each of the different histological types of tumours, though none reached statistical significance. A lowered point estimate was also reported by Yang for those cases with oligodendroglioma, but this was not statistically significant (OR = 0.57, 95% CI = 0.27-1.20).

4.3.5.f. ERCC2 K751Q Polymorphism

The Wrensch et al (191) and Caggana et al (40) papers were the only two papers found that evaluated the association between the K751Q genetic polymorphism on the *ERCC2* gene and adult brain tumours. Both used the same patient population, though the Caggana paper was restricted to whites enrolled between 1991 and 1995, whereas the Wrensch paper included participants of all ethnicities and covered those enrolled between 1991 and 2000. There were no significant associations established and there were no clear trends to be found. Non-significantly increased risk was found in the Caggana study for all tumour types (OR = 1.46, 95% CI = 0.91-2.34) and for those cases with GBM (OR = 1.62, 95% CI = 0.88-2.96) and oligoastrocytoma (OR = 2.19, 95% CI = 0.93-5.15). The Caggana cases with astrocytoma produced a reduced point estimate (OR

= 0.92, 95% CI = 0.40-2.09). Wrensch also found elevated risk associated with all tumour types (OR = 1.25, 95% CI = 0.85-1.83) and GBM (OR = 1.31, 95% CI = 0.82-2.08), while for non-GBM the point estimate was below 1.0 (OR = 0.93, 95% CI = 0.68-1.28).

4.3.6. Results of Studies Involving CYP (Cytochrome P450) Genes

The *cytochrome P450 (CYP)* genes serve a similar function as the *GST* genes, encoding enzymes which are involved in the metabolism and detoxification of a variety of chemicals in the body. Acting in a positive feedback system, the *CYP2E1* gene produces an enzyme which metabolizes and activates an assortment of solvents, including benzene, styrene, carbon tetrachloride, ethylene glycol, and ethanol, which in turn induce further expression of the gene (188). The *CYP2D6* gene responds to environmental challenges generated by environmental exposure to carcinogens such as polycyclic aromatic hydrocarbons (PAHs), nitrosureas, and methyl halides, which serve as substrates for the enzymes formed by the gene (187). The enzyme coded for on the *CYP2D6* gene has also been proposed to be involved in the metabolism of nicotine (189). Finally, the *CYP1A1* gene codes for the enzyme aryl hydrocarbon hydroxylase, whose function is to metabolize PAHs.

Individuals with variant genetic sequences on the *CYP* genes differ in their ability to metabolize the various environmental compounds, which can lead to an altered risk of cancer. Two variant forms of the *CYP2E1* gene have been identified, *RsaI* and *Ins96*, which have been hypothesized to play a role in the development of primary brain tumours (188). Genetic polymorphisms on the *CYP2D6* gene produce a phenotype known as

“poor metabolizers” (PM), an autosomal recessive trait which allows for molecules to remain in the cytoplasm and collect, which over time may become carcinogenic or mutagenic (195). As a result, it has been proposed that this variant genotype can lead to an altered risk of brain tumours. The variant Val/Val genotype of the *CYP1A1* gene leads to the biotransformation of PAHs into reactive diol epoxide metabolites. These metabolites have carcinogenic potential, leading to the consideration of this polymorphism as a potential risk factor for PBTs in adults (196).

4.3.6.a. *CYP2E1* Polymorphisms

The hospital-based case control study conducted by de Roos et al (188) was the only paper found that considered the association between genetic polymorphisms in *CYP2E1* and the odds of adult brain tumours. The authors looked at two variant forms, RsaI and Ins96, and included both heterozygotes and homozygotes as variants. The analysis of the RsaI polymorphism included 568 cases and 573 controls, with 46 of the cases and 33 of the controls presenting the variant genotype of interest. The Ins96 polymorphism had 32 variant cases from a pool of 572 cases and 40 of the 575 controls also had the polymorphism present. The cases were further separated according to histology into those with glioma and those with meningioma.

In the overall analysis of RsaI, an elevated point estimate was associated with the variant genotype, but this result was not statistically significant (OR = 1.44, 95% CI = 0.91-2.29). In contrast to this, individuals that were heterozygous or homozygous variants for Ins96 were at a reduced risk of having a PBT compared to homozygous non-variants, but again this was not significant (OR = 0.79, 95% CI = 0.49-1.28). When the

analysis was limited to those cases with glioma the findings were similar, with a non-significant odds ratio of 1.47 (95% CI = 0.89-2.43) for RsaI and 0.66 (95% CI = 0.38-1.16) for Ins96. For the meningioma cases, the point estimate of RsaI was again non-significantly elevated (OR = 1.37, 95% CI = 0.70-2.67), however de Roos found that for meningioma, having the variant Ins96 genotype increased one's odds, though the finding was not statistically significant (OR = 1.12, 95% CI = 0.59-2.15).

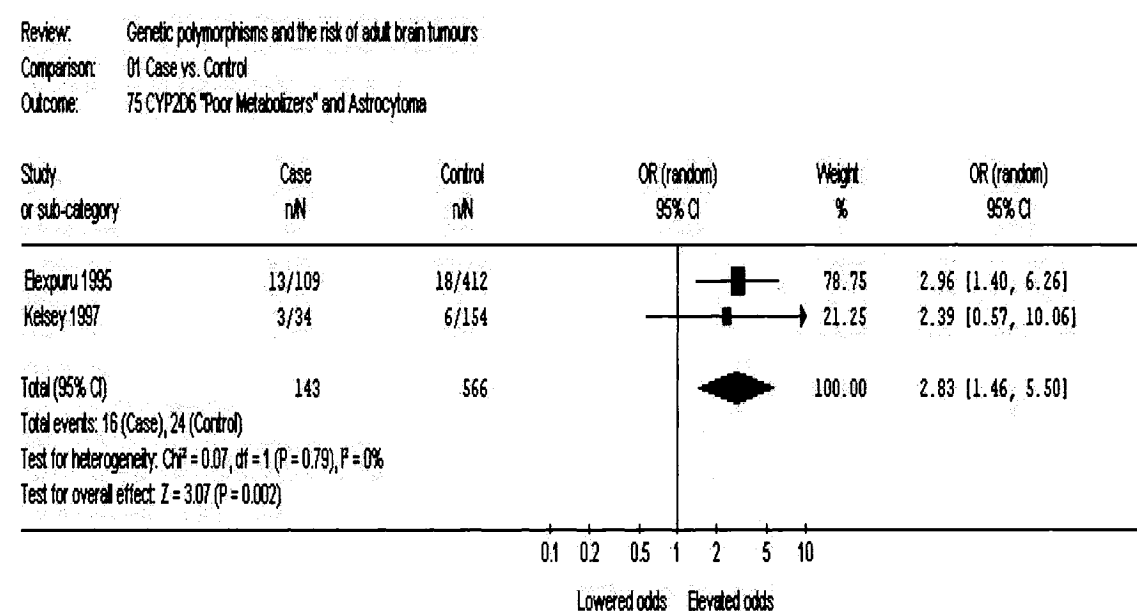
4.3.6.b. CYP2D6 Polymorphisms

For the analysis of the association between SNPs on the *CYP2D6* gene and adult brain tumours, three separate eligible studies were found. Elexpuru-Camiruaga et al (187) conducted a hospital-based case-control study in the United Kingdom using adult whites. 157 cases divided into those with astrocytoma (n = 109) and those with meningioma (n = 48) were included, along with 412 controls. Wundrack et al (195) evaluated 31 German cases of meningioma and 720 white controls. Kelsey et al (189), as part of the San Francisco Bay Area adult glioma study, genotyped 151 cases of PBTs, including 86 with GBM, 34 with astrocytoma, and 15 with oligodendroglioma, and compared these individuals to 154 population-based controls. Since the *CYP2D6* is an autosomal recessive trait (195), homozygous variants were compared against homozygous normal and heterozygous individuals when calculating odds ratios.

Figure 13 is the forest plot representing the quantitative data synthesis of the association between the variant *CYP2D6* phenotype and astrocytomas in adults. The Elexpuru-Camiruaga and Kelsey studies resulted in a total of 143 cases, for which 16 homozygous variants were identified, and 566 controls, with 24 of these individuals

having the “poor metabolizer” phenotype. Overall, there was a significantly increased risk of astrocytoma associated with the polymorphism (OR = 2.83, 95% CI = 1.46-5.50), as well as within the Elexpuru-Camiruaga study (OR = 2.96, 95% CI = 1.40-6.26). Kelsey also found an elevated point estimate (OR = 2.39), but this was based on only three variant cases and six variant controls, resulting in wide confidence intervals (0.57-10.06) and a lack of statistical significance.

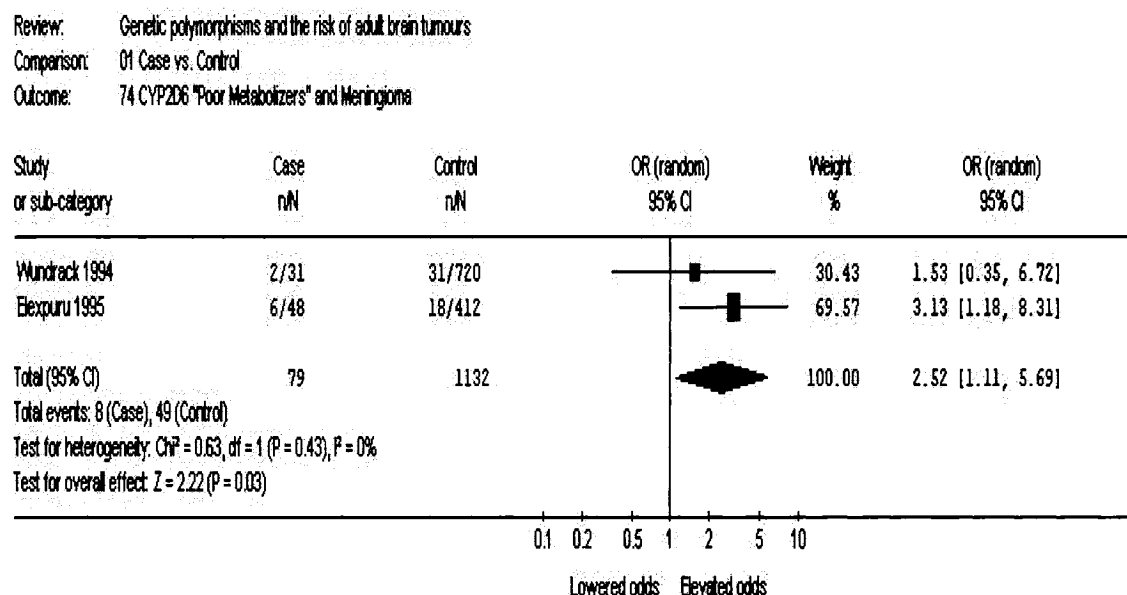
Figure 13: Odds of astrocytoma in adults associated with *CYP2D6* “poor metabolizer” phenotype: pooled results from two case-control studies.



As mentioned, the Wundrack and Elexpuru-Camiruaga studies assessed the association between the *CYP2D6* variants and meningioma in adults. The synthesis of these findings is presented in figure 14. As with astrocytoma, there was a significantly increased odds of meningioma associated with the genetic polymorphism (OR = 2.52, 95% CI = 1.11-5.69), though the odds ratio was generated on the basis of only eight total meningioma cases with the “poor metabolizer” phenotype. The point estimate of the

Elexpuru-Camiruaga study was more than two-fold higher than the Wundrack estimate (3.13 versus 1.53) and the Elexpuru-Camiruaga finding was statistically significant while the Wundrack results were not.

Figure 14: Odds of meningioma in adults associated with *CYP2D6* “poor metabolizers” phenotype: pooled results from two case-control studies.



When all PBTs in adults were considered, regardless of histology, the quantitative synthesis of the Wundrack, Elexpuru-Camiruaga, and Kelsey papers produced a point estimate of 1.98, suggesting elevated risk of PBTs associated with the *CYP2D6* “poor metabolizer” variant phenotype (forest plot not shown). The p-value for this association was 0.05, but the lower end of the 95 percent confidence interval did cross 1.0 (95% CI = 0.99-3.97), meaning that this association closely bordered statistical significance. All three studies found point estimates greater than 1.0 and the results were fairly consistent ($I^2 = 27.8\%$), suggesting a possible association.

4.3.6.c. CYP1A1 Polymorphisms

Only one eligible study was found which looked at the potential association between the variant Val/Val genotype of the *CYP1A1* gene and adult brain tumours. Trizna et al (196) compared the odds of glioma in individuals who were either homozygous for the variant or heterozygous to those who were homozygous wildtype. 18 of 90 cases had at least one of the variant alleles, compared to 13 of the 90 healthy controls, which produced an odds ratio of 1.48 (95% CI = 0.68-3.24). Due to the manner in which the data was presented in the paper, it was not possible to evaluate the point estimate restricted to those individuals who were homozygous for the variant genotype.

4.3.7. *Results of Studies Involving the p53 Gene*

The *p53* gene is involved in regulating the cellular cycle (197), encoding a nuclear phosphoprotein that serves a role in cell cycle arrest, apoptosis, and genetic stability (198). There are three different functional domains on the *p53* gene, which act to induce other genes, leading to a variety of actions including nucleotide excision repair in response to DNA damage, oligomerization, and halting cellular division (198). The gene is also part of a known tumour-suppressor region and has been shown to be a site of frequent genetic mutation (199).

Polymorphisms in the *p53* gene have been previously associated with elevated risk of cancer at numerous sites, including the breast and cervix (200). Autosomal dominant germ line *p53* mutations are also known to be associated with Li-Fraumeni syndrome, leading to a predisposition to various forms of cancer, which includes tumours of the brain (201). It has been estimated that nearly 25 percent of gliomas have a mutated

p53 gene (199) and recent research has focused on the possible association between SNPs on the *p53* gene and PBTs in adults.

Four case-control studies were included in this review which evaluated the influence that *p53* polymorphisms might have on the development of glioma, meningioma, and astrocytoma in adults. These polymorphisms occur in promoter, coding, and non-coding regions of the gene, inducing changes in the biochemical properties of the gene products (199). In the promoter region, a polymorphism has been identified at -12256 in which guanine is the nucleotide instead of the wildtype cysteine. An SNP located on the coding region exon four of codon 72 replaces a cysteine nucleotide with guanine, which in turn, leads to the production of arginine instead of proline. Intron six of the non-coding region has also been found to be a common site of genetic mutation.

4.3.7.a. *p53* Promoter Region Polymorphisms

The Malmer et al (200) population-based case-control study using Swedish participants was the only article found which evaluated the association of the C/G SNP at position -12256 of the promoter region on the *p53* gene and adult brain tumours. The 354 cases consisted of 199 glioma patients and 155 adults with meningioma. These cases were compared with 364 healthy controls. The wildtype CC genotype was used as the referent group, while the homozygous variant GG and heterozygous CG individuals were grouped together. There were 33 glioma cases with the variant allele, 37 meningioma cases, and 77 controls. For glioma alone, the point estimate was non-significantly lower than 1.0 (OR = 0.74, 95% CI = 0.47-1.16). When only the meningioma cases were

considered, the risk of PBT associated with the promoter region SNP was elevated (OR = 1.17, 95% CI = 0.75-1.83). Finally, all of the cases were evaluated together, meaning that there were 70 variant cases and 284 wildtype homozygotes. The point estimate was close to 1.0 and was not statistically significant (OR = 0.92, 95% CI = 0.64-1.32).

4.3.7.b. p53 Arg72Pro Polymorphism

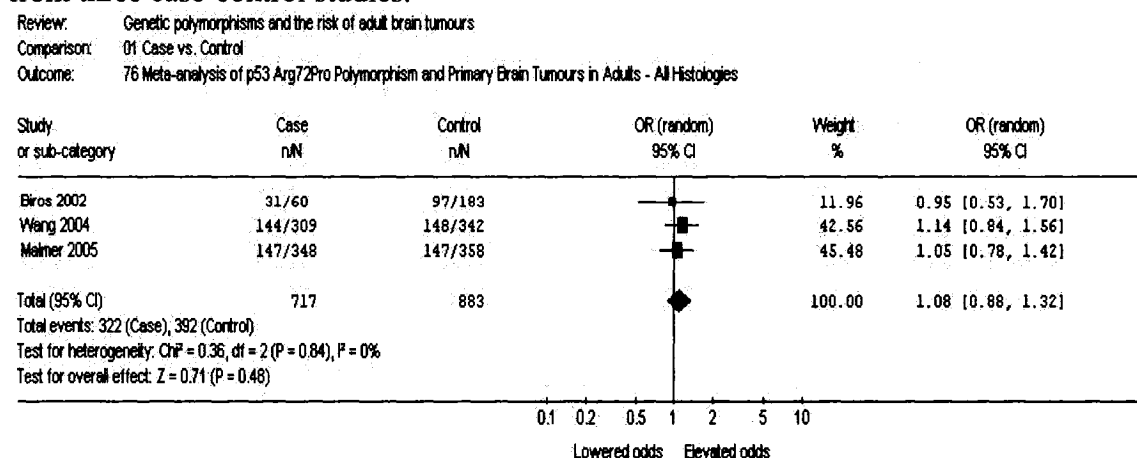
Four studies evaluated the association between the Arg72Pro polymorphism and adult PBTs. Malmer et al (200) and Wang et al (197) both considered cases with glioma; meningioma cases were only included in the Malmer case-control study; and patients with astrocytoma were part of both the Biros et al (199) and Parhar et al (198) studies. The Parhar paper also included 54 adult cases with tumours labeled as “non-astrocytoma”, which included cases of oligodendrogliomas and oligoastrocytomas, but for which no detailed breakdown for the number of each PBT type was given. Unfortunately, since the Parhar participants included both adult (n = 92) and pediatric (n = 43) cases that were not separated by age, they could not be included in the quantitative synthesis. The 309 cases of the Wang study consisted of 151 GBMs, 70 astrocytomas, and 88 “others”, which included oligodendroglioma. However, the data presented did not separate the cases by histology and attempts made by Mr. Tomson to contact the corresponding authors were unsuccessful. The same was true for the Biros data. 60 cases were genotyped, consisting of 34 meningiomas and 26 astrocytomas, but there was no separation by histology in the given results.

There were 198 glioma cases in the Malmer study that were successfully genotyped, of which 82 had at least one variant allele at codon 72, and 358 controls

which included 147 variants. Performing chi-square analysis with the homozygous wildtype as the reference led to an odds ratio of 1.01 (95% CI = 0.71-1.44). The association between the Arg72Pro polymorphism and meningioma was investigated using 150 cases and 358 controls by Malmer. 65 variant cases and 147 variant controls were identified, producing a slightly elevated non-significant point estimate of 1.10 (95% CI = 0.71-1.44).

The evaluation of the association between the Arg72Pro SNP on the *p53* gene and brain tumours of all histologies in adults included 717 cases and 883 healthy controls from the case-control studies by Biros, Malmer, and Wang. As can be seen in figure 15, there was a great deal of consistency amongst the results of the included studies ($I^2 = 0\%$). 322 of the 717 cases were either homozygous or heterozygous variants, as well as 392 of the 883 controls. This produced an overall point estimate of 1.08 (95% CI = 0.88-1.32). All three of the individual study odds ratios were very close to 1.0, with the Biros study the only one found below 1.0 (0.96) and the Wang study suggesting the greatest increase in odds of adult PBT (1.14). None reached statistical significance and all of the point estimates were located within the other studies' confidence intervals.

Figure 15: Odds of PBT in adults associated with *p53* CG/GG genotype: pooled results from three case-control studies.



4.3.7.c. p53 Intron 6 Polymorphism

The intron six polymorphism on the *p53* gene, also referred to as *p53* MspI, was investigated for its association with adult meningiomas and astrocytomas by the Biros hospital-based case-control study and for its association with gliomas and meningiomas by the Malmer population-based case-control study. As mentioned, the Biros paper did not present the data separated by histology, so their information could only be included in evaluating the association between the polymorphism and tumours of all types.

Using the CC homozygous wildtype genotype as the referent category, Malmer et al found no significant difference in the odds of glioma or meningioma associated with the variant genotypes (OR = 0.92, 95% CI = 0.59-1.42). Of the 192 cases, 38 were found to be variants compared to 74 variants amongst the 349 controls. The odds ratio was found to be similar for meningioma (OR = 0.93, 95% CI = 0.58-1.49). There were a total of 155 meningioma cases, of which 31 had either the CT or TT genotype.

For the association between the *p53* intron six polymorphism and all tumour types using the Biros and Malmer data, an overall non-significant point estimate of 0.95 was found (95% CI = 0.69-1.31). 86 of the 407 total cases were genotypic variants, compared to 124 of the 532 controls. The results of the two studies were similar ($I^2 = 0\%$), despite the fact that the Biros study produced an elevated odds ratio (1.05, 95% CI = 0.55-2.01) and the point estimate for Malmer et al was less than 1.0 (0.92, 95% CI = 0.64-1.33).

4.3.8. *Results of the Other Included Studies*

The remaining studies in the systematic review were not considered for quantitative data synthesis because of a paucity of information for the particular genetic

polymorphisms. This included all of those polymorphisms for which only one or two studies could be found which addressed the possible association with PBTs in adults. Table 25 provides the odds ratios, 95 percent confidence intervals, and associated p-values for each of these studies and the various polymorphisms which they investigated. Also included in this table are the results of studies included in sections 4.3.3.-7 that considered other polymorphisms on genes not covered in those sections.

There were 18 significant associations at the $p = 0.05$ level of statistical significance found amongst the 92 different genotypic polymorphisms covered in table 25. Each one of these 18 significant associations was restricted to analysis by only one study, so it was not possible to perform any quantitative synthesis. For three of the 18 associations, the cases consisted of all tumour types. Seven were restricted to GBM only, four to glioma, three to meningioma, and one to oligodendroglioma.

Platten et al (202) found a highly significant increase in the risk of brain tumours associated with a polymorphism adjacent to the 3' splice site of intron four on the *Tuberous Sclerosis 2* gene (OR = 2.48, 95% CI = 1.52-4.06). This finding was significant only when individuals that were either homozygous or heterozygous for the SNP were considered; homozygous alone did produce an elevated odds ratio (OR = 3.16, 95% CI = 0.57-17.38), but due to low numbers of cases ($n = 4$) and controls ($n = 2$) homozygous for the SNP, this result did not reach statistical significance. The hospital-based case-control study by Zhou et al (203) found a nearly three-fold increase in the risk of GBM associated with *Peroxisome Proliferator Activated Receptor H449H* heterozygotes (OR = 2.74, 95% CI = 1.46-5.16), based on 31 variants among the 95 cases compared to 21 of the 140 controls.

Table 25: Odds ratios, 95 percent confidence intervals, and associated p-values for the evaluation of the association between genetic polymorphisms and PBTs in adults: results from 37 studies.

First Author	Polymorphism Studied	Type of Tumour	Genotype	Odds Ratio	95% CI	P-value
Koopman ¹	<i>WAF1/CIP1</i> Arg31Ser	All	Arg/Ser & Ser/Ser	0.86	0.47-1.54	0.60
Platten	<i>TSC2</i> Intron 4/Exon 5 Splice Site	All	A2/A2	3.16	0.57-17.38	0.19
			A1/A2 & A2/A2	2.48	1.52-4.06	<0.0001
Rothberg	<i>RB</i> Intron 2 Deletion	All	Homozygous variants	2.77	0.54-14.14	0.22
		GBM	Homozygous variants	7.38	0.69-79.01	0.10
		Meningioma	Homozygous variants	2.21	0.25-19.46	0.47
Trizna	<i>NAT2</i> "Slow" Acetylator	Glioma	Slow (phenotype)	0.61	0.32-1.17	0.14
Kondratieva	<i>L-MYC</i> "Small" EcoRI Sensitive	Glioma	S/S	0.97	0.44-2.14	0.94
			S/S & S/L	0.97	0.47-2.00	0.93
Nishimori	<i>PCAF</i> Asn386Ser	Glioma	Asn/Ser	0.45	0.16-1.24	0.12
Zhou	<i>PPARγ</i> P12A	GBM	C/G	1.63	0.88-3.03	0.12
	<i>PPARγ</i> H449H	GBM	Heterozygotes	2.74	1.46-5.16	0.002
Peters	<i>NAT2</i> "Slow" Acetylator	Glioma	Slow (phenotype)	1.47	0.93-2.31	0.10
	<i>NQO1</i> C609T	Glioma	C/T & T/T	0.95	0.61-1.50	0.84
Reis	<i>hBUB3</i> ATG Initiator Codon C-6T	GBM	C/T & T/T	1.26	0.35-4.60	0.73
Vega	<i>HRAS1</i> Rare Alleles	All	1 or 2 Rare Alleles	2.00	0.93-4.27	0.08
		Glioma	1 or 2 Rare Alleles	2.72	1.17-6.32	0.02
		Meningioma	1 or 2 Rare Alleles	1.70	0.59-4.92	0.32
Sasaki	<i>DMBT1</i> Deletion 2-4/2-7	All	Homo- & Heterozygous Variants	0.79	0.38-1.64	0.53
	<i>DMBT1</i> SNP at 5' Upstream Region	All	Homo- & Heterozygous Variants	0.72	0.38-1.35	0.30
Baeza ²	<i>AXIN1</i> Codon 31 A94C	GBM	N/A	N/A	N/A	N/A
	<i>AXIN1</i> Intron 4 G16A					
	<i>AXIN1</i> Codon 291 C874T					
	<i>AXIN1</i> Codon 657 C874T					
Inoue	<i>MGMT</i> Leu84Phe	All	C/T & T/T	0.81	0.42-1.59	0.55
		GBM	C/T & T/T	2.50	1.03-6.05	0.04
Leone ³	<i>RAD54L</i> C2290T	Meningioma	C/T	S ⁴ : 0.36	0.08-1.66	0.19
				E ⁵ : 11.29	5.07-25.14	<0.0001

Table 25 (Cont): Odds ratios, 95 percent confidence intervals, and associated p-values for the evaluation of the association between genetic polymorphisms and PBTs in adults: results from 37 studies.

Bhowmick	EGF 5' Untranslated Region	GBM	G/G	3.07	1.09-8.62	0.03
Sciacca			A/G & G/G	1.55	0.68-3.57	0.30
	F2 G20210A	All	G/A	1.19	0.51-2.74	0.69
	F5 G1691A	All	G/A	0.18	0.04-0.83	0.03
	MTHFR C677T	All	T/T	0.81	0.54-1.21	0.30
	VEGF C936T	All	T/T	1.08	0.31-3.78	0.90
	PAI-1 4G/5G	All	5G/5G	1.62	1.08-2.43	0.02
Wang	PLAT tPA Deletion	All	Deletion/Deletion	1.00	0.68-1.49	0.98
	XRCC1 Arg399Gln	Glioma	Gln/Gln	0.81	0.51-1.29	0.38
			Arg/Gln & Gln/Gln	0.81	0.59-1.11	0.19
	XRCC3 Thr241Met	Glioma	Met/Met	0.83	0.53-1.32	0.44
			Thr/Met & Met/Met	0.98	0.72-1.34	0.92
	XRCC7 G6721T	Glioma	T/T	1.20	0.88-1.65	0.25
			G/T & T/T	1.82	1.13-2.92	0.01
	RAD51 G135C	Glioma	C/C	N/A ⁶	N/A	N/A
			G/C & C/C	1.22	0.77-1.92	0.40
	PDGFR4 Exon 1 C-1074A	All	C/A & A/A	2.40	0.49-11.80	0.28
De Bustos						
Degerli Sadetzki	CCR5 delta-32 Allele	All	Heterozygous Variants	N/A ⁷	N/A	N/A
	NF2 Rs731647	Meningioma	T/T	1.20	0.61-2.33	0.60
			A/T & T/T	0.96	0.57-1.60	0.86
	Ki-ras Rs9266	Meningioma	C/C	1.75	1.01-3.04	0.05
			T/C & C/C	1.89	1.17-3.05	0.01
	p16 Rs2811708	Meningioma	T/T	1.30	0.62-2.73	0.49
			G/T & T/T	0.94	0.62-1.43	0.77

Table 25 (Cont): Odds ratios, 95 percent confidence intervals, and associated p-values for the evaluation of the association between genetic polymorphisms and PBTs in adults: results from 37 studies.

Sadetzki	<i>Cyclin D1</i> Rs647451	Meningioma	T/T	1.33	0.78-2.28	0.30
	<i>PTEN</i> Rs1234214	Meningioma	C/T & T/T	1.21	0.76-1.93	0.43
			A/A	1.28	0.72-2.29	0.40
	<i>E-cadherin</i> Rs2010724	Meningioma	C/A & A/A	1.12	0.74-1.69	0.60
			A/A	1.21	0.71-2.05	0.49
	<i>TGFBI</i> Rs2241715	Meningioma	G/A & A/A	1.24	0.77-2.01	0.37
			G/G	1.33	0.77-2.27	0.30
	<i>TGFBR2</i> Rs877572	Meningioma	T/G & G/G	1.13	0.70-1.83	0.61
			G/G	0.80	0.52-1.21	0.28
	<i>XRCC1</i> Rs1001581	Meningioma	C/G & G/G	0.87	0.59-1.29	0.49
Yang			T/T	1.04	0.57-1.89	0.90
	<i>XRCC3</i> Rs861539	Meningioma	C/T & T/T	0.93	0.64-1.36	0.71
			C/C	1.11	0.62-1.98	0.73
	<i>XRCC5</i> Rs828699	Meningioma	T/C & C/C	1.07	0.63-1.83	0.80
			T/T	1.59	0.93-2.69	0.09
	<i>GLTSCR1</i> Exon 1 S397S	Oligodendroglioma	G/T & T/T	1.45	0.95-2.23	0.08
			T/T	3.38	1.06-10.82	0.04
	<i>IL-4RA</i> Ser478Pro	GBM	C/T & T/T	1.93	0.92-4.07	0.08
			C/C	0.95	0.31-2.90	0.93
	<i>IL-4RA</i> Gln551Arg	GBM	T/C & C/C	1.61	1.04-2.49	0.03
Schwartzbaum			G/G	2.24	1.06-4.72	0.03
	<i>IL-13</i> Arg130Gln	GBM	A/G & G/G	0.99	0.65-1.49	0.95
			A/A	0.46	0.14-1.57	0.22
	<i>IL-13</i> -1112 C/T	GBM	G/A & A/A	0.74	0.47-1.15	0.17
			T/T	0.76	0.22-2.68	0.67
	<i>ADAM33</i> T1	GBM	C/T & T/T	0.55	0.33-0.93	0.02
			C/C	0.58	0.13-2.63	0.48
	<i>COX-2</i> -765 G/C	GBM	T/C & C/C	0.79	0.48-1.29	0.35
			C/C	0.46	0.06-3.69	0.46
			G/C & C/C	0.89	0.55-1.43	0.62

Table 25 (Cont): Odds ratios, 95 percent confidence intervals, and associated p-values for the evaluation of the association between genetic polymorphisms and PBTs in adults: results from 37 studies.

Tang	<i>HLA A24</i>	Glioma	Homo- & Heterozygous Variants	0.97	0.53-1.78	0.92
	<i>HLA A25</i>	Glioma	Homo- & Heterozygous Variants	0.75	0.25-2.21	0.60
	<i>HLA B27</i>	Glioma	Homo- & Heterozygous Variants	1.01	0.43-2.41	0.98
	<i>HLA DRB1*15</i>	Glioma	Homo- & Heterozygous Variants	1.02	0.61-1.70	0.95
	<i>HLA DRB1*07</i>	Glioma	Homo- & Heterozygous Variants	0.88	0.52-1.49	0.63
	<i>HLA B07</i>	Glioma	Homo- & Heterozygous Variants	2.56	1.48-4.44	<0.001
	<i>HLA B13</i>	Glioma	Homo- & Heterozygous Variants	5.34	1.15-24.81	0.03
	<i>HLA Cw01</i>	Glioma	Homo- & Heterozygous Variants	0.34	0.12-0.97	0.04
	<i>TNFB b4</i>	Glioma	Homozygous Variants	1.58	0.88-2.83	0.13
	<i>MMP-1 Promoter 1G Allele</i>	GBM	1G/1G	0.43	0.18-1.02	0.06
McCready			2G/1G	0.40	0.18-0.91	0.03
Miller	<i>MDR1 C3435T</i>	Glioma	T/T	0.84	0.59-1.18	0.31
			C/T & T/T	0.91	0.69-1.20	0.51
Rajaraman	<i>ALAD G177C</i>	All	1-2 & 2-2	1.05	0.76-1.46	0.75
		Glioma	1-2 & 2-2	0.89	0.61-1.29	0.53
		Meningioma	1-2 & 2-2	1.49	0.96-2.32	0.08

¹ Study included five other SNPs for which odds ratios were not appropriate due to either no variant cases or no variant controls.

² Not possible to determine the number of controls with each genotype. Inquiries to the corresponding author were made, but no response was received.

³ Due to significant differences in population characteristics, results for the Spanish and Ecuadorian participants were considered separately.

⁴ S = Spanish results.

⁵ E = Ecuadorian results.

⁶ There were no controls with the C/C genotype.

⁷ There were no cases with the *CCR5 delta-32* allele.

The Vega et al study (204) found a significantly elevated risk of glioma (OR = 2.72, 95% CI = 1.17-6.32) associated with the presence of rare *HRAS1* alleles, but due to the manner in which the data was presented by the authors it was not possible to restrict the analysis to one particular polymorphism. Instead, all rare alleles were considered together, so in fact, it would be more appropriate to say that there is an association between microsatellite instability in the *HRAS1* gene and glioma. The author also notes that when all tumour types were considered together, the significant association did not remain (OR = 2.00, 95% CI = 0.93-4.27).

Inoue et al (205) considered an SNP on the *MGMT* gene and its association with PBTs in adults. While a significantly elevated odds ratio was found for GBM (OR = 2.50, 95% CI = 1.03-6.05), when the authors included all of the study participants, regardless of tumour type, the point estimate actually suggested a non-significant lowered risk of brain tumour associated with the polymorphism (OR = 0.81, 95% CI = 0.42-1.59). The Leone et al study (206) included cases and controls from Spain and Ecuador. Due to significant differences in the population demographics, the two groups were considered separately. While the Spanish group produced a non-significant odds ratio of less than 1.0 (OR = 0.36, 95% CI = 0.08-1.66), the Ecuadorian point estimate was significantly greater than 1.0 (OR = 11.29, 5.07-25.14). Only two of the 29 Spanish cases were found to have the variant genotype, whereas 30 of the 41 cases from Ecuador were found to have the polymorphism.

The hospital-based case-control study by Bhowmick et al (207) did find a three-fold significant increase in the risk of GBM associated with a SNP in the 5' untranslated region of the *Epidermal Growth Factor* gene (OR = 3.07, 95% CI = 1.09-8.62).

However, caution must be taken in interpreting these results. Though the investigation is of a previously identified polymorphism, the authors note in their discussion of the results that due to the lack of normal tissue from the cases, they were unable to determine whether the variants seen were germline genetic polymorphisms or single somatic mutations.

Sciacca et al (208) conducted a study which examined six different SNPs on various genes and considered their possible association with adult PBTs. On the gene *F5*, which codes for coagulation factor FV, heterozygotes for the polymorphism G1691A were found to be at significantly reduced risk of a brain tumour (OR = 0.18, 95% CI = 0.04-0.83). However, this was based on only two variant cases and 11 variant controls. Sciacca also found significantly increased risk of PBT associated with homozygous individuals for the 5G SNP on the *PAI-I* gene (OR = 1.62, 95% CI = 1.08-2.43), based on the findings that 72 of the 250 cases possessed the polymorphism compared to 54 of the 270 hospital-based controls.

In the analysis of the association between the G6721T polymorphism on the gene *XRCC7* and adult glioma, Wang et al (197) found an elevated odds ratio (OR = 1.82, 95% CI = 1.13-2.92) when heterozygous and homozygous variants were grouped together. This significant association did not persist when homozygous variants were considered alone, though the point estimate was still greater than 1.0 (OR = 1.20, 95% CI = 0.88-1.65). In the nested case-control study conducted by Sadetzki et al (193), SNPs on 12 different genes were considered for their association with meningiomas. There was only one polymorphism found, on the *Ki-ras* gene, which achieved statistical significance. For both homozygous variants alone and for the group of homozygous and heterozygous

variants, the point estimates were significantly greater than 1.0 (OR = 1.75, 95% CI = 1.01-3.04 and OR = 1.89, 95% CI = 1.17-3.05, respectively).

Yang et al (194) assessed the association of oligodendrogliomas and seven SNPs on six different genes, though due to the data provided in the publication, it was only possible to consider the odds of oligodendroglioma associated with the S397S polymorphism in exon one of the *Glioma Tumour Suppressor Candidate Region* gene. There was a significantly elevated odds ratio (OR = 3.38, 95% CI = 1.06-10.82) found for homozygous individuals, but this was based on only seven variant cases and eight variant controls. When individuals that were either homozygous or heterozygous for the polymorphism were grouped together and compared to homozygous wildtype participants, the point estimate dropped to 1.93 and the association was no longer significant (95% CI = 0.92-4.07).

Schwartzbaum et al (209) identified three significant associations between various polymorphisms and adult GBM. On the *Interleukin-4 Receptor Alpha* gene, the polymorphism Ser478Pro was found to be associated with a significantly increased risk of tumour (OR = 1.61, 95% CI = 1.04-2.49) when both homo- and heterozygous variants were considered together. However, when only those participants that were homozygous for the polymorphism were considered, the point estimate dropped below 1.0 and was non-significant (OR = 0.95, 95% CI = 0.31-2.90). The reverse could be said for the Gln551Arg polymorphism on the same gene. Homozygous variants were found to be at 2.24 times greater risk of GBM (95% CI = 1.06-4.72), while when homo- and heterozygous variants were grouped together, the non-significant point estimate was 0.99 (95% CI = 0.65-1.49). Finally, the *Interleukin 13* -1112 C/T polymorphism produced

lowered risk of GBM for homozygous variants alone (OR = 0.76, 95% CI = 0.22-2.68) and together with heterozygotes (OR = 0.55, 95% CI = 0.33-0.93), but only the latter was statistically significant.

As part of the San Francisco Bay Area adult glioma study, Tang et al (210) examined the relationships of human leukocyte antigen and related polymorphisms on the *HLA* gene with glioma. For each of the eight variants studied on the *HLA* gene, the authors considered all homozygous and heterozygous variant individuals together. Significant associations were found with two SNPs. The B07 variant led to a highly significant risk of adult glioma (OR = 2.56, 95% CI = 1.48-4.44), based on 49 variants amongst 144 cases and 24 variants from the 157 healthy controls. The Cw01 polymorphism was associated with a significantly lowered risk of glioma (OR = 0.34, 0.12-0.97), though this was based on just five variant cases and 14 variant controls.

The final significant association between a genetic polymorphism and adult brain tumours was found in the results of the McCready et al case-control study (211). They looked at the *Matrix Metalloproteinase-1* gene and the 1G allele. A functional SNP is known at position -1607 which leads to the presence (2G) or absence (1G) of a guanine nucleotide adjacent to another guanine at -1606. While individuals homozygous for the 1G allele were at a lower risk of GBM compared to those with the 2G/2G genotype, this result bordered, but did not reach, statistical significance (OR = 0.43, 95% CI = 0.18-1.02). When these 1G homozygotes were grouped with the heterozygotes, the point estimate was lowered to 0.40 and this finding was significant (95% CI = 0.18-0.91).

4.3.9. Sensitivity Analysis

Due to the heterogeneity amongst the studies included in this systematic review, both in terms of the polymorphism and tumour histology studied, there were very few instances where a sufficient number of studies were found in a quantitative data synthesis to warrant any sensitivity analysis. As a result, only the evaluation of the association between the *GSTM1* null genotype and all brain tumours (eight studies) and between the *GSTT1* null genotype and all histologies (seven studies) were considered for sensitivity analysis. The author assessed the impact of the study quality, the type of controls used, and the detail in reporting of the ages of the participants.

The modified version of the Black and Downs scale (152) was applied to all of the studies and scored out of a total of 17 by both Dr. Little and Mr. Tomson. The average score given was used for the purpose of the sensitivity analysis. The mean score for the *GSTM1* null analysis was 11.6, ranging from a low of 7.5 for the Kondratieva study (190) to a high of 16.5 for the Wrensch paper (186), and for *GSTT1* null the mean was 12.2, with Ezer's (182) score of 8.0 and Wrensch's 16.5 representing the extreme values. The mean scores were arbitrarily selected as the cut point for the sensitivity analysis.

For those studies which scored lower on the Black and Downs scale (182,183,190,196), the overall point estimate was 1.18 (95% CI = 0.95-1.47) and the results were consistent across the studies ($I^2 = 0\%$) for the *GSTM1* null polymorphism. However, for those studies which were deemed to be of better reporting quality, the I^2 value jumped to 71.4%, a significant level. This was due to the inclusion of the Pinarbasi study, whose point estimate of 2.33 (95% CI = 1.30-4.20) was much different than the

other three studies. The reason for this heterogeneity is not clear. Pinarbasi did use hospital-based controls, but so too did Elexpuru-Camiruaga (OR = 1.16, 95% CI = 0.81-1.66). The Pinarbasi study was conducted in Turkey, but geographic differences also existed between Wrensch and de Roos (USA) compared to Elexpuru-Camiruaga (UK) and their findings were similar. As previously mentioned, there was a significantly greater proportion of cases who smoked in the Pinarbasi study compared to the controls, but smoking has not been identified as an accepted risk factor for brain tumours, so this is not likely to explain the different point estimate.

Significant heterogeneity was found when the lower quality studies were considered for the association between the *GSTT1* null polymorphism and all histologies ($I^2 = 86.6\%$). The two hospital-based studies conducted in the UK (183,187) both suggested an increased risk associated with the polymorphism, while the studies based in the USA (182,196) found a reduced risk, implying that geographical differences may exist that are impacting the results. As expected, significant inconsistency was also found across the studies which scored higher on the Black and Downs scale since this group included the Pinarbasi study ($I^2 = 79.3$). The two studies conducted in the United States had different findings, as the de Roos study suggested an elevated risk (OR = 1.62, 95% CI = 1.20-2.20) and the Wrensch study found a lowered point estimate (OR = 0.82, 95% CI = 0.58-1.17). The author notes that all of the studies which scored below the mean Black and Downs value were published prior to 2003, implying that the quality of reporting the potential association between adult brain tumours and the *GSTT1* null polymorphism is improving.

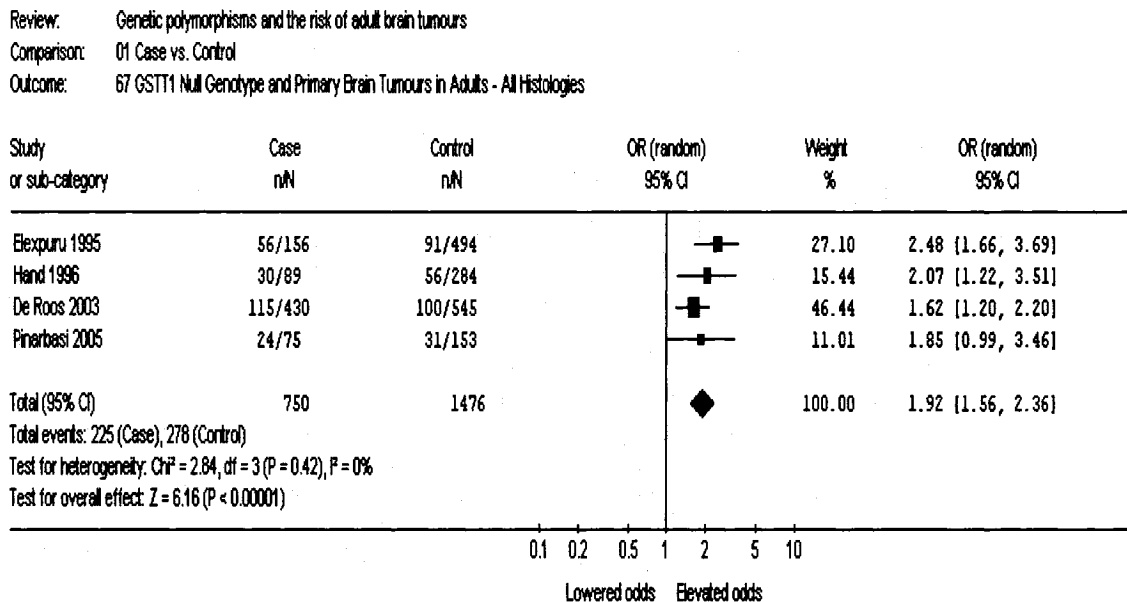
The type of control population was also considered. The only true population-based case-control study included in the *GSTM1* null and *GSTT1* null groups was the Wrensch study (186). Trizna (196) did not use participants that were admitted patients in the hospital, but their controls were blood donors so they cannot be considered randomly selected population-based controls. Ezer (182) based their control population on previous literature and it was difficult to determine if the controls were hospital- or population-based.

When the Wrensch data was dropped from the quantitative data synthesis for the association between the *GSTM1* null polymorphism and all brain tumours there was very little change in the overall odds ratio. Whereas before the point estimate was 1.12 (95% CI = 0.93-1.35), the removal of the Wrensch study led to only a slight increase in the risk of a tumour (OR = 1.16, 95% CI = 0.92-1.45). When Trizna and Ezer were removed, leaving only those studies which selected controls directly from a hospital, the point estimate returned to 1.12 (95% CI = 0.82-1.53). Since there was only one true population-based study, it is difficult to assess the impact that the type of control has on the results, but it does not appear to affect the overall finding.

For the evaluation of the association between the *GSTT1* null polymorphism and brain tumours in adults, removing the Wrensch study only slightly improved the I^2 value (78.5% compared to 81.4%), but there still remained too much inconsistency across the study results to find an overall point estimate. However, when only those studies which implicitly stated that their controls were selected from the hospital were included, the I^2 value became 0%, as seen in figure 16. The overall odds ratio suggested a significant increase in risk (OR = 1.92, 95% CI = 1.56-2.36) and all four studies had individual point

estimates of greater than 1.0, with Pinarbasi (184) the only one that failed to reach statistical significance. This suggests that caution must be taken in interpreting the results of future studies based on the selection of the control population.

Figure 16: Odds of brain tumour in adults associated with *GSTT1* null genotype: pooled results from four hospital-based case-control studies.



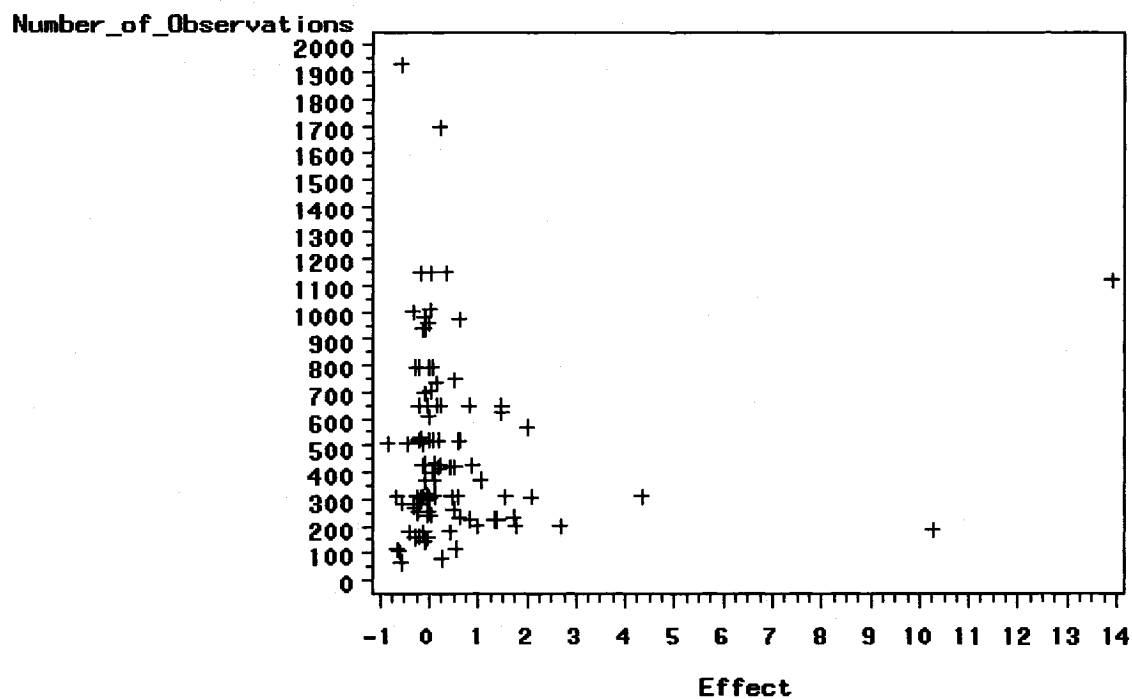
The Kondratieva study (190), which evaluated the *GSTM1* null polymorphism but not the *GSTT1* null variant, never implicitly stated the ages of their cases. As a means of removing this potential bias, sensitivity analysis was performed which dropped this study from the quantitative data synthesis. The Kondratieva results held the least weight in the synthesis, so as expected there was little change in the overall point estimate and the associated 95 percent confidence interval (OR = 1.14, 95% CI = 0.93-1.39).

4.3.10. Publication Bias

A funnel plot was created in order to assess the possible existence of publication bias amongst case-control studies which evaluate the association between genetic

polymorphisms and brain tumours in adults. As discussed in the methods section, the funnel plot does not unequivocally imply publication bias. Rather it can point out gaps in the findings and raises the possibility that publication bias might exist. Figure 17 plots the total number of study participants (cases and controls) on the vertical axis for each of the included studies per distinct polymorphism. The horizontal axis represents the effect of the polymorphism on the risk of brain tumours. The value '0' represents no effect and the horizontal values are equal to one minus the point estimate for the study. Figure 17 only represents the findings of the included studies as they pertain to all histologies.

Figure 17: Funnel plot of the included studies in the systematic review.



Due to the logarithmic nature of the effect size value, estimates below zero will have values closer to zero as compared to those estimates above zero. Therefore, the

inverted funnel shape that one should expect in the absence of publication bias for no association should be slightly skewed to the left. Looking at figure 17, one can see that this is the case. As the total number of study participants increases, the estimated effect tends to be closer to the zero value. There were two outliers, but for both of these the number of exposed cases and controls was very low (less than five) so the confidence intervals associated with these point estimates are extremely wide (182,206). For the most part the point estimates were close to zero. This suggests that overall there tends to be no association between genetic polymorphisms as a whole and brain tumours in adults. The even spread of studies which have found no effect, increased risk, or decreased risk, whether significant or not, suggests that publication bias is likely not an issue.

5.0. DISCUSSION

The purpose of this thesis was to evaluate the association of a family history of cancer in first-degree relatives and PBTs in adults, specifically gliomas and meningiomas, using a large population-based case-control dataset. We also completed a systematic review to examine the association of various genetic polymorphisms and adult PBTs, as determined by case-control studies, and where possible, performed quantitative data synthesis of the results. The aim of this discussion is to focus on the findings of the SEARCH study data and the systematic review, highlighting the strengths and limitations of each, as well as to suggest the possible direction of future research in the area.

5.1. THE SEARCH STUDY

5.1.1. Findings of the SEARCH Study

The SEARCH study represents the largest population-based case-control study conducted to date which examines the potential association between a family history of cancer in first-degree relatives and the odds of glioma and meningioma in adults. A total of 1089 glioma cases and 307 meningioma cases were included, compared to 1922 and 1095 controls, respectively. Unconditional logistic regression, controlling for the matching variables age, sex, and study centre, was used to produce odds ratios and 95 percent confidence intervals associated with 20 different categories of cancer occurrence amongst first degree relatives.

Only two categories of reported family history of cancer were statistically significantly associated with the risk of adult glioma: any type of cancer amongst all first degree relatives produced a lowered point estimate of 0.8 (95% CI = 0.7-0.99) and any

type of cancer excluding brain tumours was also associated with a significantly lowered odds ratio of 0.8 (95% CI = 0.7-0.9). There were only 18 cases and 15 controls that were included in the first association that were not included in the second. Therefore, the results for “any type” and “any type except brain tumour” were very similar. Also, when the data was modeled using the fifth model variation, which was the best fitting model and adjusted for the matching variables as well as the interview type, the p-value was bordering statistical significance ($p = 0.05$) for both of the exposures. For the meningioma data there were no significant associations found at the $p = 0.05$ significance level, though two exposures did approach this level. Those who reported having a father with lung cancer were twice as likely to have an adult-onset meningioma (OR = 2.0, 95% CI = 0.99-4.0, $p = 0.06$). One’s odds of meningioma were greatly reduced if they reported having one or more parents with an unspecified cancer (OR = 0.4, 95% CI = 0.2-1.1, $p = 0.07$), but this was based on only five cases with such a family history.

It is interesting to note that the presence of a family history of any form of cancer would suggest reduced risk of glioma. Hill et al (11) conducted a hospital-based case-control study which looked at cancer in first degree relatives and the risk of glioma in adults. They found odds ratios for 21 different categories of a family history of cancer, including a category which considered any type of malignancy. Contrary to the findings based on the SEARCH data, Hill’s data produced an elevated odds ratio of 1.2 (95% CI = 0.9-1.6) for adult glioma. The San Francisco Bay Area adult glioma case-control study did not find a significant change in the risk of glioma associated with reported family histories of cancer (8), nor did Malmer et al (1) detect a difference in the standard incidence ratios of glioma for spouses of patients with PBTs as compared to first degree

relatives. In general, there has been a lack of consistent findings relating the risk of adult glioma associated with familial cancer. While the lowered odds ratio reported in this thesis did not maintain statistical significance for all of the unconditional models, there is the possibility that the true odds might have been influenced by recall bias.

Previously, it has been suggested that individuals with cancer may be more likely than controls to recall incidence of cancer amongst first degree relatives (212). In particular, since the SEARCH study used population-based controls, the recall of these generally healthy controls may be less accurate than that of the cases who may have compiled their family history of cancer in search of a cause for their disease (213). This would lead to more false negatives amongst the controls and possibly more false positives for the cases, especially since the SEARCH study did not verify the accuracy of the reported cancer histories. If this had occurred, then the odds ratio would have been biased away from the null to suggest a greater odds ratio than truly existed. Consequently, the lowered odds ratio that was reported here could actually have been lower still, but due to recall bias was influenced towards a value closer to 1.0.

This idea of the cases being more aware of their family history of cancer could also have contributed to the lowered odds ratios observed for both glioma and meningioma associated with an unspecified form of cancer in either parents or siblings. The percentage of cases reporting a first degree relative with an unspecified cancer was lower in every instance when compared to the controls, with the lowest point estimate found for unspecified cancer in parents associated with meningioma (OR = 0.4, 95% CI = 0.2-1.1). Recently, the 2004 HealthStyles Survey conducted in the United States by the Center for Disease Control found that respondents with a personal history of disease were

more likely to have actively collected health information from their relatives (214). Therefore, it is possible that the cases in the SEARCH dataset were more likely to actively construct their own family cancer histories and have a greater understanding of the specific forms of cancer that could be found within them. This would result in fewer instances of “unspecified” cancers for the cases as compared to the cancer-free controls.

A second observation of interest amongst the PBT cases and controls was the discrepancy between the association of lung cancer and glioma as opposed to meningioma. The point estimates were all very close to 1.0 for the glioma dataset with respect to reporting lung cancer in parents (OR = 0.9, 95% CI = 0.7-1.1), in fathers (OR = 0.9, 95% CI = 0.6-1.7), or in siblings (OR = 1.0, 95% CI = 0.8-1.5). However, for the meningioma cases and controls a nearly significant two-fold increase in odds was found for those reporting a father with lung cancer (OR = 2.0, 95% CI = 0.99-4.0), with an elevated point estimate for lung cancer in either parent as well (OR = 1.6, 95% CI = 0.9-3.1). As reported in section 2.3.13, numerous studies have focused on the potential association between cigarette smoke exposure and brain tumours in adults, with highly inconsistent results (112). Due to the established association between both passive and active smoking and lung cancer, it is reasonable to suggest that finding a strongly significant positive association between a family history of lung cancer, particularly in parents, and PBTs might indicate a possible association between cigarette smoke exposure and glioma or meningioma. The findings reported in this thesis suggest that environmental exposure to cigarette smoke may not have an effect on the development of glioma, but that parental smoking may influence the odds of adult meningioma. However, a great deal of further investigation is required which would take into account

the smoking status of the first degree relatives, in particular those with lung malignancies, exposure levels and exposure length for the cases and controls, and the active smoking history of the study participants themselves.

Several hereditary syndromes have been consistently found to be associated with familial clustering of PBTs. These syndromes include neurofibromatosis I and II (4), tuberous sclerosis (5), Li-Fraumeni syndrome (6), and von Hippel-Lindau disease (7). However, most estimations suggest that only about five percent of all adult gliomas and meningiomas can be attributed to these diseases. Based on this, one would expect that little or no association should be found between a family history of brain neoplasms and PBTs in adults, which was the case for both the glioma cases and the meningioma cases included in the SEARCH study. For the meningioma subset, 13 cases and 41 controls reported having a first degree relative with a brain tumour, which produced an adjusted odds ratio of 1.2 (95% CI = 0.6-2.4), a slightly elevated point estimate that was to be expected based on the literature concerning familial clustering of PBTs. However, for the glioma cases and controls, there was a slight non-significant decrease in the adjusted odds (OR = 0.9, 95% CI = 0.6-1.4), though the best-fit model adjusted for age, sex, study centre, and interview type suggested no change in the odds (OR = 1.0, 95% CI = 0.6-1.4).

Differences could be found between the glioma cases and the meningioma cases, which can be attributed to the distinction in both the severity and survival time for each of the tumour types. Gliomas tend to be much more aggressive than meningiomas, resulting in reduced lengths of survival following diagnosis (23). As a result, there were large differences in the proportion of cases for each tumour type that required some form of assistance in completing the questionnaire, either by proxy, part proxy, or from the

interviewer, and in the age of the participants. Whereas 36.6 percent of the glioma cases were not direct respondents, only 12.0 percent of the meningioma cases required assistance. Also, 45.9 percent of the glioma subset cases were less than 50 years of age, compared to just 33.8 percent for those with meningiomas. With median survival times of glioma patients being estimated at 12 months or less and decreasing with age (9-11) and concern over the mental concentration of the participants while in hospital (2), it can be seen why these differences exist in the study population.

Associated with this is the fact that for both glioma and meningioma a much greater proportion of the cases required assistance in completing their interview compared to the controls. As a result, differences could be found in the quality of the interview, as judged by the SEARCH team member who conducted the interviews. The best category that a participant could be classified as was “very good”. For the glioma study, 63.2 percent of the controls fell under this heading compared to just 40.6 percent of the cases. In the meningioma subset, 60.6 percent of the controls were considered “very good” as opposed to just 48.2 percent of the cases. Again, this highlights the concern over the validity of the responses provided by the cases, as incorrect responses could seriously bias the estimates produced in this data analysis. However, when interview type was controlled for in the unconditional logistic regression, no significant differences were found in the point estimates as compared to those produced by the model which only controlled for the matching variables. This suggests that, while differences did exist in the quality of interviews given by the cases and the controls, these differences did not significantly influence the estimates of the association between a family history of cancer and PBTs in adults.

Following the methods of previous studies conducted using the SEARCH dataset for adult PBTs (2,131,134,135), both conditional and unconditional regression models were fitted to the data. As seen in tables 10 and 19 in sections 4.1.4 and 4.2.4, there were little or no differences found between the odds ratios and 95 percent confidence intervals produced by either method, with any differences coming as a result of rounding performed by the author. This implies that the pooled analysis of all of the study centres using unconditional logistic regression is appropriate. The benefit associated with this is that it allows for larger numbers of cases and controls to be included in the analyses, which improves the study power and reduces the size of the confidence intervals around the point estimates.

When constructing the models to be used for the unconditional logistic regression analysis, a balance was sought between model fit and clarity of what the model was adjusting for. The R^2 value, c-statistic, Wald chi-square value, the -2 log likelihood value, and the Hosmer and Lemeshow goodness-of-fit test were all used to evaluate the ability of the models to fit the data. The base model considered for both glioma and meningioma was one which only adjusted for the age, sex, and study centre matching variables. Decisions on whether to include a variable in the model were based on the changes that its inclusion introduced on each of the model fit statistics as compared to this base model.

For the SEARCH adult glioma data, the base model did not fit the data very well. In particular, the p-value for the Hosmer and Lemeshow test was less than 0.05, meaning that the null hypothesis that there is no difference between the observed values and those predicted by the model can be rejected. This implies that the odds ratios predicted after

adjusting for the three variables are not representative of the collected data. The inclusion of the interview type did push the Hosmer and Lemeshow p-value past statistical significance ($p = 0.13$), while also introducing large changes in the other model fit statistics. Though this means that the predictive ability of the model is improved, it also means that in interpreting the results the reader must remember that the point estimates mean the odds of glioma if you are a male compared to a female, if you are a certain age compared to 25-29 year olds, if you live in a certain area as compared to Heidelberg, and if you were deemed to have given very good, questionable, or unsatisfactory responses as compared to those who gave reliable responses. It is easy to see how the model can quickly become difficult to interpret as more and more variables are added. Due to the large improvement in the fit of the model, the inclusion of the three matching variables and the interview quality was deemed to produce the best model for interpreting the glioma data. Based on the model fit statistics found in table 16 pertaining to the meningioma data, it was decided that the most reasonable model to use was that which only controlled for the three matching variables.

The random-effects model analysis of the association between any form of cancer in a first degree relative and glioma showed a great deal of heterogeneity amongst the centre-specific results, as shown in figure 1 in section 4.1.8.a. Heterogeneity was also found amongst the centres when any cancer except brain tumours, any cancer in mothers, and any cancer in siblings were considered as exposure variables. The greatest disparity seemed to take place between the Toronto and Stockholm centres, as well as the Heidelberg and Stockholm centres for any form of cancer. Consulting appendix A, it is clear that a number of differences existed between these centres.

While both the Toronto and Heidelberg centres allowed for the use of proxy interviews, the Stockholm centre did not. The reliability of proxy reporting for glioma patients concerning a family history of cancer has been found to be very good, ranging from 75 (8) to 84 percent (11), but it still represents the use of answers concerning a study participant that were not directly provided by the participant themselves. This could have contributed to the lowered point estimates seen in Toronto and Heidelberg if the proxy respondents had not shown the same interest in a family history of cancer as the case. However, all of the other centres, excluding Los Angeles, also included proxy respondents and their point estimates were all closer to the odds ratio of 1.51 found in Stockholm than the estimate produced by the Los Angeles centre.

The Stockholm centre did use individual matching, as opposed to the Heidelberg and Toronto centres which employed frequency matching. Since Stockholm cases and their matched controls would have been the same age, and the Heidelberg and Toronto cases and controls could have differed by up to two and five years respectively, it is possible that the frequency matched controls were consistently older than the cases. This could have produced longer potential exposure times in their first degree relatives if it meant that their parents, siblings, and children were also older on average. However, the Grenoble centre also used a five-year age group in their frequency matching and the point estimate produced by this centre was the most elevated one aside from Stockholm (OR = 1.28).

Another possible explanation for the differences observed between the centres lies in the fact that the Stockholm centre did not conduct interviews of their population-based controls. Instead, questionnaires were mailed out to each of the willing participants.

Two possible situations could have arose that would lead to an increased odds of glioma being found. Either the controls may have taken the time to complete the questionnaire accurately, including a thorough investigation into their family history of cancer, which would suggest a more accurate point estimate, or they could have taken the questionnaire with less sincerity as opposed to an interview conducted by one of the SEARCH study members. This would have produced less reliable responses and the difference between the point estimates for Stockholm and Toronto and Heidelberg may not have truly been as large.

5.1.2. Strengths of the SEARCH Study

The greatest asset of the design of the SEARCH study was the large number of included participants. Table 26 highlights the impact of the SEARCH study on the evidence base of the association between a family history of cancer and adult glioma and meningioma completed within the past 20 years. The SEARCH study meningioma data had 114 more cases than the largest previous study and was nearly 50 percent larger in total number of participants than the next biggest case-control study. There were more than twice as many glioma cases included in this analysis compared to any previous study. In fact, only one study had more total participants than the number of glioma cases in the SEARCH data. The 3318 different family histories reported in this thesis are more than twice the number included in the two Hill papers, the largest case-control evaluation of the association between a family history of cancer and adult brain tumours completed prior to now. This large study size provided a number of advantages. Rather than just considering the effect of any cancer in first degree relatives, 20 different cancer

exposures could be assessed for their impact on the odds of adult glioma and meningioma. Due to the size of the population, point estimates of the odds of PBTs associated with the various cancers had fairly tight 95 percent confidence intervals, including those exposures that were rare. Also, each type of cancer exposure could be further defined to consider specific types of first degree relatives. The obvious benefit to this is a more highly specific knowledge of the potential associations that may exist.

Table 26: Number of included cases and controls in studies examining the association between cancer in relatives and adult glioma and/or meningioma (1987-2006).

Author, year	Type of Tumour	# of Cases	# of Controls	Total # of Participants
Burch, 1987	All types	215	215	430
Preston-Martin, 1989	Glioma	202	202	404
	Meningioma	70	70	140
Hochberg, 1990	Glioma	160	128	288
Wrensch, 1990	Glioma	77	77	154
Zampieri, 1994	Glioma	195	195	390
Wrensch, 1997	Glioma	462	443	905
Hill, 2003	Glioma	468	768	1236
Hill, 2004	Meningioma	193	768	961
SEARCH STUDY	GLIOMA	1089	1922	3011
	MENINGIOMA	307	1095	1402

A second strength of the SEARCH study was the use of population-based controls instead of hospital- or clinic-based controls. The latter types of controls have been common in previous case-control analyses of the association of a family history of cancer and glioma or meningioma (11,154). Population-based controls have the primary advantage over other forms of controls in that their random selection from the general population of interest usually can assure investigators that their controls are comparable to their cases with regards to their demographic variables (213). In other words, population-based controls are the most likely to satisfy the “would criterion”. Since the controls are selected from the same base population as the cases, if a member of the

control group were to develop a glioma or meningioma, he or she “would” become part of the case group.

Since the SEARCH study was an international investigation, it was also possible to look at whether country of residence had any influence on the various associations investigated. Rather than being restricted to a single country or geographic area, as has been the case in previous investigations on the effect of a family history of cancer (8,11,154), the SEARCH dataset had the advantage of looking at the different odds ratios associated with each of the exposures for each of the eight centres included in the glioma analysis and the six centres in the meningioma data. Previous research has shown that the incidence rates of adult brain tumours vary by geographic region, including from country to country within Europe (22). Particularly striking differences in incidence rates have been found between developed, industrial countries and developing nations, thought to be as a result of under-ascertainment in the latter, though this was not an issue here as each of the six included countries can be considered to be developed regions (22). The inclusion of centres from multiple global areas allowed for the assessment of possible changes in the association of a family history of cancer and PBTs depending on where the person resides.

5.1.3. Limitations of the SEARCH STUDY

One limitation of the SEARCH study was that there was no verification of the reported family history of cancer provided by each of the participants. Previous reports on the validation of family history of cancer data have taken numerous steps at checking reporting accuracy, including reviewing pathology reports, checking hospital admission

and discharge statistics, death certificates, and cancer registries (212). At this time, the focus of the literature has been on the accuracy of reporting of patients with breast, colorectal, and prostate cancers, though the general trend suggests that using self-reported family histories of cancer amongst first degree relatives is a very accurate approach. Two previous studies looked at validation of self-reported information amongst glioma patients and both found that more than 75 percent of the reported cancers in relatives could be confirmed by medical records (8,11). Love et al (215) found that the accuracy of correct cancer site identification in first degree relatives was 83.7 percent. A recent meta-analysis concluded that self-reporting is a useful, accurate method but cautioned that accuracy may vary depending on the specific type of cancer (216).

The most obvious problem associated with this limitation of self-reported data is the potential for the introduction of false positives and false negatives to the data. Participants reporting the presence of a family history of cancer where none exists or failing to realize that a true history does exist will present biased results. Intellectual decline has been associated with PBTs, with cases being faced with impaired judgment, loss of memory, and a reduced level of consciousness (17), so the possibility exists that the accuracy of the responses provided by the cases was biased by the disease itself. If this had occurred, the bias introduced would have been differential since it would not have taken place in the controls. The direction on the point estimates would depend on whether the cases were more likely to report a family history that was not there (bias away from null) or to forget to report a true history of cancer in first degree relatives (bias towards null).

It seems likely that there is also an opportunity for this misclassification bias in the controls who report no cancer history when in fact one does exist. While verification of the self-reporting would have helped to reduce this potential source of bias, it should be noted that the SEARCH study was restricted to only first degree relatives. Previous research has shown that the validity of self-reported familial cancer history is highest amongst first degree relatives and steadily decreases as the bloodline is extended (215). Limiting the self-reporting to parents, siblings, and children reduces the chances for introducing bias and helps to maintain more valid results.

A second limitation of the SEARCH study involves missing data. 154 (4.9%) of the glioma participants and 16 (1.1%) of the meningioma participants could not be included in any of the analyses because they were missing information pertaining to either the size of their family at risk of having cancer or the number of first degree relatives reported to have cancer. Though these numbers represent less than five percent of a very large dataset, there exists the possibility that the inclusion of these individuals may have influenced the findings and made associations that were not statistically significant become significant or vice versa.

Concern has been raised in previous literature over the possible bias that may be introduced by not taking into account the number of relatives at risk for cancer or the total number of relatives with cancer (11,154). In particular, the use of a simple dichotomous yes or no response for cancers in first degree relatives was of concern. Due to the structure of the SEARCH questionnaire, it was possible to determine the number of first degree relatives at risk for each of the included cases and controls. As seen in tables 6 and 15 in section 4.1.2 and 4.2.2, there was little or no change in the odds of either

glioma or meningioma associated with increasing family size and the trend statistic was not significant in either instance ($p = 0.99$ and $p = 0.78$, respectively). However, it was not possible to determine the exact number of first degree relatives that were reported to have cancer. As a result of the constraints of the questionnaire, the author was limited to assessing the risk associated with reported cancer in one or more parent, sibling, or child. This means that participants who had more than one parent, sibling, or child with a specific form of cancer would be considered the same 'analytically' as those with only one relative with cancer. Therefore, associations might have been underestimated if, for example, cases were more likely to have larger proportions of their siblings and children with cancers as compared to the controls.

A problem that arose for a number of the associations investigated came as a result of low cell values. Breslow and Day (134) recommend that for associations in which the true odds ratio lies less than a two-fold difference away from 1.0 all strata should contain at least 10 cases and 10 controls, with even greater numbers required as the point estimate moves further away from 1.0. The result is point estimates associated with extremely wide confidence intervals and very little statistical power in detecting a true difference between the cases and the controls. For this thesis, Fisher exact test values were used as a correction factor for situations in which cell values are low. This lack of exposed cases and controls was not as much of an issue for the glioma data since the number of participants was much greater than that for the meningioma subset. Still, only four glioma cases reported having a child with any form of cancer, just six cases identified a parent as having lip, oral, or pharyngeal cancer, only six cases had a sibling with unidentified cancer, and only six total participants (one case and five controls) were

found to have reported having a sibling with lip, oral, or pharyngeal cancer. Considering that the adjusted odds ratio was 0.5 (95% CI = 0.2-1.6) for any cancer in children and 0.4 (95% CI = 0.1>-3.7) for lip, oral, or pharyngeal cancer in siblings, there is the possibility that a true association might have been missed as a result of an insufficient number of observed exposures.

For the meningioma data, 10 of the 20 exposure variables had at least one cell which included less than 10 participants. For the association of lung cancer in siblings, breast cancer in mother, breast cancer in sister, gastrointestinal cancer in siblings, genitourinary cancer in siblings, unspecified cancer in parents, and unspecified cancer in siblings, the number of meningioma cases with the self-reported exposure failed to reach 10. For any type of cancer in children and for lip, oral, or pharyngeal cancer in both parents and siblings, the cell values were less than 10 for both the exposed cases and the exposed controls. Some of the adjusted point estimates reported deviated largely from 1.0 but were considered to be non-significant associations due to the lack of statistical power. In particular, greatly lowered odds ratios were found for breast cancer in mother (OR = 0.5, 95% CI = 0.2-1.4) and sister (OR = 0.3, 95% CI = 0.1-1.4); lip, oral, or pharyngeal cancer in parents (OR = 0.2, 95% CI = 0.1>-1.9); and unspecified cancer in parents (OR = 0.4, 95% CI = 0.2-1.1), none of which were statistical significant. A non-significantly elevated odds ratio of 1.9 (95% CI = 0.5-7.7) was found associated with a self-reported history of any cancer amongst children.

5.1.4. Conclusions and Future Research

The analysis of the SEARCH study data makes an important contribution to the field of risk factors for primary brain neoplasms in adults, as well as making a significant addition to the sparse amount of literature currently available concerning the impact of a family history of cancer on the odds of adult glioma and meningioma. The present results suggest that the risk of glioma in adults may actually be decreased with the presence of cancer in first degree relatives, as well as with cancer of any form excluding those family members with brain tumours. No other significant associations for glioma were identified, though there were occasions where the point estimate was more than +/- 0.4 away from 1.0 but there was not sufficient enough statistical power to eliminate the possibility of a difference due to chance. No significant associations were found in any of the 20 different cancer exposures in the analysis of the meningioma data. This relative lack of significant findings suggests that cancers in first degree relatives, particularly those in sites other than the brain, may not be a contributing factor to the development of PBTs in adults.

Differences in the odds ratios associated with each of the various forms of cancer, the location of the study centre, and the type of PBT suggest that these issues should be considered for future research investigating the relationship between cancer amongst relatives and adult glioma and meningioma. The wide range of point estimates found for the different cancer sites suggests that it might be improper to consider the impact of all cancers in relatives as a whole. The heterogeneity found between some of the study centres implies that the geographic location of interest may play a role and further research must be done to look at the possible association in other countries not included

in the SEARCH study. The discrepancy between the results of the two tumour types indicates that grouping all forms of PBTs together may miss specific associations, meaning that continuing studies must establish clear case definitions.

PBTs, including glioma and meningioma, have been associated with very poor survival times (9-11) and the incidence of the disease is on the rise (22). With so little known about the risk factors associated with brain tumours, future research directed at establishing consistent results for the variety of proposed associations is likely to be an important contribution to the literature. Perhaps this thesis will help to establish a better understanding of the bearing that a family history of cancer amongst first degree relatives may have on the development of adult glioma and meningioma.

5.2. DISCUSSION OF THE SYSTEMATIC REVIEW

5.2.1. Findings of the Systematic Review

A total of 41 case-control studies were eligible for inclusion in the assessment of the association of genetic polymorphisms and PBTs in adults. Adding to the complexity of this review was the fact that the studies completed on the same gene often differed in the particular polymorphism being considered, as well as the particular type of brain tumour investigated. Only three of the 46 different genes covered in the 41 included articles were part of more than two different studies, and of these, often times the association between a particular polymorphism and a specific tumour type was limited to only one study making it difficult to perform a great deal of quantitative data synthesis.

Complete agreement on the number of genes that each human possesses vary, but recent estimates tend to place the number around 30 000 (217). Current estimates

concerning the frequency of SNPs suggests that they may occur as often as every 100-300 bases, meaning that there is the potential for upwards of 30 million SNPs in the human genome (218), with over four million already having been identified by various groups, such as The SNP Consortium. These numbers make it understandable why such a wide variety of literature exists with regards to the association of SNPs and adult PBTs and why retrieving enough articles focused on the same polymorphism and tumour type to conduct a quantitative synthesis becomes difficult.

Studies included in this systematic review required genotyping to identify those cases and controls that were positive for the genetic polymorphism exposures. In February of 2001, the coordinated publication of the Human Genome Project was accomplished (219,220), an international collaboration which made available for the first time a draft sequence of the entire human genome. These published reports made it possible to use an established reference sequence in order to identify changes of single nucleotides amongst all of the genes. The advantage of using this universal database is reflected in the fact that a much larger proportion of the included studies in this review were published after the release of the Project's results (28 studies, or 68.3%).

5.2.1.a. General Findings of Studies Involving the GST Genes

This systematic review allowed for the quantitative data synthesis of four genotypic variants: the *GSTM1* null genotype, *GSTT1* null, *GSTP* Ile105Val, and *GSTP* Ala114Val. Further analysis distinguished the cases by the specific form of PBT: glioma, astrocytoma, oligodendroglioma, or meningioma. A total of 10 studies which evaluated

SNPs on the GST genes were eligible for inclusion in the review, though the included numbers for each of the specific genes and histologies varied.

There were no significant findings in the quantitative synthesis of the association between the *GSTM1* null genotype and all tumour types (OR = 1.12, 95% CI = 0.93-1.35), glioma (OR = 1.15, 95% CI = 0.83-1.59), or astrocytoma (OR = 1.05, 95% CI = 0.85-1.29). The lack of an association between *GSTM1* null and glioma found in this review is similar to the findings of a recent systematic review (14) which included seven different case-control studies and produced an overall point estimate of 1.08 (95% CI = 0.92-1.26). The odds ratio found in the Lai review for astrocytoma (OR = 0.98, 95% CI = 0.75-1.28) was not statistically significant and was similar to our finding, suggesting that the genetic polymorphism on the *GSTM1* gene which results in the loss of the enzymatic function of the gene product does not contribute to an increased risk of developing either glioma or astrocytoma in adults.

There is the possibility that a true association does exist between the *GSTM1* null genotype and PBTs and that this review was underpowered to observe a significant difference. Based on the reported odds ratios and the frequency of the polymorphism, the total number of participants required to detect a statistically significant difference at $p = 0.05$ with 90 percent power would be: 7736 for all tumour types, 9273 for glioma, and 24830 people for astrocytoma. The number of participants included in this review was much lower than this and as a result the statistical power was well below 90 percent (All = 5551, $P = 0.47$; Glioma = 2363, $P = 0.20$; Astrocytoma = 3869, $P = 0.08$). This lack of statistical power means one cannot rule out the possibility of a type II error, meaning the false reporting of no association when in fact one truly does exist. However, calculating

statistical power *post hoc* will always produce low values (less than 60%) for non-significant differences which is why these calculations are not very helpful (221).

Ignoring this idea ignores the very possibility that there truly is no association.

The author notes that there was little consistency across the studies for the association between the *GSTM1* SNP and oligodendroglioma ($I^2 = 75.4\%$), as well as meningioma ($I^2 = 71.9\%$). Heterogeneous results are observed in the de Roos et al (188) study as compared to the findings of Wiencke et al (185) and Ezer et al (182) for the risk of oligodendroglioma. All three studies used subjects from the United States and had similar eligibility criteria. Each of the studies was conducted at around the same time period and case ascertainment involved a neuropathologist, so differences in the identification of eligible cases due to diagnostic methods was likely not an issue. However, De Roos used hospital-based controls while Wiencke's controls were selected from the general population. Ezer used controls from previous literature so there cases did not come from the same source population as the controls. There were differences in the study sizes and the genotyping methods as well.

For the odds of meningioma associated with the *GSTM1* null genotype, the variability across the studies can primarily be attributed to the findings of Pinarbasi et al (184). This hospital-based case-control study conducted in Turkey found significantly increased odds associated with *GSTM1* null for any type of brain tumour (OR = 2.33, 95% CI = 1.30-4.20), glioma (OR = 2.94, 95% CI = 1.33-6.51), and meningioma (OR = 2.87, 95% CI = 1.17-7.05), but due to its relatively low number of participants it only caused a significant level of heterogeneity amongst the pooled meningioma analysis, which was restricted to just three studies. Based on the information provided in the

publication, there are no major differences between this study and the others except for the global location of the participants. As mentioned, the Pinarbasi participants were all recruited in Turkey compared to the UK for Elexpuru-Camiruaga et al (187) and the US for De Roos et al. However, since the Pinarbasi cases were confirmed according to the WHO international guidelines, the different results cannot be attributed to a difference in classification methods, suggesting instead that there may be geographic differences in the impact of the *GSTM1* null polymorphism. Pinarbasi did find that the proportion of cases that were smokers was significantly higher compared to the cases, but as discussed in section 2.3.13, there is little conclusive evidence supporting an association between cigarette smoke exposure and PBTs in adults. This evidence does provide reason to further investigate the potential influence that smoking history may have on the odds of PBTs in those individuals who have this genetic polymorphism on the *GSTM1* gene.

There was no overall significant association between the *GSTM1* null genotype and glioma (OR = 1.03, 95% CI = 0.80-1.33) or oligodendroglioma (OR = 1.03, 95% CI = 0.63-1.70). Variability across the studies was an issue for the analysis of the association between the *GSTM1* null polymorphism and PBTs of all types ($I^2 = 79.1\%$), astrocytoma ($I^2 = 71.4\%$), and meningioma ($I^2 = 68.6\%$). All of the included articles that suggested lowered PBT odds used population-based controls, while each of the studies that produced elevated odds ratios made use of hospital-based controls. Though the authors mention that the hospital-based controls were free of neoplastic conditions, this does not mean that selection bias was not introduced. There are a whole host of possible situations that could have led to the polymorphism contributing to the control being in the hospital, such as increased drug or allergen susceptibility. All four of the studies with

lowered odds were conducted in the United States, implying that there may be a geographical explanation for the heterogeneity, but de Roos et al (188) also used American participants and their odds ratio was significantly greater than 1.0. Date of publication also seemed to have no influence over the outcome of the study, as the four most recent articles produced two lowered point estimates and two elevated point estimates, meaning that evolving methods of classification have not influenced any possible association.

Despite helping to form the most predominant enzyme of all produced by the various *GST* genes in protecting the brain from exposure to carcinogenic agents (222,223), SNPs on the *GSTP* gene were investigated in less studies than either *GSTM1* or *GSTT1*. For the evaluation of the association of both the Ile105Val and Ala114Val polymorphisms and PBTs in adults, only three eligible case-control studies were found (182,186,188). Each used cases from the United States and was published within the last four years. Each used frequency matching, though the matching variables did differ from study to study, and for the Ala114Val SNP, all three found point estimates of greater than 1.0. However, highly significant levels of heterogeneity were found for both evaluations, meaning that the results of each study were significantly different from one another and any overall odds ratio is difficult to interpret.

In the analysis of the association of the Val/Val genotype on codon 105 and adult PBTs, de Roos found an odds ratio of greater than 1.0 using hospital-based controls, while Ezer and Wrensch both found lowered point estimates and enrolled population-based controls. Contrary to this, in the study of the Val/Val or Ala/Val polymorphic genotypes on codon 114 the findings of de Roos and Wrensch closely mirrored one

another while the point estimate found by Ezer was much different (OR = 14.92 compared to 1.03 and 1.08). Ezer used tumour samples as a source of DNA for the cases and the source for the controls varied since they were based on controls used in previous studies, while de Roos and Wrensch used the same DNA sources for their cases and controls (white blood cells and buccal cells, respectively). There is the possibility that the DNA source used by Ezer to identify controls with the polymorphism was not appropriate and so there were a high number of false negatives amongst the control population, leading to an increase in the point estimate. Only nine of the 898 controls were found to have the variant (1.00%), compared to 13.54% of the De Roos controls and 15.89% of the controls used in the Wrensch paper. Finally, by using different control sources, Ezer cannot ensure that the cases have come from the same population that has given rise to the controls which can allow for selection bias to impact the study results (213).

5.2.1.b. General Findings of Studies Involving the ERCC Genes

Three case-control studies were found which evaluated the association between adult PBTs and SNPs on the *ERCC1* gene, and four were found which addressed the relationship as it pertains to polymorphisms on the *ERCC2* gene. A total of six different SNPs were included amongst these studies, two being found on *ERCC1* and four on *ERCC2*. However, differences in the histologies of the cases, the use of the same patient population, or only one study being found for a particular polymorphism made it impossible to conduct any sort of quantitative data synthesis for any of the SNPs found

on the *ERCC* genes. No previous systematic reviews were identified which addressed the possible association between *ERCC* polymorphisms and adult PBTs.

The C8092A polymorphism on *ERCC1* was found to significantly lower the risk of astrocytoma in the study conducted by Chen et al (192), but was based on only five people that were heterozygous variants amongst the 28 cases. There were no homozygous variant cases found and only eight of the 159 controls were homozygous for the polymorphism. This study was part of the San Francisco Bay Area adult glioma study. Though its findings suggest that there may be an association, the analysis was restricted to white participants. Wrensch et al (191) found almost no change in the odds (OR = 0.99, 95% CI = 0.76-1.28) for adult PBTs associated with having at least one polymorphic allele when all of the San Francisco Bay Area adult glioma study participants were included, regardless of ethnicity. Future studies are needed to further assess the possible relationship, though it would seem that due to the rarity of the polymorphism, much larger numbers of both cases and controls will be needed for sufficient statistical power.

None of the studies which examined the impact of the N118N polymorphism on *ERCC1* or the D312N, D711D, and K751Q polymorphisms on *ERCC2* found any sort of significant associations with any type of PBT in adults. In fact, the only change in odds which attained statistical significance was that for the white participants of the San Francisco Bay Area adult glioma study as reported by Caggana et al (40). They found an elevated odds ratio associated with the R156R polymorphism on *ERCC2* for adults with any form of glioma (OR = 2.1, 95% CI = 1.2-3.8) and for those with GBM specifically (OR = 2.6, 95% CI = 1.3-5.5). These findings are not consistent with those reported by

Wrensch et al (191), which were based on the entire San Francisco study population and not restricted to whites like the Caggana study. Wrensch found point estimates that were very close to 1.0 (OR = 0.98, 95% CI = 0.71-1.36 for all tumour types and OR = 1.02, 95% CI = 0.68-1.53 for GBM), suggesting that perhaps there is a difference in the effect of the R156R polymorphism in adults based on ethnic group. Unfortunately, there is a lack of sufficient information available at this time to further explore this issue, but it should be a point of consideration for future research.

5.2.1.c. General Findings of Studies Involving the CYP Genes

There were three broad classes of genetic polymorphisms within the *CYP* genes that were considered for possible associations with adult PBTs amongst the included studies in this systematic review. One study (188) looked at two SNPs on the *CYP2E1* gene, three considered variants of the *CYP2D6* gene (187,189,195), and one evaluated the possible association on the *CYP1A1* gene (196). Due to the paucity of published case-control studies available concerning the *CYP* genes, there were only two instances where data synthesis was possible. To the best of the author's knowledge, this is the only systematic review to consider the association between polymorphisms on the *CYP* gene and PBTs in adults.

The *CYP2D6* "poor metabolizer" phenotype is an autosomal recessive trait, meaning that only homozygous variants will display a reduced ability to metabolize carcinogens such as PAHs, nitrosureas (187), and nicotine (189). When this polymorphism was considered for its possible association with adult astrocytomas by Elexpuru-Camiruaga et al (187) and Kelsey et al (189), a significantly elevated odds ratio

was found (OR = 2.83, 95% CI = 1.46-5.50). The results were consistent from study to study, though the Kelsey paper did not achieve statistical significance. This seemed to be more due to a lack of sufficient exposures than to a point estimate closer to 1.0. In fact, the point estimates suggested by Elexpuru-Camiruaga and Kelsey were very similar (2.96 and 2.39, respectively), but Kelsey only managed to identify three variant cases and six variant controls. This helps to highlight the need for further study. Of the 143 included cases in the systematic review, only 16 were homozygous variants and only 24 of the 566 controls possessed the “poor metabolizers” phenotype. Therefore, even though the overall estimate achieved statistical significance, it was still associated with fairly wide confidence intervals. Larger studies would help to better estimate the overall effect that this polymorphism might have on astrocytoma in adults.

This same problem was encountered in the systematic review of the association between the *CYP2D6* polymorphism and meningioma, where only eight variant cases and 49 variant controls were found from the Elexpuru-Camiruaga and Wundrack (195) studies combined. Unlike the situation with astrocytomas where the individual study results were similar, the point estimate found by Elexpuru-Camiruaga was more than twice that of Wundrack (3.13 versus 1.53, respectively). Both studies used hospital-based controls and did not use any form of matching in their control selection. However, the Wundrack study did not select their own controls, instead using information provided by previous studies. This might have led to incorrect assignment of control exposure, which would influence the point estimates. Also, the Wundrack study used German cases, while the Elexpuru-Camiruaga paper had cases from the UK, suggesting that a difference in odds may exist depending on geographic location. Yet with only two

exposed cases reported by Wundrack (compared to 19 in the Elexpuru-Camiruaga study), this difference is most likely attributed to the small numbers. For instance, if only one more case in the Wundrack study had been found to have the polymorphism, the point estimate would jump to 2.38.

5.2.1.d. General Findings of Studies Involving the p53 Gene

There were three different regions of the *p53* gene which were assessed for possible SNPs that may influence one's odds of an adult brain tumour. One study looked at a polymorphism located in the promoter region of the gene; four took into consideration the SNP which substitutes a proline for an arginine at codon 72 of the gene; and two measured the association between PBTs and a polymorphism on intron six. Across each of these different polymorphic sites, there were no significant associations established, either by an individual study or in an overall quantitative data synthesis. Though there was point estimates found that were above and below 1.0, the general trend found was that polymorphisms on the *p53* gene were not associated with a change in risk of adult PBTs.

In particular, the risk of all PBT histologies associated with the homo- and heterozygous variant genotype on codon 72 of *p53* suggests that the polymorphism plays no role in the development of brain neoplasms, with each of the three studies point estimates found within +/- 0.15 of 1.0 and an overall odds ratio of 1.08. This finding was somewhat surprising since germ line *p53* mutations have been associated with Li-Fraumeni syndrome, which predisposes family members to increased odds of brain cancer (201), and almost one quarter of all gliomas are estimated to have either a germ

line or somatic mutation on the *p53* gene (199). However, as mentioned, it is believed that hereditary syndromes such as Li-Fraumeni account for less than five percent of adult gliomas and meningiomas (8), so it is possible that these polymorphisms only play a role in those tumours which arise in adults afflicted with one of these syndromes and not in sporadic PBTs. A greater amount of research in the area would be beneficial, as only three studies were found to be eligible and no previous systematic review or meta-analysis could be found.

5.2.1.e. General Findings of the Other Included Studies

The systematic review led to a further 92 reported evaluations of the association between genetic polymorphisms and PBTs in adults. The overriding trend seemed to be that too few study participants were available to establish many statistically significant associations. In many instances, point estimates that were well above or below 1.0 could not be ruled out to be due to chance at the $p = 0.05$ level and were surrounded by extremely wide 95 percent confidence intervals. These findings suggest that potential associations may exist, but that until more large studies are completed, none of these relationships can be confirmed. However, there were 18 separate instances where the association between the polymorphism and a change in odds of brain tumour did reach the level of statistical significance set *a priori*.

Vega et al (204) did find significantly elevated odds of glioma associated with a multitude of polymorphisms on the *HRAS1* allele, though the significance was not maintained when the authors considered meningioma alone and all tumour types together. This finding is of interest since the precise role of *HRAS1* has not been established and

polymorphisms on this gene have been shown to cause an inherited predisposition to other forms of cancer (204). Due to the manner in which the results were presented by Vega, it was not possible to consider the association related to any particular polymorphism; instead, only all SNPs taken together could be evaluated. There remains the possibility that when each SNP is considered one at a time, some may show no association, whereas others might produce even larger point estimates. Future research in the area will help to answer some of these questions.

An interesting result was produced by the Leone et al study (206). The authors considered the association between the C2290T SNP on the *RAD54L* gene and meningioma in two different populations: one in Spain and another in Ecuador. Not only were the raw numbers markedly different, but the resultant odds ratios were too. In the Spanish population the point estimate was well below 1.0 (0.36), but since they only found the polymorphism in two of the 29 cases (6.90%), the estimate failed to attain statistical significance. When those in Ecuador were genotyped, 30 of the 41 cases were found to be variants (73.17%) and the odds of meningioma were significantly elevated (OR = 11.29, 95% CI = 5.07-25.14). This point estimate was easily the most elevated of all of those found during this systematic review. There was one large difference in the methodology between the two study centres. While both controls were genotyped by donated blood samples, the Spanish cases donated blood and tumour samples in order to confirm the polymorphism, whereas the Ecuadorian cases contributed only tumour samples. Therefore, there is the possibility that there were genotyping errors committed that were missed due to the lack of quality control measures. If these errors had produced false positives for the polymorphism, the odds ratio would have been artificially elevated.

However, there is no mention in the article that there were any differences found in the genotypes produced by the blood samples compared to the tumour samples in the Spanish patients, suggesting that their methodologies were sound. It would be useful to further investigate this possible difference due to geography and the possible reasons for this distinction, since it might mean that country-specific associations exist for this polymorphism and adult PBTs.

Polymorphisms on the *GLTSCR1* gene, or *glioma tumour suppressor candidate region* gene, associated with adult PBTs was considered by only one of the included case-control studies (194). Despite having only seven cases and eight controls that were homozygous for the S397S polymorphism on the *GLTSCR1* gene, Yang et al still managed to find a statistically significant increase in the odds of adult oligodendroglioma (OR = 3.38, 95% CI = 1.06-10.82). When they included heterozygotes as exposed individuals, the point estimate still remained above 1.0 (OR = 1.93, 95% CI = 0.92-4.07), but the finding was not statistically significant, suggesting that this polymorphism might have an autosomal recessive effect on gene function. The significantly increased risk found, despite the lack of large numbers of exposed cases and controls, highlights the idea that this particular polymorphism could be of significance in trying to understand the causes of adult PBTs. Yet the lower end of the 95 percent confidence interval did approach 1.0, so more studies with greater participation are needed to establish a better understanding of the impact that this SNP might have.

5.2.2. Strengths of the Systematic Review

The greatest strength of this systematic review is the broad scope that was used in terms of the exposure of interest. While previous reviews have been conducted which looked at the association of genetic polymorphisms and adult PBTs, they have focused on one particular gene or family of genes. These are still very useful reviews but they do not provide the comprehensive overview of the associations between genetic polymorphisms in general and adult brain tumours that this thesis does. This review will allow researchers to identify those genes that have been previously considered and especially detect those which demand further investigation. Nearly 50 different genes were found amongst the 41 included studies and a wide variety of point estimates were produced. With a number of odds ratios found that significantly influenced the risk of brain tumours, as well as a multitude of point estimates that require further consideration before statistical significance can be obtained, there is a great deal of work to be done in the area. This review provides a thorough summation of what has been accomplished to date.

A second strength of this review was the high level of inter-observer agreement. A random 10 percent sample was selected and reviewed independently by two people at two different stages of the review. A Cohen kappa score was generated to establish the degree of homogeneity between the opinions of the two reviewers regarding the eligibility of the 293 selected abstracts and 22 selected full-text articles. The Cohen kappa score corrects for the possibility that the two reviewers would have sometimes agreed just on the basis of chance alone, thus providing a more reliable estimate of inter-observer agreement compared to using only percentage of agreement (148). Ranging

from a low of 0.0 to a maximum of 1.0, guidelines have been suggested for the interpretation of kappa scores by Landis and Koch (224). A value of less than 0.60 is considered to be a less than substantial level of agreement and a close evaluation of the study selection process is needed (148). In this review, the Cohen kappa score for the review of the abstracts was 0.67 and a perfect 1.0 for the full-text articles, meaning that the two authors exhibited high levels of agreement on study eligibility (178). This suggests that the inclusion and exclusion criteria established were clear and helped to reduce the potential for bias or errors.

Finally, the assessment of the reporting quality of the included studies was a strength of this review. Using a modified version of the Black and Downs checklist for the assessment of the methodological quality of non-randomised studies (152), the authors were able to report on how well the included studies presented their methods and results, how valid their methods were, and how they dealt with issues such as confounding and bias. Included in the sensitivity analysis of the review, the Black and Downs scores allows for readers to consider the estimated validity of a study's results. The Black and Downs scale has been published in a peer-reviewed journal, which separates itself from a number of other quality assessment tools used for non-randomised studies. Previous research has shown that the use of these unpublished scales and checklists can introduce bias into the interpretation of the results (167), supporting the selection of the Black and Downs for this review. However, these scores did not in any way influence the inclusion or exclusion of a study from the review. Due to the level of uncertainty surrounding the use of quality assessment tools in systematic reviews (139),

the author only scored articles after their inclusion in the review and presented their results prior to their Black and Downs score.

5.2.3. Limitations of the Systematic Review

A limitation to this systematic review and most reviews in general is the possibility that not all of the relevant studies were identified. The search was limited to three electronic databases and the reference lists of all of the included studies and literature reviews related to the topic. It has been estimated that electronic searches of the literature may only identify three-quarters of all of the relevant articles (141). As mentioned, the only hand-searching that was performed was the reference lists of all eligible studies found through the electronic search and there was no gray literature obtained, although there have been questions about the usefulness of this practice (142). As well, there were constraints on the language of the publication. Only those articles published in English, French, Spanish, Italian, Portuguese, or German were eligible for inclusion. This led to the removal of two potentially relevant articles published in Japanese. Attempts to contact the corresponding authors of these studies were unsuccessful, so there exists the possibility that relevant information might have been missed in these articles.

Though the breadth of the literature covered in this review makes it useful for the consideration of all genetic polymorphisms associated with adult PBTs, the nature of the subject matter meant that the relevant data is limited due to different histologies of brain tumours, genes, SNPs, and populations studied. This led to a number of instances where there were extremely low cell frequency values, particularly for exposed cases and

controls. With such low counts comes a lack of statistical power and imprecision leading to wide confidence intervals so that highly elevated or lowered point estimates could not be ruled out to be due to chance. Obviously this is a limitation of the available evidence more than the methods of the review, but it does serve to highlight the need for more research in the area. A greater number of case-control studies evaluating the association of these genetic polymorphisms and adult PBTs would also allow for a more detailed sensitivity analysis. Differences in risk relating to the type of tumour or the country of residence or whether the individual was a homo- or heterozygous variant are all issues that could be clarified with more available evidence.

Associated with this were the high levels of heterogeneity that were found in the review. We used a random-effects model, with the study as the random effect, which assumes that the studies included in the review represent only a random sample of all of the theoretical studies that could exist and their results are randomly placed around a central value (225). This model is considered to be more statistically conservative than the fixed-effects model since it incorporates both a within-study and between-study measure of variance (148). When a significant level of inconsistency exists, it becomes inappropriate to report an overall odds ratio since you are trying to pool together data from two or more studies which have found significantly different results. In cases such as this, it becomes more useful to report the individual study results and suggest explanations for why such differences exist. For this review, there was little evidence available concerning causes and risk factors for PBTs so even trying to discern reasons for distinct study result differences became difficult. Again, future research on the topic

will help to elucidate factors which may have contributed to the significant heterogeneity that was found.

Tied into this idea of heterogeneity and diverse subject matter was the inability to perform a meta-regression. Meta-regression analysis would have been useful for controlling for potential biases introduced in the quantitative data synthesis, such as by the year of publication, the country of origin for the study, and the country of publication of the journal to name just a few examples. However, just as logistic regression uses the individual as a data point, meta-regression uses the individual studies. Therefore, large numbers of studies are required in order to produce reasonable estimates. With the variety of polymorphisms and histologies covered, this was not possible for this review.

5.2.4. Conclusions and Future Research

This thesis represents the first systematic review of the association between all genetic polymorphisms and PBTs in adults. This review should serve as a useful tool for future research focused on trying to gain a better understanding of the risk factors leading to the development of brain tumours in adults. At the present time, there is little knowledge pertaining to SNPs that may place individuals at different odds of developing a PBT. One earlier systematic review (161) was conducted in 2000 and provided an overview of the genetic alterations in adult diffuse glioma, highlighting their occurrence, significance, and prognostic implications. However, there is no mention of the methods used to generate the sources used, none of the data is pooled in a meta-analysis, and there is little provided regarding the details of the included studies, including crucial pieces of information for genetic studies such as age, gender, and ethnicity of the participants and

the methods of control selection. A more recent review by Lai et al (14) focused on the association between genetic polymorphisms of *GSTs* and adult brain tumours, but did not consider the impact of polymorphisms located on any other genes. With this thesis comes the first review that incorporates all polymorphisms that have been considered for their involvement in PBT development.

A number of significant associations were found in the results of the studies included in this systematic review, such as the *GSTP* Ala114Val polymorphism and PBTs, *CYP2D6* “poor metabolizers” and meningioma, and the *RAD54L* C2290T SNP and meningioma amongst Ecuadorian subjects, to name just a few. Generally speaking however, achieving statistical significance was often made difficult by the paucity of relevant data. In some instances point estimates were changed by a magnitude of three or four and yet there still remained insufficient statistical power to eliminate the result due to chance. This raises the need for more research investigating these potential associations.

It is the hopes of this author that this review will allow for the identification of future areas of concentration, in particular, specific histologies and genetic polymorphisms. With this pooling of pertinent information, areas which suggest that an association likely exists and those where there is seemingly no relationship can be identified. As well, polymorphisms and tumour types that have yet to be considered will be evident and gaps in the literature will be found, allowing for even more potential associations to be considered. All of this research will help to gain a better understanding of the little understood risk factors of adult PBTs.

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7.1. APPENDIX A

Details of the SEARCH Study Design by Centre

	Adelaide	Grenoble	Heidelberg	Los Angeles	Melbourne	Stockholm	Toronto	Winnipeg
Reference population	Metropolitan Adelaide area (English speakers only)	Isere Department	Rhein-Neckar region	Los Angeles County (female, English speakers only)	Major cities Victoria	Area of Uppsala, University hospital	Metro-politan Toronto	Winnipeg + 100 km + city of Brandon
Date of diagnosis	Feb. 1987-March 1990	1987-1991	Jan. 1987-Dec. 1988		July 1987- Dec. 1991	March 1987- Feb. 1990	1987-1991	1980-1988
Selection of cases								
Source	Hospital list, central cancer registry + Australian Brain Tumour Registry	Cancer registry	All neurosurgical units and pathology labs	County tumour registry	14 Melbourne hospitals, Victoria Cancer Registry	Cancer registry, Uppsala hospitals	All hospitals and treatment centres	Cancer registry, hospitals
Age range (years)	25-74	25-75	25-75	25-74	20-70	25-74	20-80	20-74
ICD codes	191, 192.1	191, 192	191, 192.1, 192.0	191	191	191, 192.1, 192.0	191-192.1	191, 192.0, 192.2
Histology	983-945, 953 + some others	9380/3-9539/3	938-948/3, 953 9580/0, 9560/0	9830-9473	938-948	983-948, 953	983-948	938-948, 9530/3
Proxy interview	Yes	yes	Yes	No	Yes	No	Yes	Yes
Selection of controls								
Matching	Frequency, sex, age $\pm$ 2 years, post code	Individual, sex, age, $\pm$ 5 years, urban/rural	Frequency, sex, age $\pm$ 2 years	Individual, sex, ethnicity, birth year $\pm$ 5 years	Individual, sex, age	Individual, sex, age, parish	Frequency, sex, age $\pm$ 5 years, area of residence	Individual, sex, age, urban/rural
Source	Electoral roll	General population	Population register	Random neighborhood controls	Electoral roll	Parish registers	Residential list	Random digit dialing of selection area
Proxy interview	Yes	Yes	Yes	No	No	No	No	Yes
Questionnaire	Standard diet separate	Standard minor differences	Standard some differences	Standard	Standard and mailed	Mailed questionnaire	Standard	Standard

7.2. APPENDIX B

Model-fit Statistics Definitions

R-square – also known as the *coefficient of determination*, R-square is found by first determining the ratio of the residual variability of the dependent variable to the original variance of the relationship between the dependent and independent variables. The smaller the variability of the residual values (the deviation of a particular point from the fitted regression line predicted by the model), the better the predictive ability of the model. R-square is found by subtracting this ratio from 1.0, so the extreme values are 0.0 (the model has no predictive value) and 1.0 (the model perfectly predicts the value of the dependent variable). In other words, if there is no relationship between the dependent and independent variables, the ratio value is 1.0 and R-square is equal to 0.0. If the variables are perfectly related, the ratio value is 0.0 since there is no residual variability and the R-square value is 1.0.

An R-square value of 0.40, for example, means that the model has explained 40 percent of the original variability and that the remaining 60 percent is residual variability that has not been explained by the model. Evaluating the fit of different models involves looking at the change in the R-square value. The inclusion of an additional independent variable in the model can never cause R-square to decrease. Therefore, one must look at how great the improvement in the R-square value is depending on the model used and the number of independent variables included.

c-statistic – the c-statistic produces a goodness-of-fit test for models that is very useful when there are low numbers of observations in case-control studies (less than 10 in a cell). It represents the area under the receiver-operating characteristic (ROC) curve and ranges in value from 0.0 to 1.0. For binary outcomes, such as whether a participant in the SEARCH study was a case or not, the c-statistic is used for evaluating the efficacy of a model in predicting whether or not the subject will experience the event (that is, be classified as a case) based on the inclusion of the different independent variables. A c-statistic value of 0.5 indicates no ability to discriminate based on the model; a value of 1.0 says the model perfectly predicts whether someone will be a case or a control, with model-fit improving as one moves from 0.5 to 1.0; and a value of less than 0.5 suggests that the inclusion of the independent variables actually worsens the predictive ability.

Wald chi-square – the Wald chi-square test is commonly used to test the significance of individual logistic regression coefficients for each of the included independent variables. When the inclusion of an independent variable in a multiple logistic regression model produces a significant increase in the Wald chi-square value, it means that the null hypothesis that that particular logit (effect) coefficient is zero must be rejected. This means that the variable significantly improves the ability of the model to predict the dependent outcome (whether the subject is a case or a control).

The global Wald chi-square used in this thesis represents the test that at least one of the predictors' regression coefficients is not equal to zero. By looking at the change in

Wald chi-square due to the inclusion of different independent variables, one can get a sense of the improved ability of the model due to the inclusion of that variable. As was the case with R-square, including a new variable in the model will never cause a decrease or no change in the Wald chi-square value. Therefore, one must compare the size of the increase from model to model to determine which particular model best fits the data.

-2 log likelihood ratio (-2LL) – also referred to simply as the *likelihood ratio*, -2LL has approximately a chi-square distribution and is used for testing the significance of the unexplained variance found in the dependent variable. For model significance testing, the -2LL test is used, which is the difference between the -2LL for the new model and the -2LL for the baseline model. For this thesis, that baseline model includes only the three matching variables: age, sex, and study centre. Independent variables which produce a large drop in the value of -2LL will mean that the fit of the model to the data has been greatly improved. Again, the inclusion of new variables will improve the -2LL value, so comparing models means looking at the relative changes in -2LL.

Hosmer and Lemeshow goodness-of-fit test – another model goodness-of-fit test that is based on a chi-square distribution. The Hosmer and Lemeshow test divides subjects into deciles based on predicted probabilities. A chi-square value is generated based on the difference between the observed frequencies and those frequencies predicted by the model. The reliability of the model is interpreted via a p-value with eight degrees of freedom. Those models which produce p-values of greater than 0.05 allow one to reject the null hypothesis that there is no difference between the observed and model-predicted values, meaning the model's estimates fit the data at an acceptable level. The further the p-value is from 0.05, the better the fit of the model. In using the Hosmer and Lemeshow test, one must be careful about cell sizes. As the number of participants in each cell gets larger, the ability of the test to detect smaller differences in the observed and expected frequencies improves. However, the test assumes that no group has an expected value of less than one and that 95 percent of the cells have at least five people in them.

7.3. APPENDIX C

Search Strategy for Medline

1. exp polymorphism, genetic/
2. polymorph\$.mp.
3. gene\$ muta\$.mp.
4. exp Genetic Phenomena/ge [Genetics]
5. 1 or 2 or 3 or 4
6. exp genes/
7. exp chromosomes/
8. exp genetic code/
9. exp genome/
10. exp genome components/
11. exp neoplasm proteins/
12. exp enzymes/
13. exp heterocyclic compounds/
14. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. exp brain neoplasms/
16. exp glioma/
17. glio\$.mp.
18. exp meningioma/
19. meningiom\$.mp.
20. astrocytom\$.mp.
21. oligoastrocytom\$.mp.
22. oligodendroglio\$.mp.
23. anaplastic\$.mp.
24. brain tum\$.mp.
25. brain cancer\$.mp.
26. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. 5 and 14 and 26

7.4. APPENDIX D

Search Strategy Used for Embase

1. exp genetic polymorphism/
2. polymorph\$.mp.
3. gene\$ muta\$.mp.
4. 1 or 2 or 3
5. exp Gene/
6. exp "Genetic and Familial Disorders"/
7. exp cancer genetics/
8. exp genome/
9. exp GENOTYPE/
10. exp genetic code/
11. exp human genetics/
12. exp population genetics/
13. exp cancer epidemiology/
14. exp genetic epidemiology/
15. exp chromosome/
16. exp Tumor Protein/
17. exp Enzyme/ct, ec [Clinical Trial, Endogenous Compound]
18. exp aromatic compound/ or exp heterocyclic compound/
19. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp Brain Tumor/
21. exp Glioma/
22. glio\$.mp.
23. exp Meningioma/
24. meningiom\$.mp.
25. exp Astrocytoma/
26. astrocytom\$.mp.
27. oligodendroglio\$.mp.
28. brain □eoplasm\$.mp.
29. brain cancer\$.mp.
30. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. 4 and 19 and 30

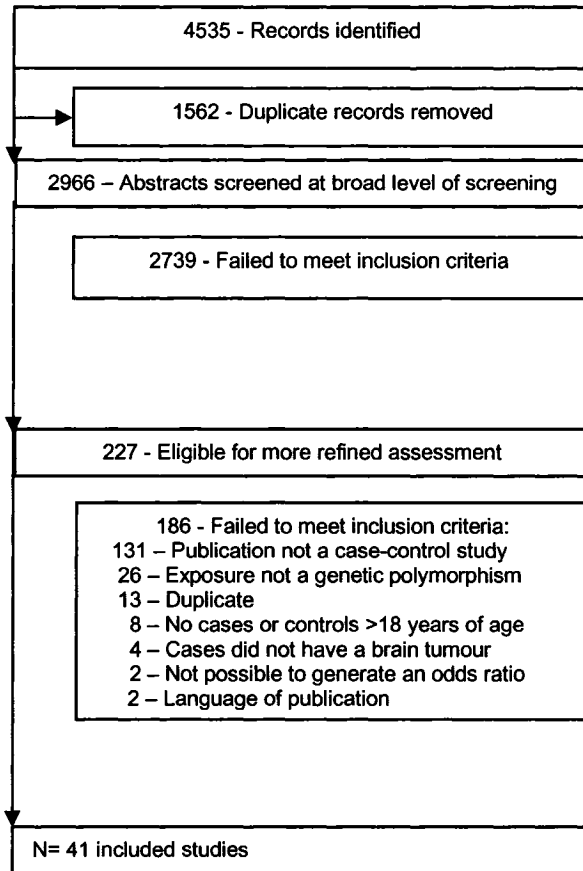
7.5. APPENDIX E

Search Strategy Used for PubMed

1. "Polymorphism, Genetic" [MeSH]
2. polymorph*
3. gene muta*
4. genetic muta*
5. genes muta*
6. #1 or #2 or #3 or #4 or #5
7. "Genes" [MeSH]
8. "Chromosomes" [MeSH]
9. "Genetic Code" [MeSH]
10. "Genome" [MeSH]
11. "Genome Components" [MeSH]
12. "Neoplasm Proteins" [MeSH]
13. "Enzymes" [MeSH]
14. "Heterocyclic Compounds" [MeSH]
15. #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
16. "Brain Neoplasms" [MeSH]
17. glio*
18. "Meningioma" [MeSH]
19. meningiom*
20. astrocytom*
21. oligoastrocytom*
22. oligodendroglio*
23. anaplastic*
24. brain tum*
25. brain cancer*
26. #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
27. #6 and #15 and #26

7.6. APPENDIX F

Flow Chart for the Systematic Review



7.7. APPENDIX G

Data Abstraction Form for Included Studies

Section 1: Publication Details				
RefWorks #				
Author(s)				
Title			Date of Publication	
Journal			Language	
Was the article peer-reviewed?	YES	NO	Source(s) of Funding	
Section 2: Study Characteristics				
	CASES		CONTROLS	
Accrual Dates				
Eligibility Criteria				
Population Selected From				
Method of Diagnosis			N/A	
Type of Controls (Population- or Hospital-based)	N/A			
# Identified				
# Included in Final Analysis				
Was adequate detail provided regarding reason for exclusion? Explain	# Excluded		# Excluded	
Was matching done?		If yes, what type (individual or frequency) and what characteristics?		

Were any significant differences found between cases and controls regarding population characteristics? Explain			
Section 3: Study Methods			
What genetic polymorphism(s) were assessed for association with primary brain tumours?			
Was the DNA source (i.e. blood sample, tumour sample, buccal cell) the same for cases and controls? State the DNA source used, if applicable.			
Were the methods used for DNA isolation and extraction explained in detail, including how the DNA was obtained and the solutions used to isolate the desired DNA?			
Were the DNA amplification techniques explained, including the primers used?			
Were the sequencing methods used to identify polymorphisms described in detail?			
Were there any quality control measures taken concerning genotyping, such as repeated samples or sub-samples?			
Section 4: Results of the Study			
CASES in which a polymorphism was identified	Raw Number	Percentage	
CONTROLS in which a polymorphism was identified	Raw Number	Percentage	
Crude Odds Ratio		LCL	UCL
Adjusted Odds Ratio		LCL	UCL
Explain any subgroup or sensitivity analysis done (i.e. histopathologic subgroups, age, gender)			

7.8. APPENDIX H

Included Genes in the Systematic Review and their Function

Cytochrome (CYP) “pigment at 450 nm” (P450) – generic term for 63 human genes coding for the various CYP P450 enzymes which are involved in the modification or degradation of chemicals, including drugs and endogenous compounds. They produce membrane-associated proteins which metabolize lipophilic compounds and thus play a crucial role in detoxification and provide defense against various toxic environmental factors. Most of the gene products can metabolize multiple substrates and many can catalyze multiple reactions. Also play important roles in hormone synthesis and breakdown, cholesterol synthesis, and vitamin D metabolism.

Glutathione S-Transferase Mu 1 (GSTM1) – located on chromosome 1p13.3, the *GSTM1* gene is responsible for producing a class of enzymes which function in the detoxification of electrophilic compounds. These compounds may include known carcinogens, therapeutic drugs, environmental toxins, and products of oxidative stress. The enzymes function via the conjugation of reduced glutathione to a wide number of exogenous and endogenous hydrophobic electrophiles.

Glutathione S-Transferase Theta 1 (GSTT1) – located at 22q11.13, the *GSTT1* gene acts similarly to *GSTM1* in that its enzymes catalyze the conjugation of glutathione to electrophilic species, providing the first step in the elimination of toxic compounds from the body. *GSTT1* acts on 1,2-epoxy-3-(4-nitrophenoxy)propane, phenethylisothiocyanate chloride, and 4-nitrophenethyl bromide.

Glutathione S-Transferase Pi (GSTP) – located at 11q13, these *GSTs* also play a role in drug and xenobiotic metabolism. They play an important role in the development of acquired drug resistance.

Glutathione S-Transferase Mu 3 (GSTM3) – similar role to the rest of the *GSTs*, in particular *GSTM1*. Expressed in the brain, the gene products may govern the uptake and detoxification of both endogenous compounds and xenobiotics at the testis and brain blood barriers.

WAF1/CIP1 – a cyclin-dependent kinase inhibitor, this gene encodes a protein which may interrupt the *p53* pathway and become a negative regulator of the cell cycle progression at G1. Can act to prevent the induction of a G1 arrest and subsequent DNA repair or apoptosis by *p53*.

Tuberous Sclerosis 2 (TSC2) – the exact function of this gene is not yet fully understood. The *TSC2* gene product is believed to be a tumour suppressor and acts to stimulate specific GTPases. The protein produced forms a cytosolic complex with hamartin, thus it has been proposed that it may act as a chaperone for hamartin.

Retinoblastoma (RB) – acts as a tumour suppressor gene. The *RB* gene is involved in suppressing the development of retinoblastoma, an embryonic malignant neoplasm of retinal origin.

N-Acetyltransferase 2 (NAT2) – encodes the enzyme N-acetyltransferase 2, which functions to both activate and deactivate arylamine and hydrazine drugs and carcinogens. The gene product also is responsible for metabolizing other primary aromatic amines and some drugs, dyes, pesticides, and cooking-related carcinogens.

Excision Repair Cross-Complementing Rodent Repair Deficiency Complementation Group 1 (ERCC1) – part of the nucleotide excision repair complex, *ERCC1* is required for the incision step in nucleotide excision repair. The gene product is the structure-specific DNA repair endonuclease responsible for the 5-prime incision made during DNA repair.

Excision Repair Cross-Complementing Rodent Repair Deficiency Complementation Group 2 (ERCC2) – like *ERCC1*, *ERCC2* is also part of the nucleotide excision repair complex. The gene product is an ATP-dependent 5-prime to 3-prime DNA helicase, which is a component of one of the core DNA transcription factors. The helicase acts by opening the DNA double-stranded helix around the damaged site. The *ERCC2* product is also involved in RNA transcription.

L-MYC – acts as an oncogene. Possesses a polymorphic EcoRI site which results in the appearance of either L (“large”, EcoRI-resistant) or S (“small”, EcoRI-sensitive) alleles.

p300/CBP Associated Factor (PCAF) – the protein encoded by this gene associates with p300 and CBP, two large nuclear proteins which bind to a variety of sequence-specific factors involved in cell growth and cellular differentiation. The *PCAF* gene encodes the PCA factor, a histone acetyltransferase, which regulates the *p53* gene, suggesting a possible pathway for inactivating the *p53* pathway and thus playing a direct role in transcriptional regulation.

Peroxisome Proliferative Activated Receptor Gamma (PPAR γ) – producing a nuclear receptor transcription factor, the *PPAR γ* gene plays an important role in adipocyte (fat cell) differentiation. Activation of the gene results in a powerful adipogenic response and enhanced insulin sensitivity. This activation can lead to slowing or cessation of cellular growth.

NAD(P)H Dehydrogenase Quinone 1 (NQO1) – the *NQO1* gene is a member of the NAD(P)H dehydrogenase family and encodes a cytoplasmic 2-electron reductase, an enzyme which is involved in the metabolism of a number of carcinogenic agents. The reductase binds to FAD to form homodimers and reduces quinones to hydroquinones, preventing the electron reduction of quinones that results in the production of radical species.

Human Homologue Budding-Uninhibited-by-Benzimidazole 3 (hBUB3) – the expression of the *hBUB3* gene is required for the execution of the mitotic spindle checkpoint. The protein produced is part of the checkpoint kinase complex and plays a major role in proper chromosome segregation by preventing aneuploidy.

Harvey Rat Sarcoma Homolog (HRAS) – a viral oncogene homolog which produces Ras proteins that bind to GDP/GTP and possess intrinsic GTPase activity. These proteins alternate between an inactive form that is bound to GDP and an active form which is bound to GTP. Guanine nucleotide-exchange factor facilitates the change from the inactive to the active form, while a GTPase-activating protein reverts the Ras protein from active to inactive.

p53 – the gene product is a nuclear protein which has an essential role in the regulation of the transition from G0 to G1 in the cell cycle. *p53* produces a protein with DNA-binding, oligomerization, and transcription activation domains and has been proposed to act as a tumor suppressor by activating the expression of downstream genes that inhibit cellular growth.

Deleted in Malignant Brain Tumours 1 (DMBT1) – the *DMBT1* gene encodes a secreted or membrane-linked protein belonging to the scavenger receptor cysteine-rich superfamily. The protein may have a role in mucosal immune defense since it binds to collectins, which are surfactant proteins. *DMBT1* may not be a classical tumour suppressor gene, but instead might be involved in the interaction between tumour cells and the immune system.

Axis Inhibition Protein 1 (AXIN1) – axin is a negative regulator of the *Wnt* pathway, which plays a crucial role during embryonic development and organogenesis through the control of cell proliferation and apoptosis.

O-6-Methylguanine DNA Methyltransferase (MGMT) – the *MGMT* produces one of the most important DNA repair enzymes which is responsible for catalyzing the transfer of the methyl group from O-6-methylguanine, as well as O-4-methylthymine adducts of DNA, induced by alkylating agents to the cysteine residue in its own molecule. The result is the prevention of a G:C to A:T transition. This cellular defense against the biological effects of O-6-methylguanine is a suicide reaction because the enzyme becomes irreversibly inactivated.

RAD54L – the *RAD54L* gene encodes a helicase which shares similarity with a yeast protein that is known to be involved in the homologous recombination and repair of DNA. The protein binds to double-stranded DNA breaks, inducing a topological change which is thought to help facilitate homologous DNA pairing and stimulate DNA recombination. A member of the *SNF2/SWI2* family of DNA-dependent ATPases, *RAD54L* has been identified as a candidate oncosuppressor gene.

Epidermal Growth Factor (EGF) – the *EGF* gene has been shown to alter the mitogenic signaling ability of the *EGF* receptor via the production of a receptor tyrosine

kinase, which is critical to normal cell proliferation and differentiation. The precursor is believed to be a membrane-bound molecule which is proteolytically cleaved resulting in a peptide hormone that stimulates cells to divide.

Coagulation Factor II (F2) – the gene codes for coagulation factor [FII]/prothrombin, which is proteolytically cleaved to form thrombin in the first step of the coagulation cascade. The *F2* gene also functions in maintaining vascular integrity during development and post-natal life.

Coagulation Factor V (F5) – coagulation factor FV activates the FII into thrombin, which in turn regulates the maturation of fibrinogen into fibrin. The FV factor circulates in the plasma and is activated by the release of an activation peptide by thrombin during coagulation.

5, 10-Methylenetetrahydrofolate Reductase (MTHFR) – the gene product is the MTHFR enzyme which regulates the homocysteine plasma level, which is part of the coagulation cascade. The enzyme catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a co-substrate for homocysteine remethylation to methionine.

Vascular Endothelial Growth Factor (VEGF) – the *VEGF* gene is a member of the *PDGF/VEGF* growth factor family. The gene product is a disulfide linked homodimer that acts on endothelial cells as a glycosylated mitogen. The gene influences the coagulation cascade because the protein that it produces can cause increased vascular permeability, angiogenesis, vasculogenesis, endothelial cell growth, and by inhibiting apoptosis. The *VEGF* gene also serves to regulate the balance between fibrin production and degradation.

Plasminogen Activator Inhibitor 1 (PAI-1) – similar to the *VEGF* gene, the *PAI-1* gene plays an influential role by regulating the balance between the production of fibrin and its degradation. Also known as the serpin peptidase inhibitor clad E, expression of the *PAI-1* gene can impede the coagulation cascade.

Plasminogen Activator – Tissue (PLAT) – the *PLAT* gene encodes a tissue-type plasminogen activator, a secreted serine protease which converts the proenzyme plasminogen to plasmin, a fibrinolytic enzyme. This enzyme plays a role in cell migration and tissue remodeling and increased enzymatic activity causes hyperfibrinolysis, which manifests as excessive bleeding, while decreased activity leads to hypofibrinolysis which can result in thrombosis or embolism.

X-Ray Repair Cross Complementing 1, 3, 5, 7 (XRCC 1, 3, 5, 7) – each of these four genes are involved in DNA single- and double-strand break repairs to maintain genomic stability. *XRCC1* is required for single-strand break repair, *XRCC3* for homologous recombination repair, *XRCC5* helps to complete double-strand break repair by non-homologous end joining, a similar role to that held by *XRCC7*.

Platelet Derived Growth Factor Receptor Alpha (PDGFRA) – expressed in early embryonic development, the *PDGFRA* gene encodes a tyrosine kinase receptor for platelet-derived growth factors that act as mitogens for cells of mesenchymal origin. The alpha gene is important for kidney development and may be a key component in the pathogenesis of a variety of brain tumours.

Chemokine (C-C motif) Receptor 5 (CC5) – the *CC5* gene encodes a beta chemokine receptor predicted to be a seven transmembrane protein similar to G protein-coupled receptors. The protein constitutes the major co-receptor for the macrophage-tropic strains of HIV-1. The location of the gene is at the chemokine receptor gene cluster region. Chemokines have been implicated in tumor progression and metastasis. They also indirectly affect tumor development by attracting immunocompetent cells with pro- or anti-tumoural activities.

Neurofibromin 2 (NF2) – the *NF2* gene encodes a protein that is thought to link cytoskeletal components of the cell with proteins located in the cell membrane, including cell-surface proteins, proteins involved in cytoskeletal dynamics, and ion transport regulating proteins. Expressed at high levels during embryonic development and in the central nervous system in adults, the *NF2* gene is involved in CNS tumourigenic pathways including meningioma, schwannoma, and neurofibromatosis type II.

Kirsten Rat Sarcoma Homolog (KRAS) – part of the *ras* oncogene family, which is involved in multiple human neoplasia pathways. The *KRAS* gene encodes a protein that acts a GTPase enzyme which may be putatively involved in meningioma formation.

Phosphatase and Tensin Homolog (PTEN) – encodes the protein phosphatidylinositol-3,4,5-triphosphate 3-phosphatase which acts to negatively regulate intracellular levels of phosphatidylinositol-3,4,5-triphosphate in cells and functions as a tumour suppressor by negatively regulating signaling pathways. *PTEN* has been identified as a tumour suppressor that is mutated in a large number of cancers at a high frequency.

Epithelial-cadherin (E-cadherin) – the gene encodes a calcium dependent cell-cell adhesion glycoprotein which is involved in extracellular interaction and is intimately involved in the Wnt pathway. Loss of function of the *E-cadherin* gene is thought to contribute to cancer progression by increasing proliferation, invasion, and metastasis.

Transforming Growth Factor Beta 1 (TGFB1) – the *TGFB1* gene produces a multifunctional peptide that controls proliferation, differentiation, and other functions in many cell types. The hormone acts as a negative autocrine growth factor and the dysregulation of its activation and signaling may result in apoptosis.

Transforming Growth Factor Beta Receptor II (TGFB2) – belonging to the serine-threonine kinase family, the *TGFB2* gene mediates the induction of growth inhibition and hypophosphorylation of the *RB* gene product. The transmembrane protein encoded by the gene has a protein kinase domain and forms a heterodimeric complex with another receptor protein and binds TGF-beta. This receptor/ligand complex phosphorylates

proteins which then enter the nucleus and regulate the transcription of a subset of genes related to cell proliferation.

Glioma Tumour Suppressor Candidate Region 1 (GLTSCR1) – expressed at moderate levels in the heart, brain, placenta, skeletal muscle, and pancreas, and at lower levels in the lung, liver, and kidney, the *GLTSCR1* gene has been proposed to help suppress the development of glioma in adults.

Interleukin-4 Receptor Alpha (IL-4RA) – the alpha chain of the IL-4R is a type I transmembrane that regulates IgE production by binding to interleukin 4 and 13. The gene product of *IL-4RA* also promotes the differentiation of Th2 cells.

Interleukin-13 (IL-13) – the *IL-13* gene encodes an immunoregulatory cytokine that is produced in response to activated Th2 cells. The cytokine is also involved in the maturation and differentiation of beta cells and down-regulates macrophage activity, which inhibits the production of pro-inflammatory cytokines and chemokines. The *IL-13* gene product also up-regulates CD23 and MHC class II expression and promotes the IgE isotype switching of beta cells.

A Disintegrin And Metalloprotease Domain 33 (ADAM33) – the *ADAM33* gene encodes a membrane-anchored protein that has been suggested to be involved in cell-cell and cell-matrix interactions such as fertilization, muscle development, and neurogenesis.

Cyclooxygenase-2 (COX-2) – also known as *PTGS* (Prostaglandin-endoperoxide synthase), the *COX-2* gene is responsible for producing an enzyme involved in prostaglandin biosynthesis. The enzyme acts as both a dioxygenase and a peroxidase.

Major Histocompatibility Complex (HLA) – consists of a group of genes which produce class I heavy chain paralogues, which are heterodimers that have both a heavy and light chain. The molecules formed by these genes are keys to the immune system since they present peptides derived from the lumen of the endoplasmic reticulum.

Tumour Necrosis Factor Beta (TNFb) – the *TNFb* gene produces a cytokine which is highly inducible and once secreted it exists as a homotrimeric molecule. These heterotrimers anchor lymphotoxin-alpha to the cell surface. *TNFb* is also responsible for mediating a wide variety of inflammatory, immunostimulatory, and antiviral responses. It is also involved in organ development and cellular apoptosis.

Matrix Metalloproteinase 1 (MMP1) – the *MMP1* gene encodes a protein that is responsible for the breakdown of the extracellular matrix required for embryonic development, reproduction, tissue remodeling, and disease processes. Specifically, it breaks down the interstitial collagens found in the extracellular matrix. The protein is first secreted in its inactive proprotein form and is activated by extracellular proteinases.

Multi-drug Resistance 1 (MDR1) – *MDR1* is part of one of the seven distinct subfamilies of the ATP-binding cassette (ABC) transporters superfamily. The protein

produced by the expression of this gene is involved in multi-drug resistance. It is an ATP-dependent drug efflux pump for xenobiotic compounds with broad substrate specificity. Due to its responsibility for decreased drug accumulation in multi-drug resistant cells, the *MDR1* gene often mediates the development of cellular resistance to the effects of anti-cancer drugs. The *MDR1* protein also serves as a transporter protein in the blood-brain barrier.

Aminolevulinate Delta-dehydratase (ALAD) – the *ALAD* gene is responsible for encoding an enzyme which catalyzes the condensation of two molecules of delta-aminolevulinate to form porphobilinogen, which is a precursor of heme, cytochromes, and other hemoproteins. The gene product catalyzes the second step of the porphyrin and heme biosynthetic pathway.