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Chapter 1

Epidemiology of meningiomas

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Abstract

More than 70,000 primary central nervous system tumors are diagnosed in the United States each year. Approximately 36% of these are meningiomas, making it the most common primary brain tumor. Because meningioma risk increases dramatically with age, the healthcare burden of meningioma in the developed world will continue to rise as demographics shift toward an older population. In addition to demographic factors associated with increased meningioma risk (i.e., older age, female sex, African American ethnicity), increased body mass index is a strong risk factor. A history of atopic allergies, eczema, and increased serum IgE are all consistently associated with reduced meningioma risk, suggesting a potential role for immunosurveillance. Although ionizing radiation is a strong meningioma risk factor, it accounts for very few cases at the population level. Recent studies suggest that diagnostic radiation (e.g., dental X-rays) increases meningioma risk. Because radiation dosages associated with medical imaging have decreased dramatically, the public health impact of this exposure is likely in decline. Genome-wide association studies have identified common inherited variants in the gene *MLLT10* and *RIC8A* as low-penetrance meningioma risk alleles. To provide further insight into the etiology of meningioma, future studies will need to simultaneously examine genetic and environmental risk factors, while also stratifying analyses by subject sex.

MENINGIOMA INCIDENCE[1]

Although primary brain tumors are relatively rare compared with metastatic brain tumors, they constitute an important source of morbidity and mortality. More than 70,000 new cases of primary malignant and benign brain and central nervous system (CNS) tumors are diagnosed in the United States each year. Of these, 36.0% are meningiomas and 28.6% are gliomas (Ostrom et al., 2015b). This makes meningioma the most common primary brain tumor in adults, although glioma remains the most common primary malignant brain tumor in adults, accounting for approximately 80% of malignant brain tumor diagnoses (Ostrom et al., 2015b). Meningioma incidence rates have increased over the last 30 years, with increased use of diagnostic imaging, improved reporting, and changing outlooks toward diagnosis in the elderly suspected to account for this observed increase (Ostrom et al., 2013). In the United States, from 2008 to 2012, meningioma had an average age-adjusted incidence rate of 7.86 per 100,000 population per year (Ostrom et al., 2015b). The Central Brain Tumor Registry of the United States (CBTRUS) data from 2004 to 2010 indicate that 94.6% of newly diagnosed meningioma are classified as WHO grade I tumors, 4.2% as WHO grade II and 1.2% as WHO grade III (Kshettry et al., 2015b).

[1]Gene abbreviations used in the chapter are listed at the end of the chapter before References section.

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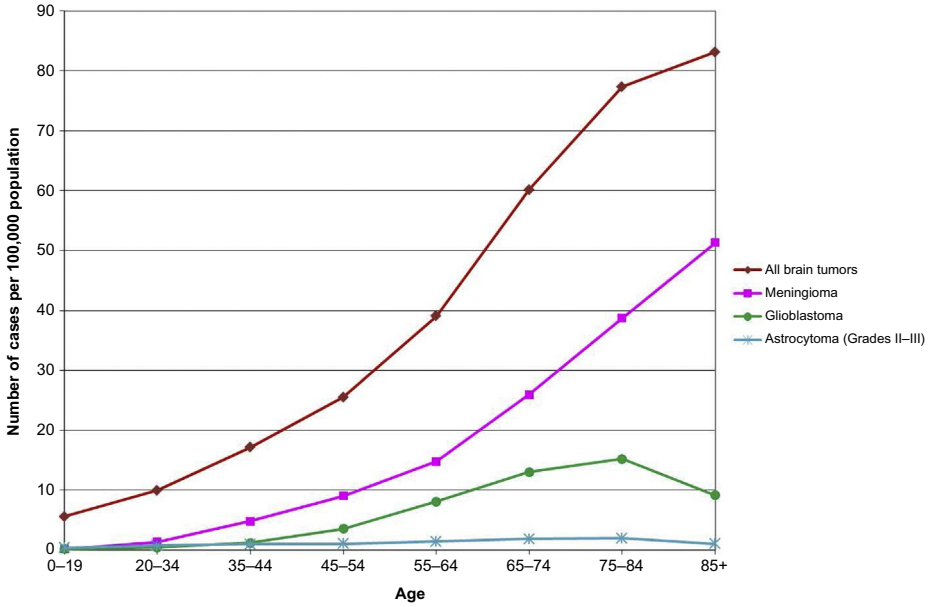

Fig. 1.1. Incidence of common adult brain tumor histologies, by age at diagnosis. Data from Central Brain Tumor Registry of the United States (CBTRUS), 2008–12, table 12, age-adjusted to the 2000 US standard population.

In the United States, the median age at diagnosis of a meningioma between 2006 and 2010 was 65 years (Ostrom et al., 2015b). Meningiomas are rare in children, accounting for just 2.9% of primary brain tumors in pediatric populations (age 0–14 years) (Ostrom et al., 2015a). The average annual incidence rates for selected adult brain tumor histologies, stratified by age at diagnosis, are shown in Fig. 1.1. Incidence rates of meningioma increase monotonically with advancing age, reaching a peak incidence of 51.3 cases per 100,000 population per year in individuals aged 85 and older. As with other neoplasms, the increased incidence of meningioma with age could be due to the length of time required for cellular transformation, the necessity of key genetic alterations prior to the onset of clinical disease, diminished immunosurveillance, or increased opportunity for detection of subclinical tumors over longer periods of time.

DIFFERENCES IN INCIDENCE BY SEX

Men are at increased risk of glioma, embryonal tumors, germ cell tumors, and primary CNS lymphoma, whereas women are at increased risk of pituitary tumors and meningioma (Ostrom et al., 2014b, 2015a, b). In the case of meningioma, the incidence rate in females aged 0–19 is approximately the same as that in males aged 0–19, meaning that the female-to-male incidence rate ratio (IRR) is approximately 1.0 (Wiemels et al., 2010). In individuals aged 20–34, the female:male IRR increases to approximately 2.0, before reaching a maximum of 3.1 in individuals aged 35–44 (Wiemels et al., 2010). Subsequently, this IRR begins to taper off, dropping to approximately 1.5 in individuals aged 85+ (Fig. 1.2). Because female sex confers the largest relative risk for meningioma during peak reproductive years, investigators have examined factors associated with endogenous and exogenous female hormones as potential meningioma risk factors. A comprehensive understanding of meningioma etiology must account for these sex differences. However, this important epidemiologic observation remains poorly understood.

DIFFERENCES IN INCIDENCE BY GEOGRAPHY AND ETHNICITY

Interpretations of ethnic and geographic variation in the occurrence of brain tumors are complicated by problems in ascertainment and reporting. Regions with the highest reported rates of primary brain tumors (e.g., Northern Europe, United States, and Israel) generally have better access to medical imaging than areas with the lowest rates (Inskip et al., 1995). The absolute variation in the occurrence of brain tumors between high-risk and low-risk areas

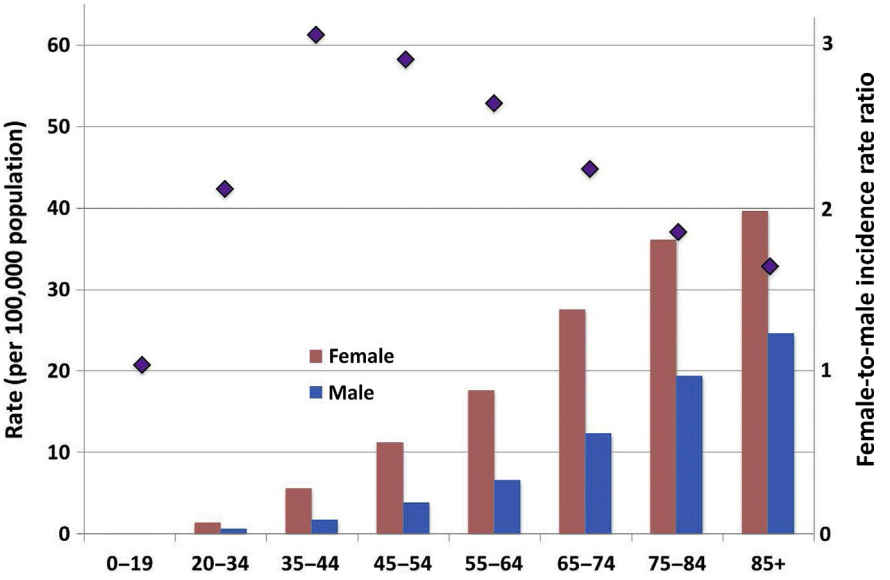

Fig. 1.2. Age- and sex-specific annual incidence rates (per 100,000 population) for meningioma in the United States (2002–06). The left *Y*-axis scale refers to the bar graphs of meningioma incidence. The female-to-male incidence rate ratio (IRR) is indicated by a *diamond* at each age group, and the axis for the female-to-male IRR is on the right *Y*-axis. The peak IRR of 3.1 occurs in the 35–44 year age group. Modified and adapted from Wiemels, J., Wrensch, M., Claus, E.B., 2010. Epidemiology and etiology of meningioma. J Neuro-Oncol 99, 307–314.

is of the order of fourfold, compared with a 20-fold difference for lung cancer and a 150-fold difference for melanoma (Forman et al., 2013). Thus, for meningioma, it seems unlikely that there are strong environmental risk factors associated with geography. However, some of this variation in incidence suggests that interethnic differences may exist in inherited susceptibility or exposure to yet unknown risk factors of relatively small effect (Kshettry et al., 2015b).

Within the United States, African Americans have a 1.23-fold higher rate of meningioma than non-Hispanic whites and a 1.21-fold higher rate of meningioma than Asians/Pacific Islanders (Ostrom et al., 2015b). This increased risk of meningioma in African Americans is difficult to attribute to differences in access to medical care or diagnostic practices, as African Americans typically experience reduced access relative to white and Asian populations in the United States. Interethnic differences in meningioma incidence are even more pronounced when stratifying by WHO tumor grade (Fig. 1.3). African Americans have a 1.33-fold increased risk of grade II meningioma relative to whites, and a 1.56-fold increased risk of grade III meningioma relative to whites. In addition, Asian Americans have a 1.35-fold increased risk of grade II meningioma relative to whites, and a 1.63-fold increased risk of grade III meningioma relative to whites (Kshettry et al., 2015b).

When analyses are stratified by tumor site (spinal vs intracranial), a different picture is revealed. The highest incidence of spinal meningioma is observed in Hispanics, who have a 1.21-fold increased risk of spinal meningioma relative to non-Hispanic whites (Kshettry et al., 2015a). Non-Hispanic whites have a 1.39-fold increased risk of spinal meningioma relative to African Americans, who have the lowest rate of spinal meningiomas (Kshettry et al., 2015a). Why African Americans are at significantly increased risk of intracranial meningioma but significantly decreased risk of spinal meningioma relative to whites has not been explored.

PATIENT PROGNOSIS

Population-based data from Scandinavia suggest that survival of patients with meningioma improved during the latter half of the 20th century (Sankila et al., 1992; Helseth, 1997). This improvement may be partly due to earlier diagnoses accompanying advances in imaging technology. In 2011, Cahill and Claus estimated the 3-year survival rate for US patients with nonmalignant intracranial meningioma to be 85% (Cahill and Claus, 2011). Although patients with WHO grade I tumors have good overall survival, prognosis is substantially poorer for patients with malignant histology. Between 2008 and 2012,

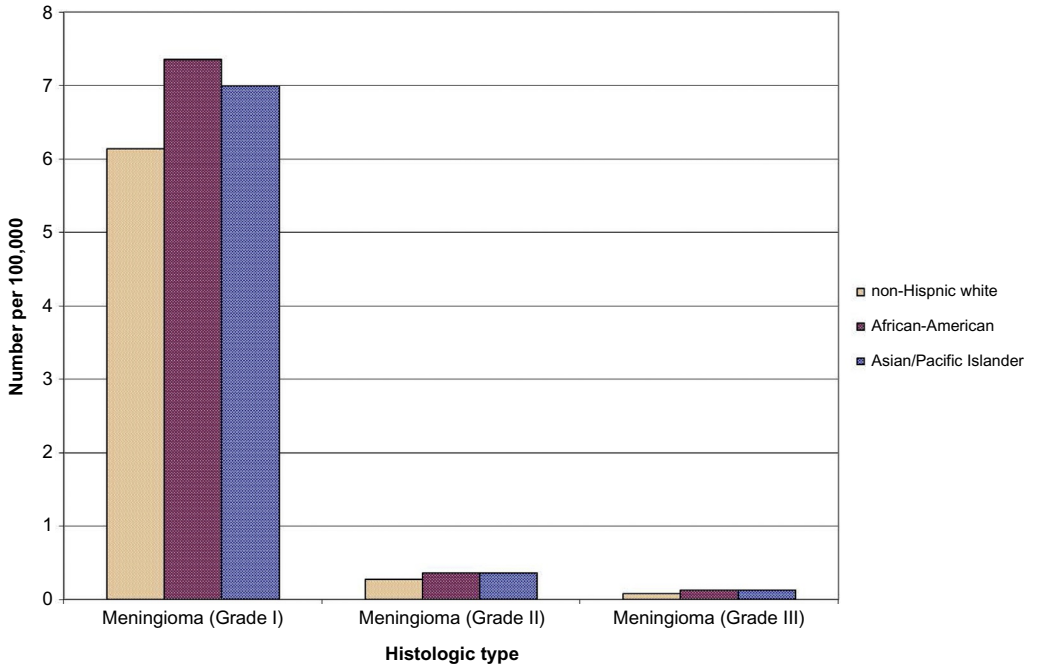

Fig. 1.3. Meningioma incidence, by WHO tumor grade and ethnicity. Data from Central Brain Tumor Registry of the United States (CBTRUS), 2004–10, table 6, age-adjusted to the 2000 US standard population.

US patients with malignant meningiomas experienced 3-year, 5-year, and 10-year "all-cause" survival probabilities of 71.0%, 65.2%, and 57.5%, respectively, but malignant meningioma patients ages 20–44 had a 10-year survival probability of 82.2% (Ostrom et al., 2015b).

Prognostic factors for patients with meningioma have not been thoroughly studied, perhaps because these patients typically have a more favorable prognosis than those in whom other brain tumors (e.g., gliomas) are diagnosed. Generally, older age at diagnosis and higher tumor grade contribute to poorer prognosis. The results from a large study of 9000 patients revealed the following additional prognostic factors for benign meningioma: female sex, tumor size, resection, and radiotherapy. For malignant meningioma, the prognostic factors included only age, resection, and radiotherapy (Cahill and Claus, 2011).

In the last 3 years, two major whole-exome sequencings projects were completed to investigate genomic alterations in meningioma tumor genomes. Clark et al. performed whole-exome sequencing on 50 WHO grade I meningiomas and identified mutations in *NF2*, *TRAF7*, *KLF4*, *AKT1*, and *SMO* (Clark et al., 2013). *NF2* mutations rarely co-occurred with these other mutations. The *TRAF7* mutation, however, tended to co-occur with mutations of either *KLF4* or *AKT1*. The investigators then validated these findings by performing targeted sequencing of the five genes and copy-number analysis of chromosome 22 (where *NF2* is located) in an additional 250 tumors. Brastianos et al. performed whole-genome or whole-exome sequencing on 17 WHO grade I meningioma samples, followed by validation sequencing in 30 additional WHO grade I samples and 18 grade II/III samples. They found mutations similar to those of Clark et al. and also identified mutations in *NF2*, *SMO*, and *AKT1* (Brastianos et al., 2013).

Abedalthagafi et al. analyzed 150 meningiomas using array-comparative genomic hybridization, followed by targeted sequencing of *AKT1*, *KLF4*, *NF2*, *PIK3CA*, *SMO*, and *TRAF7*. They found that *PI3K* mutations are as common as those in *AKT1* and *SMO*, and also commonly co-occurred with those in *TRAF7* (Abedalthagafi et al., 2016). Recently, mutations in the *TERT* gene promoter have been identified in 6%–7% of meningioma patients (Goutagny et al., 2014; Sahm et al., 2016), where they are associated with significantly shorter time to progression (10 months vs 179 months) (Sahm et al., 2016). These mutations generate a novel transcription factor binding site, leading to increased expression of *TERT*, reactivation of telomerase, competent telomere maintenance, and cellular immortalization (Bell et al., 2015).

Genomic analyses of meningioma have largely been limited due to a lack of long-term clinical

follow-up, leaving investigators unable to evaluate samples for predictors of tumor recurrence, progression, or overall survival. Thus, with the exception of *TERT* promoter mutations, the clinical relevance of these newly identified somatic changes remains unknown. Whether the somatic driver mutations underlying meningioma development are also associated with patient outcome will require additional investigation using larger well-annotated datasets.

INHERITED RISK

A genetic predisposition to meningioma has long been suspected because of the increased risk of meningioma observed in first-degree relatives of affected patients and also because of the existence of meningioma in rare familial cancer syndromes (e.g., Neurofibromatosis type II). A recent case–control study revealed that meningioma patients were four times more likely than controls to report a first-degree family history of meningioma (Claus et al., 2011). Many studies have attempted to identify rare genetic mutations conferring increased meningioma risk within families, leading to the identification of several genes, including *SMARCB1* (van den Munckhof et al., 2012), *SMARCE1* (Smith et al., 2013; Gerkes et al., 2016), *SUFU* (Aavikko et al., 2012; Schulman et al., 2016), and *PTCH1* (Kijima et al., 2012) (Table 1.1). Although such methods can identify genes contributing to meningioma risk in families with rare Mendelian tumor predisposition syndromes, these genes likely explain only a small proportion of meningioma incidence at the population level (Claus et al., 2011).

GENOME-WIDE ASSOCIATION STUDIES

Prior to the advent of genome-wide association studies (GWAS), numerous candidate–gene association studies were conducted in meningioma case–control sets, exploring polymorphisms involved in folate metabolism (Li et al., 2013), innate immunity (Rajaraman et al., 2010), insulin-like growth factor pathways (Lonn et al., 2008), and DNA repair (Leone et al., 2003; Bethke et al., 2008; Kiuru et al., 2008). In general, these studies have not been subjected to replication testing in an independent sample and are highly susceptible to false-positive findings. Indeed, candidate–gene approaches to identify common inherited variants that are reproducibly associated with brain tumor risk have had limited success in stark contrast to the GWAS approach (Walsh et al., 2013).

Table 1.1

Exposures studied as possible meningioma risk factors

	Association (magnitude and direction)	Subgroup specificity
Established risk factors		
High dose radiation	$^{+++}$	None
Female vs male gender	$^{++}$	Strongest for WHO grade I tumors
Increasing age	$^{+++}$	None
African American vs non-Hispanic white ethnicity	$^{+}$	Strongest for WHO grade II/III tumors
Asian American vs non-Hispanic white ethnicity	$^{+}$	WHO grade II/III tumors
Increased BMI	$^{+}$	None
Familial cancer syndromes (*gene*)		
Neurofibromatosis type 2 (*NF2*)	$^{+++}$	None
Melanoma–astrocytoma syndrome (*CDKN2A*)	$^{+++}$	None
SMARCE1 mutation	$^{+++}$	Clear-cell meningioma
SMARCB1 mutation	$^{+++}$	None
SUFU mutation	$^{+++}$	None
Gorlin syndrome (*PTCH1*)	$^{+++}$	None
Inherited single-nucleotide polymorphisms		
rs11012732-A (*MLLT10*)	$^{+}$	None
rs2686876-T (*RIC8A*)	$^{+}$	Unknown
Probable risk factors		
Allergies/asthma	$^{-}$	None
Eczema	$^{-}$	None
Elevated IgE	$^{-}$	None
Family history of brain tumors	$^{+}$	None
Dental X-rays	$^{+}$	None
Cigarette smoking	$^{+}$	Meningioma in men
Cigarette smoking	$^{-}$	Meningioma in women
Hispanic vs non-Hispanic white ethnicity	$^{+}$	Spinal meningioma
Non-Hispanic white vs African American ethnicity	$^{+}$	Spinal meningioma
Possible risk factors		
NSAID use	$^{+}$	None
Infant head circumference	$^{+}$	None
Probably not risk factors		
Head injury	$^{\times}$	None
Alcohol use	$^{\times}$	None
Residential power lines/EMF	$^{\times}$	None
Reproductive factors	$^{\times}$	None
Viral infections	$^{\times}$	None
Cell phone use	$^{\times}$	None

$^{+++}$Odds ratio $\geq$5.0; $^{++}$5.0 > odds ratio $\geq$2.0; $^{+}$2.0 > odds ratio $\geq$1.0; $^{\times}$odds ratio = 1.0; $^{-}$1.00 > odds ratio $\geq$0.50.

In a GWAS, individuals with the disease of interest (e.g., meningioma) and healthy controls are genotyped for hundreds of thousands of single-nucleotide polymorphisms (SNPs) to discover alleles that are significantly more common in those with the disease than in those without. GWAS have had great success in revealing the genetic etiology of primary brain tumors, especially glioma (Walsh et al., 2015). For meningioma, a GWAS conducted in Europeans has identified a highly statistically significant low-penetrance susceptibility locus (rs11012732) in the *MLLT10* gene on chromosome 10, conferring a 1.5-fold increased risk of meningioma (Dobbins et al., 2011). The association between meningioma risk and this common heritable polymorphism was subsequently validated in an independent replication dataset from the United States (Egan et al., 2015). Interestingly, SNPs in *MLLT10* have been previously associated with risk of hormone-related neoplasms, including ovarian cancer (Pharoah et al., 2013) and ER+ breast cancer (Michailidou et al., 2013). A second GWAS of American meningioma patients, which involved meta-analysis with the European GWAS data, identified a second risk locus on 11p15.5 (rs2686876) near *RIC8A*, conferring a 1.4-fold increase in meningioma risk (Claus et al., 2018).

ALLERGY, IMMUNOLOGY, AND MENINGIOMA RISK

Numerous studies have shown that allergic conditions, including asthma, hay fever, eczema, and food allergies, reduce brain tumor risk (Wigertz et al., 2007; Berg-Beckhoff et al., 2009; Turner et al., 2013). Linos et al. conducted a formal meta-analysis of a subset of these studies and concluded that allergies reduce glioma risk by nearly 40% (Linos et al., 2007). This observation appears to extend to both acoustic neuroma and meningioma (Claus et al., 2011; Turner et al., 2013). Indeed, a separate meta-analysis of meningioma indicated that eczema conferred a 25% reduction in meningioma risk (Wang et al., 2011). Similar effect sizes were observed for allergy overall and also for hay fever (Wang et al., 2011). These effects appear to be strongest for adult-onset allergies, as results from the INTERPHONE study suggested that the inverse associations with asthma and hay fever strengthened with increasing age of allergy onset (Turner et al., 2013).

Although mechanisms underlying the protective effect of allergies have not been elucidated, it may arise from increased tumor immunosurveillance in individuals with allergies and autoimmune disease (Dunn et al., 2002). It is also possible that the inverse association results from immune suppression by the preclinical tumor, but validation of the inverse association in prospective data sources makes this explanation less convincing. Meningioma patients have also been observed to have lower levels of serum IgE, a marker of atopy, than healthy controls (Wiemels et al., 2011). Although that study was conducted in meningioma patients following diagnosis, similar results have been observed for adult gliomas when using prediagnostic sera (Calboli et al., 2011).

Polyomaviruses (simian virus 40, JC virus, and BK virus), adenoviruses, retroviruses, and herpes viruses have also been investigated in relation to the genesis of meningioma in experimental animal models and in limited epidemiologic studies (Weggen et al., 2000; Poltermann et al., 2006). The potential risk from these agents has not been well addressed in epidemiologic studies, but evidence for viral involvement in meningioma etiology generally appears weak (Weggen et al., 2000; Poltermann et al., 2006). Renewed interest in a potential viral origin for some brain tumors may spark new epidemiologic studies, but such studies must consider the potential importance of low-level infection, requiring stringent technical conditions and development of more sensitive assays.

PERSONAL MEDICAL HISTORY

Cyclooxygenase-2 (COX-II) enzymes are commonly expressed in meningiomas (Ragel et al., 2005; Buccoliero et al., 2007), and treatment with selective COX-II inhibitors has shown inhibitory growth effects in vivo (Ragel et al., 2007). Therefore, nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, was hypothesized to reduce brain tumor risk (Ulrich et al., 2006). In a large nested case–control study, a paradoxical 1.35-fold increased risk of meningioma was observed with use of nonaspirin NSAIDs (Bannon et al., 2013). Although this was not the expected direction of the effect, the study was conducted using a large dataset of prospectively collected, population-based primary care patients, providing a representative sample of UK patients. Furthermore, the assessment of NSAID use via medical record review within a system of socialized medicine helped to eliminate recall biases. The authors controlled for protopathic bias by excluding NSAID/aspirin use 1 and 3 years prior to diagnosis.

Given these study strengths, the potential relationship between NSAID use and increased meningioma risk merits future study.

A recent meta-analysis identified a significant association between body mass index (BMI) and increased meningioma risk (Sergentanis et al., 2015). Overweight/obesity status was associated with a 1.27-fold increased risk of meningioma in females and a 1.58-fold increased meningioma risk in males. A significant dose–response relationship was also observed (Sergentanis et al., 2015). A Mendelian randomization approach leveraging genetic instruments known to be associated with interindividual variation in BMI provided support for obesity as a meningioma risk factor for meningioma. Genetic predisposition to higher BMI and higher body fat percentage were both associated with significantly elevated risk of meningioma (Takahashi et al., 2019). Hypothesized mechanisms underlying these associations include chronic insulin resistance, increased activity of insulin-like growth factors and increased levels of circulating estrogen in overweight persons. Other anthropometric measures, such as birth weight, have not been consistently associated with subsequent meningioma risk in adulthood. However, a larger head circumference at birth has been associated with an increased risk of developing meningioma as a young adult among subjects in a Swedish birth cohort (Tettamanti et al., 2016).

IONIZING RADIATION

Sources of exposure to ionizing radiation include occupation, therapeutic and diagnostic medical procedures, and proximity to atomic bomb explosions (including atmospheric testing of nuclear weapons). Survivors of the bombing of Hiroshima have elevated risk of meningioma, increasing with the estimated dose of radiation (Sadamori et al., 1996; Shintani et al., 1999). The use of ionizing radiation to treat tinea capitis (i.e., ringworm) and skin hemangioma in infants and children, once common practice, has been associated with relative risks of 18, 10, and 3, for nerve sheath tumors, meningiomas, and gliomas, respectively (Braganza et al., 2012). This treatment was applied en masse to Israeli immigrants coming from North Africa and the Middle East during the 1950s. Analysis of meningioma incidence data in these immigrant cohorts revealed an iatrogenic epidemic of meningioma that fundamentally shifted the national meningioma incidence pattern of Israel (Sadetzki et al., 2000).

As further evidence of iatrogenic meningioma resulting from radiotherapy, second primary brain tumors occur more frequently than expected in patients previously treated for a first brain tumor. The standardized incidence ratio for a second primary CNS tumor in brain tumor patients treated by surgery alone is 2.0 (95% CI 1.2–3.2) vs 5.1 (95% CI 2.5–9.4) for patients treated with radiotherapy (Salminen et al., 1999). However, these results may be influenced by the fact that people with higher grade tumors are more likely to both receive adjuvant radiotherapy and also to have multiple primary cancers due to underlying genetic predisposition.

Results from case–control studies investigating the link between meningioma and exposure to ionizing radiation have observed variable effect sizes, perhaps because of imprecise estimates of age at first exposure, imprecise estimates of ration dosage, or a low prevalence of exposure to high doses of ionizing radiation in large samples of controls. However, the consistent and strong results from prospective studies of people exposed to ionizing radiation provide unquestionable evidence of a linear dose–response association between ionizing radiation exposure and meningioma risk. Future studies should consider the potential for interaction between ionizing radiation and both age at exposure and genetic variation that may mediate susceptibility to the tumorigenic effects of radiation.

Despite the known association between ionizing radiation and meningioma risk, therapeutic doses of ionizing radiation contribute to the development of only a small proportion of meningiomas in adults because exposure to therapeutic levels of ionizing radiation is rare and the vast majority of meningioma patients report no such exposure. For example, in one study, between 1% and 3% of meningioma patients, as well as controls, reported a history of at least one therapeutic dose of ionizing radiation exposure before their brain tumor diagnosis (Blettner et al., 2007). However, among pediatric populations where meningioma is much rarer, previous therapeutic radiation is perhaps the second leading cause of meningioma, second to only neurofibromatosis (Erdincler et al., 1998).

Elucidating a possible role for more common radiation exposure, such as that resulting from dental radiographs, requires more precise and reliable assessment of exposure. Evidence thus far supports a role for diagnostic radiation in causing meningioma. Claus et al. reported that persons with meningioma were twice as likely as controls to have received

bitewing X-rays on an annual or more frequent basis (Claus et al., 2012a). Similar findings were recently reported for a hospital-based study of acoustic neuroma (Han et al., 2012). Because radiation dosage has decreased dramatically since the time period during which patients in these studies received X-rays, the public health impact of dental X-rays on meningioma incidence is likely on the decline.

NONIONIZING RADIATION, INCLUDING MOBILE PHONE USE

To date, epidemiologic studies of adult brain tumors do not support the hypothesis that residential power lines increase the risk of brain tumors (Wrensch et al., 1999). A limitation with studies of EMF exposures and adult brain tumors is that the pertinent exposure period and the mechanisms through which EMF might contribute to brain tumor risk are unknown. The possibility that more affluent individuals may avoid living near high-power lines further complicates analyses by generating differences in socioeconomic status between exposed and unexposed subjects.

Cellular phone technology was introduced in the 1980s and the vast majority of people in the United States now use mobile phones. Public concern over the potential health effects of mobile phones has prompted additional study of exposure to radiofrequency fields and brain tumor risk. In 2011, the International Agency for Research on Cancer (IARC) published a monograph evaluating the potential carcinogenic risks to humans of mobile phones. IARC classified radiofrequency fields as a possible carcinogen (IARC group 2B), meaning that there "could be some risk" of carcinogenicity and that "additional research into the long-term effects of mobile phone use is warranted." Recent epidemiologic studies reporting on glioma risk in relation to cellular phone use in adults have demonstrated generally null results (Ostrom et al., 2014a). Time trends of age-standardized meningioma incidence rates are an important tool to examine the possible associations between mobile phone use and meningioma risk. Although mobile phone use has increased extremely rapidly worldwide, meningioma incidence rates have remained relatively stable.

The UK Million Women study examined brain tumor risk in relation to duration of use of a mobile phone in a prospective manner (Benson et al., 2013). Meningioma risk was not significantly different for daily users of cellular phones compared with never-users in the UK sample. Although brain tumor incidence has not increased with the marked increase in mobile phone use, the latency period of brain tumors may be extremely long, especially for meningioma. Thus, the potential association between cellular phone use and meningioma risk deserves continued monitoring as data on long-term heavy users accrues.

REPRODUCTIVE AND HORMONAL FACTORS

In part because females have a lower risk for glioma and a greater risk for meningioma, investigators have examined factors associated with endogenous and exogenous female hormonal status as putative brain tumor risk factors, including ages at menarche and menopause, gravidity, parity, use of oral contraceptives, and use of hormone replacement therapy (HRT). Endogenous estrogen and other female hormone levels are highest in women between the ages of menarche and menopause; therefore investigators have examined age-specific meningioma incidence rates to look for patterns related to hormone levels. Results suggest that the female-to-male IRR reaches its apex ($\sim$3.1) during peak reproductive years (Wiemels et al., 2010).

There is no consistent or convincing evidence that parity is associated with risk for meningioma (Schlehofer et al., 1992; Jhawar et al., 2003). Inconsistent results pertaining to oral contraceptive use and HRT have been reported for meningioma risk (Hatch et al., 2005; Wigertz et al., 2006). Results from a population-based case–control study revealed elevated meningioma risk in women with increased BMI and in premenopausal women taking oral contraceptives but did not identify significant associations between meningioma risk and postmenopausal HRT (Claus et al., 2013).

Data from a large multicenter case–control study revealed that cigarette smoking significantly reduced meningioma risk in women, but increased meningioma risk in men (Claus et al., 2012b). The authors hypothesized that the increased risk of meningioma observed in male smokers was likely related to the known tumorigenic effect of chemicals contained in cigarette smoke, while the decreased risk of meningioma in female smokers was possibly related to diminished hormone levels. Because smoking could potentially abrogate a strong meningioma risk factor in women (hormone levels), it is conceivable that this effect could supersede the modest increased risk of meningioma conferred by tobacco-related chemical exposures in this population. Their results highlight the importance of analyzing meningioma risk

separately for men and for women. Additionally, although the protective effect of tobacco use on meningioma risk may seem aberrant, smoking is also consistently associated with decreased risk of acoustic neuroma (Schoemaker et al., 2007; Benson et al., 2010; Palmisano et al., 2012).

ENVIRONMENTAL FACTORS FOR WHICH EVIDENCE IS INCONCLUSIVE

Numerous dietary, experiential, and environmental factors studied in relation to meningioma risk have shown inconsistent associations. That is, one or more studies found a positive association but other studies found no association. Such factors include dietary intake of *N*-nitroso compounds (Preston-Martin and Henderson, 1984), dietary maternal intake of *N*-nitroso compounds (Baldwin and Preston-Martin, 2004), alcohol consumption (Benson et al., 2008; Galeone et al., 2013), head injury and trauma (Inskip et al., 1998; Preston-Martin et al., 1998), and exposure to electromagnetic fields (Cocco et al., 1999; Berg et al., 2006). In addition to small sample sizes, possible explanations for the inconsistent findings include invalid or imprecise measurements of exposure (due to the use of self-reported or proxy-reported exposures), unfocused hypotheses (resulting from conveniently nesting case–control studies within larger prospective cohorts), and failure to account for confounders or effect modifiers (e.g., sex). Continued progress in understanding meningioma risk factors is dependent on the construction of large studies with quality exposure assessments, along with analysis of genetic factors that modify the effects of such exposures. A synopsis of putative meningioma risk factors, including the relative strength of the associations, is summarized in Table 1.1.

CONCLUSION

Few strong environmental risk factors have been identified for meningioma, although exposure to ionizing radiation and reduced allergies are both consistently associated with increased meningioma risk. Only 1%–3% of meningiomas can be directly attributed to the inheritance of rare high-penetrance gene mutations. Using a GWAS approach, a single low-penetrance genetic variant in *MLLT10* was robustly associated with meningioma risk. As a result of the long latency period between potential tumorigenic exposures (e.g., ionizing radiation) and meningioma presentation, researchers have primarily conducted retrospective (e.g., case–control) study designs, which do not necessitate long-term subject follow-up. Progress in identifying meningioma risk factors using retrospective study designs has been impeded by potential biases (e.g., protopathic bias and recall bias). Furthermore, many case–control studies of meningioma have had insufficient sample sizes to exclude the effects of statistical variation on study results. Future studies will need to be large enough so that environmental and constitutive genetic risk factors can be examined simultaneously, while also stratifying analyses by subject sex. When these issues are addressed, the potential interaction among genetic predisposition and environmental and occupational exposures can be better elucidated, more fully revealing the etiology of meningioma, the most common brain tumor in adults.

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GENE ABBREVIATIONS

AKT1, v-akt murine thymoma viral oncogene homolog 1; *KLF4*, Kruppel-like factor 4 (gut); *MLLT10*, myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to10; *NF2*, neurofibromin 2 (merlin); *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; *PTCH1*, patched 1; *SMARCB1*, SWI/SNF related, matrix associated, actin-dependent regulator of chromatin, subfamily b, member 1; *SMARCE1*, SWI/SNF related, matrix associated, actin-dependent regulator of chromatin, subfamily e, member 1; *SMO*, smoothened, frizzled family receptor; *SUFU*, suppressor of fused homolog (Drosophila); *TERT*, telomerase reverse transcriptase; *TRAF7*, TNF receptor-associated factor 7, E3 ubiquitin protein ligase.

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