Epidemiology and etiology of meningioma

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Abstract Although most meningiomas are encapsulated and benign tumors with limited numbers of genetic aberrations, their intracranial location often leads to serious and potentially lethal consequences. They are the most frequently diagnosed primary brain tumor accounting for 33.8% of all primary brain and central nervous system tumors reported in the United States between 2002 and 2006. Inherited susceptibility to meningioma is suggested both by family history and candidate gene studies in DNA repair genes. People with certain mutations in the neurofibromatosis gene (NF2) have a very substantial increased risk for meningioma. High dose ionizing radiation exposure is an established risk factor for meningioma, and lower doses may also increase risk, but which types and doses are controversial or understudied. Because women are twice as likely as men to develop meningiomas and these tumors harbor hormone receptors, an etiologic role for hormones (both endogenous and exogenous) has been hypothesized. The extent to which immunologic factors influence meningioma etiology has been largely unexplored. Growing emphasis on brain tumor research coupled with the advent of new genetic and molecular epidemiologic tools in genetic and molecular epidemiology promise hope for advancing knowledge about the causes of intra-cranial meningioma. In this review, we highlight current knowledge about meningioma epidemiology and etiology and suggest future research directions.

Keywords Meningioma · Epidemiology · Etiology · Risk factor · Ionizing radiation · Hormones

Epidemiologic research on meningioma

Compared to the malignant glial tumors, meningiomas are relatively understudied with regards to etiologic risk factors. The challenges to meningioma research are several: (i) as a relatively rare disease, large or multicenter studies are necessary for sufficient numbers; (ii) the long latency of meningioma of 20–30 years or more, exhibited most evidently in studies with known doses of ionizing radiation [1], makes exposure ascertainment difficult due to recall bias; (iii) the prevalence of subclinical disease in up to 2.8% of the population, as suggested by autopsy studies [2, 3], indicates that the pool of susceptible persons are much larger than those with clinically confirmed diagnoses; and (iv) the problem of detection bias—many meningiomas are discovered incidentally via MRIs for conditions such as head trauma or sinus problems. These incidentally discovered meningiomas, and a significant portion of primarily discovered meningiomas, and a significant portion of primarily discovered meningiomas are managed “conservatively,” meaning by observation and not surgical removal. One way epidemiologists can minimize detection bias is to only ascertain cases who have undergone surgical removal and...
pathological confirmation, ensuring that cases have clinically-significant meningioma. Only a few epidemiologic studies of intracranial tumors to date have been adequately powered to study separately risk factors for meningioma. These include the large European cohorts such as the Interphone [4], and the Million Women Study in the United Kingdom [5]. Several large European country- or region-specific case–control studies were spawned from the Interphone study [6–8]. In 2002, The Benign Brain Tumor Cancer Registries Amendment Act (H.R. 5204) was passed, mandating registration of benign brain tumors such as meningioma in the United States. This legislation has and will continue to enhance reporting of both incidence rates and survival times for patients with meningioma. Before this act, meningioma mortality rate estimates were hampered by incomplete reporting and potential selection biases with respect to the individuals who were included in the databases, as well as limited follow-up information. The better quality of new information affords exceptional opportunities to the research and clinical communities in the coming years.

**Population statistics**

The prevalence of pathologically-confirmed meningioma is estimated to be approximately 97.5/100,000 in the United States with over 170,000 individuals currently diagnosed with this tumor [9]. Since a proportion of meningiomas are not surgically managed, these estimates are low. In addition, autopsy and imaging studies have estimated subclinical meningioma rates of up to 2.8% in women [2, 3]. Data from the Central Brain Tumor Registry of the United States (CBTRUS) demonstrates a more than twofold higher incidence among females [age-adjusted incidence rate (per 100,000 person years) of 8.36 and 3.61 for females and males, respectively] [9]. The female: male ratio of approximately 2:1 may be inverted for rare pre-pubertal meningiomas [10, 11]. Atypical and malignant meningiomas comprise a small fraction of the total (~5%) and have a slight male predominance. Reported rates for Black Non-Hispanics are slightly higher (6.67) than for White Non-Hispanic and Hispanics (5.90 and 5.94, respectively) [9]. Age-specific incidence rates (Fig. 1) reveal increasing risk with age in both men and women. Increasing risk of meningioma over the past several decades noted in CBTRUS [9] may be an artifact of increasingly accurate reporting of this disease.

**Molecular etiology**

Meningioma cells exhibit a striking similarity to arachnoid cap cells, which are the likely tumor cell of origin. Despite the fact that meningioma has a benign pathophysiology in 95% of cases, like carcinoma it always results from a clonal outgrowth derived from a single cell as exemplified by cytogenetic and array-comparative genomic hybridization (array-CGH) studies [12, 13]. Sporadic meningiomas are typically associated with one or more focal chromosomal deletion(s), and atypical and malignant grades tend to have multiple chromosomal copy number alterations consistent with the acquisition of “mutator” mutations which foster genomic instability [14]. Deletion and inactivation of NF2 on chromosome 22 is a predominant feature in sporadic meningiomas, and biallelic deletions are common [13]. Additional genes are likely involved as well, since loss of NF2 occurs in only 1/3 of patients who exhibit loss of heterozygosity of chromosome 22 [15]. Additional genomic regions which are recurrently lost in meningiomas include 14q, 1p, 6q, and 18q [16]. Although in one study, familial meningiomas did not demonstrate inherited copy number alterations, such families typically have a germline defect in NF2 or other predisposing mutations [14]. Indeed, meningiomas are reported in families of several cancer predisposition syndromes including those involving the genes NF1, PTCH, CREBBP, VHL, PTEN, and CDKN2A (reviewed in [17]). Epigenetic aberrations in meningioma have not been thoroughly assessed, but one study suggests that DNA methylation events may impact meningioma biology more significantly than DNA copy number mutations [18]. Clearly, complexity of genetic aberrations in meningioma increases with tumor grade [19]. A relatively small number of mutations may be necessary for most meningiomas; however their slow growth makes long latency an issue, lending difficulty in identifying the source and timing of the initiating mutations, presenting a further complication for epidemiology studies.
Risk factors

Ionizing radiation

At present, the primary environmental risk factor identified for meningioma is exposure to ionizing radiation (IR) with risks from six fold to ten fold reported [20–23]. At high dose levels, data exist for atomic bomb survivors showing a greatly increased risk for meningioma [21]. Evidence also exists for lower dose levels. In one of the most well-known studies of ionizing radiation and meningioma risk, children who were given radiation therapy for scalp ringworm in Israel between 1948 and 1960 (the Tinea Capitis Cohort), were observed to have a relative risk of almost 10 for meningioma [24]. A number of studies have linked the number of full-mouth dental radiographs to risk of meningioma (reviewed in [25]) although the sample sizes are limited and some subsequent studies (also small in size) did not replicate earlier studies [26, 27]. However, the most recent case/control study of 200 meningioma patients reported that patients reporting full-mouth X-rays had a significantly increased risk of meningioma (OR 2.06, 95% CI 1.03, 4.17) although evidence for a dose response relation was lacking (P for trend = 0.33) [28]. Radiation therapy for intra-cranial tumors has also been linked to meningioma risk [22]. No recent large-scale studies of meningioma risk relative to ionizing radiation exist. Such studies are still highly relevant in the current era in which X-ray doses for dental and other procedures have greatly increased risk for meningioma [21]. Evidence also exists for lower dose levels. In one of the most well-known studies of ionizing radiation and meningioma risk, children who were given radiation therapy for scalp ringworm in Israel between 1948 and 1960 (the Tinea Capitis Cohort), were observed to have a relative risk of almost 10 for meningioma [24]. A number of studies have linked the number of full-mouth dental radiographs to risk of meningioma (reviewed in [25]) although the sample sizes are limited and some subsequent studies (also small in size) did not replicate earlier studies [26, 27]. However, the most recent case/control study of 200 meningioma patients reported that patients reporting full-mouth X-rays had a significantly increased risk of meningioma (OR 2.06, 95% CI 1.03, 4.17) although evidence for a dose response relation was lacking (P for trend = 0.33) [28]. Radiation therapy for intra-cranial tumors has also been linked to meningioma risk [22]. No recent large-scale studies of meningioma risk relative to ionizing radiation exist. Such studies are still highly relevant in the current era in which X-ray doses for dental and other procedures have decreased, since new radiographic procedures with significant exposure risks have been introduced, including computed tomography (CT).

Hormones

An association between hormones and meningioma risk has been suggested by a number of findings including the increased incidence of post-pubertal disease in women versus men (2:1) with the highest ratio of 3.15:1 during the increased incidence of post-pubertal disease in women has been suggested by a number of findings including the association between hormones and meningioma risk [22]. A number of recent studies have reported that patients reporting full-mouth X-rays had a significantly increased risk of meningioma (OR 2.06, 95% CI 1.03, 4.17) although evidence for a dose response relation was lacking (P for trend = 0.33) [28]. Radiation therapy for intra-cranial tumors has also been linked to meningioma risk [22]. No recent large-scale studies of meningioma risk relative to ionizing radiation exist. Such studies are still highly relevant in the current era in which X-ray doses for dental and other procedures have decreased, since new radiographic procedures with significant exposure risks have been introduced, including computed tomography (CT).

Researchers have only begun to address the question of whether the use of exogenous hormones such as oral contraceptives (OC) and/or hormone replacement therapy (HRT) is associated with an increased risk of meningioma [5, 29, 31–35]. Data from two cohort studies and several case/control studies exist. In a case/control study nested within the Nurse’s Health Study (NHS) (including 125 cases of meningioma), the relative risk of meningioma associated with hormone use for pre-menopausal women was 2.48 (95% CI 1.29, 4.77) when compared with post-menopausal women who had never used hormones [34]. For postmenopausal women who were hormone users the relative risk was 1.86 (95% CI 1.07, 3.24). No excess risk was associated with past hormone use. No association was found for past or current use of oral contraceptives. Recently published data from a cohort study of 1.3 million women with a mean age of 55.9 and recruited from 1996 to 2001 (The Million Women Study) did not find an association between OC use (OR 1.06, 95% CI 0.81–1.38 for use within the past five years) and meningioma risk (n = 390) but did not report results for HRT use [5]. In a large and recent case/control study, the Interphone Group reported an increased relative risk of meningioma (n = 178) among postmenopausal women for ever-use of HRT (OR 1.7, 95% CI 1.0–2.8) [35]. Women who had used long-acting hormonal contraceptives also had an increased risk of meningioma; the odds ratio for at least 10 years of use was 2.7 (95% CI 0.9–7.5). A retrospective records-based cohort study using the Mayo Clinic Jacksonville patient database between 1993 and 2003 confirms the positive NHS findings (OR 2.2, 95% CI 1.9–2.6) of an association between HRT use and meningioma risk, comparing the frequency of HRT use among a case population of 1,390 with over 350,000 other women in the health system [31], while a case/control study including 219 meningioma cases identified from three Chicago area hospitals between 1987 and 1992 reports a protective effect for oral contraceptive use (OR 0.2, 95% CI 0.0–0.8) and a non-statistically significant protective effect associated with HRT use [32]. This latter study used the spouses of men with back pain as controls. Hence at present, there is limited statistical evidence of an increased risk of meningioma among users of oral contraceptives. Although not definitive, available data suggest an association between the use of hormone replacement therapy and increased meningioma risk. Further evaluation of exogenous hormone use in women with meningioma in a larger study is needed with particular attention to stratification by hormone composition (i.e. estrogen and/or progesterone), duration of and age at use as well as meningioma subgroups defined by tumor receptor expression (see below).

Researchers have also reported conflicting results when examining meningioma risk across categories of pregnancy, menstrual and anthropometric variables [5, 29, 31–36]. When examining age at first menstrual period,
investigators in the Nurse’s Health Study observed a relative risk for meningioma for women with age at menarche 12–14 years of 1.29 (95% CI 0.86–1.92) and for women with age at menarche after 14 years a relative risk of 1.97 (95% CI 1.06–3.66) compared to those with menarche before age 12 [34]. A tendency for increased risk of meningioma for parous compared to non-parous women (RR = 2.39, 95% CI 0.76–7.53) was also observed, although this value was not statistically significant [34]. In a second nested case/control study, Lambe et al. examined 1088 patients with meningioma within the Swedish Cancer Registry and matched to data from the Swedish Fertility Registry [36]. This group found no association between either parity or age at first birth and meningioma risk, however their analyses were not adjusted for other possible meningioma risk factors such as use of exogenous hormones or radiation exposure history. Data from the Interphone Study suggest that meningioma risk among women aged <50 years is increased with increasing number of livebirths (OR 1.8, 95% CI 1.1–2.8 for three versus no livebirths) but found no association with menopausal status [35]. The Million Women Cohort reported an increasing risk of meningioma with increasing body mass index (OR 1.46, 95% CI 1.11–1.91) but no association with number of pregnancies or age at first birth [5]. Body mass index, or more specifically body fat, is positively associated with aromatase activity resulting in higher endogenous estrogen exposure. An additional case/control study which included 219 cases found a protective effect for pregnancy which increased with number of pregnancies and age at first pregnancy [32]. Neither age at menarche or menopause were reported to show any effect in unadjusted analyses although menopause showed an increased risk (OR 2.0, 95% CI 1.0–4.0) in adjusted analyses. In summary, the association between traditional hormone-based pregnancy and menstrual risk factors and meningioma risk is not consistent and deserve a more formal examination. Such an examination requires precise exposure assessments as well as an incorporation of a more thorough examination of biological features of individual patients data, including the expression of hormone receptors as described below, which may reveal subtypes with more clear evidence of hormone associations.

The functional significance of hormone receptors expressed on meningiomas is still controversial. Hormone receptors (estrogen, progesterone, and androgen) are expressed in an equivalent proportion of meningiomas derived from men and women [37], but their assessment has only been performed once in an epidemiologic study [38], and different laboratory methods for receptor expression capture widely varying proportions of positive patients [39–41]. A pilot study of 31 meningioma samples reported that a specific gene expression pattern appeared more strongly associated with PR status than with ER status [42]. Genes on the long arm of chromosome 22 and near the NF2 gene (22q12) were most frequently noted to have expression variation, with significant up-regulation in PR positive versus PR negative lesions suggesting a higher rate of 22q loss in PR negative lesions. Pathway analyses indicated that genes in collagen and extracellular matrix pathways were most likely to be differentially expressed by PR status [42]. The future incorporation of receptor expression into epidemiology studies may revolutionize the field as various molecular markers have done for cancers, for example hormone receptors in breast cancer. The field first needs to harmonize methodology to classify hormone receptors so that different studies can be compared and contrasted.

Head trauma

Head trauma has been suggested as a risk factor for meningioma since the time of Harvey Cushing, although the results across studies are not consistent. While some small case/control studies report an increased risk of meningioma associated with head trauma for both males and females [43, 44], other studies report no such association [45, 46]. In a cohort study of 228,055 Danish residents hospitalized for concussion, skull fracture or other head injury between 1977 and 1992 and followed for an average of eight years, the standardized incidence ratio (SIR) for meningioma after the first year was 1.2 (95% CI 0.8, 1.7) [47]. As mentioned above, associations of head trauma and meningioma may be an example of detection bias.

Cell phone use

The question of whether cell phone use is related to meningioma risk remains a question of great interest to the general public. At least ten studies have examined the association between cell phone use and tumors of the brain. At present, little evidence exists for an association between the two although sample sizes specific to meningiomas are relatively small, the follow-up time since commencement of cell-phone use is relatively short, and, in some instances, the measurement of cell-phone use is somewhat crude [48–50]. Newly reported data from the large Interphone study may also suffer some reporting bias; this study replicated earlier negative findings even for the highest exposed groups (>10 years of heavy exposure) [4]. If the latency times of 17–36 years observed in ionizing radiation studies on the epidemiology of meningioma [24, 51] are taken as a guideline, the true extent of any possible relationship between cell phone use and meningioma risk may not be uncovered for decades and therefore this topic deserves continued attention.
Association with breast cancer

An association between breast cancer and meningioma has been examined in several studies [29, 52, 53]. A number of explanations have been proposed for this association including the presence of common risk factors such as endogenous and exogenous hormones as well as shared genetic predisposition, including variants in DNA repair polymorphisms [52]. A review of the literature as well as an analysis of the association between breast cancer and meningioma using the western Washington State cancer registry data was provided by Custer et al. [53]. The relative risks observed across existing studies range between 1.5 and 2.0 with the majority statistically significant. Most of these studies have been conducted with tumor registry data and have relatively small sample sizes and none have been able to examine the association while controlling for risk factors which are likely to be shared by the two tumors, such as pregnancy and menstrual variables and exogenous hormone use. The fact that studies which identify risk of breast cancer in women who had meningioma, and vice versa, both have similar magnitude increased risk suggests that there is not a causal relationship between these tumors, rather than they share the same risk factors such as gender, age, hormone induction, and possibly other demographic variables [53].

Occupation/diet/allergy

Attempts to link specific chemicals with meningiomas in occupationally or industrially exposed groups have proved inconclusive (reviewed in [54]). An international case/control study found no association between diet and meningioma (n = 332) [55]. Although a number of studies which examine the relationship between glial brain tumors and allergic disease such as asthma and eczema have found evidence for an association, little evidence has been found for such an association for meningioma [6, 8, 56]. A meta-analysis however demonstrated a significant inverse relationship of meningioma with allergy when excluding the single study that was most heterogeneous from the others (pooled RR = 0.84, 95% CI 0.72–0.98, P = 0.029) [57], and a large recent study showed consistent inverse risk with asthma, hayfever, and eczema [7]. A study of innate immune genes did not find strong evidence of risk imparted by variants in such genes, but more investigation is warranted [58].

Family history of meningioma

Few studies have examined the relationship between meningioma risk and family history of meningioma. Malmer et al. examined cancer risk in spouses and first degree relatives of brain tumor patients in Sweden and reported that a meningioma diagnosis conferred a two fold increase in meningioma risk to first degree relatives (standardized incidence ratio [SIR] 2.2, 95% CI 1.4, 3.1) but not to spouses of affected individuals [59]. An inverse association between risk and age at onset was observed with an SIR of 2.5 (95% CI 1.5–4.0) for probands less than 50 years of age versus 1.3 (95% CI 0.6–2.6) for probands older than 50 years of age. Similar analyses by Hemminki et al. using data from the Swedish and Norweigian Registry Databases, reveal an increased risk with increasing numbers of affected first degree relatives with persons having one or two first degree family members with meningioma (SIR 1.6, 95% CI 1.3–42.0, and SIR 5.0, 95% CI 0.9–14.8), respectively [60]. Despite the fact that up to one to three percent of the adult population may harbor a meningioma [2, 3], the total number of families with multiple members diagnosed with meningioma are relatively rare (indicating, in part, a wide spectrum of phenotypic expression with respect to clinical import and hence screening undertaken), and most such families are currently attributed to inherited NF2 mutations. At present no family based linkage or segregation analyses studies of meningioma have been reported.

Molecular epidemiology

In the most recent and largest study to date of genetic polymorphisms and meningioma risk, Interphone study investigators reported a statistically significant association with meningioma for 12 SNPs drawn from DNA repair genes [52]. These investigators examined 1,127 tagging SNPs selected to capture most of the common variation in 136 DNA repair genes as well as an additional 388 putative functional SNPs. These included 69 nonsynonymous coding SNPs that may identify functional changes in expressed proteins. A total of 631 cases and 637 controls drawn from five case/control series from the Interphone Study were genotyped. The Interphone study is a case/control project initially designed to examine the relationship between cell phone use and the risk of brain tumors, including meningioma. Study subjects are primarily Western European background. The group reported a novel and biologically intriguing association between meningioma risk and three variants in the gene that encodes breast cancer susceptibility gene 1-interacting protein 1 (BRIP1) (17q22). The most significant was SNP rs4968451 that maps to intron 4 of the gene (OR 1.61, 95% CI 1.26–2.06 heterozygotes, OR 2.33, 95% CI 1.25–4.34 homozygotes). The BRIP1 gene is involved in the repair of DNA double-strand breaks by homologous recombination in a manner that depends on its association with BRCA1. Defects in BRIP1 are linked to
breast cancer susceptibility (as well as Fanconi anemia), leading researchers to speculate that the reported association between breast cancer and meningioma risk may be due to similar defects in DNA repair genes rather than in addition to the previously assumed shared hormonal risk factors (such as hormone replacement therapy). This group also reported a statistically significant association between four variants in the ATM gene, a member of the phosphatidylinositol-3 kinase family known to be involved in homologous and non-homologous DNA break repair, and meningioma risk. Previous groups have also noted significant associations between ATM variants for meningioma as well as breast cancer [23, 61]. These findings are again of interest in light of the associations between ionizing radiation and meningioma risk as well as between breast cancer and meningioma risk.

Additional candidate genes studies have suggested a role for genes in apoptotic pathways [62], and as discussed above, immune regulatory pathways [58] and meningioma risk. Earlier studies examined variants in phase II metabolic genes, which would impact response to environmental or occupational chemical exposures; a meta-analysis of these studies implicates a potential role for the detoxifying enzyme GSTT1 in modulating meningioma risk (OR = 1.95, 95% CI 1.02–3.79) [63]. The lack of replication/confirmation and low number of variants assessed in candidate genes studies distracts from knowledge on the true genetic susceptibility of meningioma, which awaits results from agnostic genome-wide association studies.

Directions for future studies

Because of its “benign” nature, research in meningioma epidemiology and etiology has lagged behind that for more malignant intracranial neoplasms. The study of risk factors for meningioma remains challenging, and there are currently few large-scale studies. The two main known risk factors—genetic predisposition and high dose radiation exposures—account for a small proportion of cases. Although a role for hormones is possible given the gender distribution of meningiomas, little specific or consistent data exist on hormonal risk factors. Epidemiologic tools may be used to collect and define appropriate subject data from well-characterized source populations, being mindful of detection or diagnostic bias in patient ascertainment, in an effort to delineate risk factors both for the overall group of meningioma patients as well as for specific subgroups. High quality follow-up data for sufficient time periods must be collected on meningioma patients to obtain representative estimates of sex- and age-specific rates for recurrence, quality of life and overall survival. In addition to the collection of data on environmental risk factors such as hormone use, new projects will need to consider the inclusion of information on relevant genetic variants derived from ongoing whole genome and gene pathway scans. In addition to exploring environmental and genetic factors for meningioma risk separately, the interaction between the two must be examined. For example, the integration of environmental risk factors such as oral contraceptive use or radiation exposure with information on genetic polymorphisms in steroid hormone or DNA repair genes may help researchers to understand the complex relationship between genetic susceptibility and environmental exposures in the development of meningioma. Given the large numbers of subjects needed to study such gene-environment interactions, especially within defined subsets of meningioma such as the rare atypical and malignant subtypes, collaborative, multi-center efforts between a variety of researchers will be needed, including experts from such fields as neurosurgery, epidemiology, genetics, statistics, and neuropathology.

Meningioma epidemiology and etiology will benefit from the increased size and quality of disease reporting to cancer registries, facilitated in the USA by the Benign Brain Tumors Act of 2002. This act has resulted in the formation of a multicenter meningioma consortium, which is matched by several large studies in Europe. These studies will facilitate a rapid and thorough investigation into the genetic susceptibility factors for meningioma via genome-wide association and whole genome sequencing in the near future. The collection of blood and tumor material must accompany such studies to facilitate the rational classification of the disease into etiologic subtypes to further specify genetic, immunologic, and environmental risk factors. Exposure assessments will continue to hinder progress in meningioma case-control studies, which are hampered by information bias because of poor or differential recall by study subjects, and the lack of verifiable biomarkers of exposure since information is obtained in retrospect. Future large cohort studies may help to ameliorate this problem, and large linked health databases may help study iatrogenic risk factors such as diagnostic and therapeutic ionizing radiation, and therapeutic hormone use.

Acknowledgments This work was supported by NIH R01 grants CA109745, CA109468, CA109461, CA108473, CA109475, CA52689, CA097257, the Brain Science Foundation, and the Meningioma Mommas.

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