EPIDEMIOLOGY OF INTRACRANIAL MENINGIOMA

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Meningiomas are the most frequently reported primary intracranial neoplasms, accounting for approximately 25% of all such lesions diagnosed in the United States. Few studies have examined the risk factors associated with a diagnosis of meningioma with two categories of exposure, hormones (both endogenous and exogenous) and radiation, most strongly associated with meningioma risk. Limited data are also available on long-term outcomes for meningioma patients, although it is clear that the disease is associated with significant morbidity and mortality. Recent legislation passed in the United States (The Benign Brain Tumor Cancer Registries Amendment Act [H.R. 5204]) mandates registration of benign brain tumors such as meningioma. This will increase the focus on this disease over the coming years as well as likely increase the reported prevalence of the disease. The increased emphasis on research dedicated to the study of brain tumors coupled with the advent of new tools in genetic and molecular epidemiology make the current era an ideal time to advance knowledge for intracranial meningioma. This review highlights current knowledge of meningioma epidemiology and new directions for research efforts in this field.

KEY WORDS: Brain tumor, Epidemiology, Meningioma, Neurosurgery, Risk factors, Tumor

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POPULATION STATISTICS

Meningiomas account for approximately 20% of all intracranial tumors in males and 38% in females (5, 12, 71). The prevalence of meningioma is estimated to be approximately 97.5 in 100,000 in the United States with over 138,000 individuals currently diagnosed with this tumor (18). Data from the Central Brain Tumor Registry of the United States reveals an age-adjusted incidence rate (per 100,000 individuals) of 5.04 and 2.46 for females and males, respectively. Rates for Caucasians, African-American, and Hispanics are similar (3.78, 3.77, and 3.45, respectively) (12). Age-specific incidence rates are listed in *Table 1*, revealing an increasing risk with age. Data from the Central Brain Tumor Registry of the United States from 1985 through 1994 indicate that incidence rates for meningioma have remained fairly constant during this time (38). Estimates of mortality rates associated with a diagnosis of meningioma are limited and hampered by incomplete reporting, potential selection biases with respect to the individuals who are included in the databases, as well as limited follow-up information. Analyses based on information from the National Cancer Data Base, which includes data from over 1000 hospitals that participate in the American College of Surgeons tumor registry program, report overall 2 and 5 year survival rates for patients with meningioma of 81% and 69% (48), respectively, whereas population-based studies from the 1990s provide estimates of the 5 year survival rate ranging from 73 to 94% (58, 66).

Biology

Meningiomas arise from meningothelial cells of the arachnoid layer that forms the external lining of the brain and occur primarily at the base of the skull in the parasellar regions as well as over the cerebral convexities. In general, these lesions are solitary (with the exception of individuals with neurofibromatosis for whom multiple lesions are common) (1) and come to clinical attention as a result of symptoms including seizure, hemiparesis, or cranial neuropathy such as vision loss, generally associated with compression by the meningioma of surrounding neural tissues. Meningiomas may be categorized as benign (>90%), atypical/borderline (5%) and malignant (3–5%); within the benign category, there are several subtypes, including syncy-

TABLE 1. Age-specific incidence rates for meningioma in the United States (2002)

Age	0–19	20–34	35–44	45–54	55–64	65–74	75–84	85+
Rate	0.12	0.74	2.62	4.89	7.89	12.79	17.04	18.86

tial, fibrous, and transitional. With the exception of malignant meningioma, these classifications are imprecise with respect to prediction of patient outcome or response to treatment. In fact, at present, there is little in the way of any risk stratification for meningioma both with respect to initial diagnosis as well as long-term prognosis.

Quality of Life

Although generally classified as histologically benign, many meningiomas are associated with devastating clinical symptoms including loss of vision and seizures. Because of the relatively slow rate of growth for some meningiomas, many patients may also suffer subtle losses of neurological function over time including difficulty with speech such as finding words, changes in ability to concentrate, and weakness in an arm or leg causing problems with writing, gait, or walking. Despite such potentially disabling changes, little analysis of quality of life has been undertaken for patients diagnosed with and treated for meningioma (13, 20, 39, 41, 65), and no large scale population-based data exist. The data that do exist indicate that up to 30% of patients cannot read, write, drive, or think at the same level as before their meningioma diagnosis (39), highlighting the type of subtle yet disabling outcomes associated with this disease and the importance of identifying means of defining individuals at risk as well as potential areas for rehabilitation services for these patients.

Risk Factors

At present, the two factors for which the strongest evidence exists with respect to an association with meningioma risk are exposure to ionizing radiation and hormones; however, even these factors remain largely unexplored.

Ionizing Radiation

Ionizing radiation increases the risk of intracranial tumors and in particular, risk of meningioma (5–7, 9, 31, 33, 74, 75). In addition, lesions associated with this exposure may be multiple and associated with high recurrence rates. Data from atomic bomb survivors exposed to high doses (60, 70) show a greatly increased risk for meningioma. 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 (RR) of almost 10 for meningioma (62). The dose given to these children, which averaged approximately 1.5 Gy, has another common use, namely dental radiographs. Within the United States, this is the most common form of exposure to ionizing radiation. A number of studies have linked the number of full-mouth dental radiographs to risk of meningioma (55–57, 59), although the sample sizes are limited and later studies (also small in size) did not confirm these findings (61, 64, 67). The most recent case control study of 200 meningioma patients reported that the full-mouth series was associated with a significantly increased risk of meningioma (odds ratio [OR] 2.06, 95% confidence interval [CI] 1.03, 4.17), although evidence for a dose response relation was lacking (P for trend = 0.33) (45). Radiation therapy for intracranial tumors has also been linked to meningioma risk (29, 46), and animal studies support the contention that ionizing radiation can induce intracranial tumors, including meningiomas, by damaging DNA, with resultant single-strand or double strand-breaks (29). No recent large-scale studies of meningioma risk relative to ionizing radiation exist when x-ray doses for dental and other procedures have decreased but during which time new radiographic procedures have been introduced, including computed tomography. A population-based examination of this association with a large sample size will help to provide a more precise estimate of this association.

Hormones: Overview

An association between hormones and meningioma risk has been suggested by a number of findings (2–5, 17, 22, 32, 36, 42, 44, 47, 69) including the increased incidence of the disease in women versus men (2:1), the presence of estrogen, progesterone, and androgen receptors on some meningiomas, an association between breast cancer and meningiomas, and indications that meningiomas change in size during the luteal phase of the menstrual cycle and pregnancy.

Exogenous Hormones

Researchers have only begun to address the question of whether the use of exogenous hormones (i.e., the use of oral contraceptives [OC]) or hormone replacement therapy (HRT) is associated with an increased risk of meningioma (4, 36, 43). In a case control study nested within the Nurse's Cohort Study that included 125 cases of meningioma (36), researchers found an overall positive association between the use of HRT and meningioma risk. This group reported that, after adjustment for age and body mass index, the RR of meningioma associated with hormone use for premenopausal women was 2.48 (95% CI 1.29, 4.77) when compared with postmenopausal women who had never used hormones. For postmenopausal women, the RR associated with hormone use was 1.86 (95% CI 1.07, 3.24). No excess risk was associated with past hormone use or with past or current use of OC. The results from two additional studies were recently published in abstract form (4, 43). The first, a retrospective 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 (4). Conversely, a case control study including 219 meningioma cases identified from three Chicago area hospitals between 1987 and 1992 reports a protective effect for OR use (OR 0.2, 95% CI 0.0–0.8) and a nonstatistically significant protective effect associated with HRT use (43). As can be seen from these reports, a large-scale examination of these associations on a population-based data set is needed to further elucidate this issue.

Endogenous Hormones

Researchers have reported conflicting results when examining meningioma risk across categories of pregnancy and menstrual variables. A population-based study of brain tumors from the late 1980s found that women who had undergone either natural (RR 0.59, 95% CI 0.18, 1.94) or surgical (RR 0.12, 95% CI 0.01, 1.30) menopause had a reduced (although not significantly so) risk of meningioma (67). In the Nurse's Health Study (36), the RR for meningioma for women with age at menarche 12 to 14 years was 1.29 (95% CI 0.86, 1.92) and for women with age at menarche after 14 years was 1.97 (95% CI 1.06, 3.66) compared with those with menarche before age 12. The group also observed an increased risk of meningioma for parous compared to nonparous women (RR = 2.39, 95% CI 0.76, 7.53), although this value is not statistically significant. In a second nested case control study, Lambe et al. (42) matched 1088 patients with meningioma within the Swedish Cancer Registry with data from the Swedish Fertility Registry. This group found no association between either parity or age at first birth and meningioma risk; however, they were not able to adjust their analyses for other possible meningioma risk factors such as use of exogenous hormones or radiation history. A recently reported case control study (43) that included 219 cases found a protective effect for pregnancy, which increased with number of pregnancies and age at first pregnancy. 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. As this review makes evident, the association between traditional hormone-based pregnancy and menstrual risk factors and meningioma risk are not well-described and deserve a more formal examination. In addition, although researchers have examined the association between measures of male endogenous hormones such as baldness and age at puberty with risk of prostate cancer (19), no such data have been collected for men diagnosed with meningioma.

Tumor Hormone Receptors

Estrogen

The prevalence and function of estrogen receptors in meningiomas remains a controversial topic. Donnell at al. (22) first described the presence of an estrogen receptor protein in four of six meningiomas. Since that time, using a variety of testing methods, researchers have reported prevalence rates for estrogen receptor positivity from 0 to 94% of cases (2, 3, 11, 32, 47). The prevalence of these receptors by sex, age, histological subtype, or receptor isoform is not well described, although preliminary data indicate that differences do exist across these categories. Data from Brigham and Women's Hospital indicates that differences exist in the prevalence of estrogen receptor isoforms, alpha and beta, with 44% of meningiomas expressing ER-alpha mRNA and 68% expressing ER-beta mRNA in a series of 34 Brigham and Women's Hospital cases (11). Although both ER-alpha and ER-beta are capable of binding estrogen and activating genes with estrogen responsive effects, they may elicit different bioresponses in different organs, and therefore treatments targeted toward such receptors may act differently by organ as well as by receptor isoform within the same organ. These receptors have been more extensively characterized for breast cancer; ER-beta+ patients have been noted to have reduced survival as well as increased tumor resistance to tamoxifen relative to ER-alpha+ patients. No such data exist for estrogen isoform receptor prevalence and meningioma response or patient outcome; it is likely that such a relationship exists and that a more detailed subtyping of these receptors by sex, histological subtype, and isoform may explain why efforts to use anti-estrogen drugs such as tamoxifen as a treatment option for meningioma have lead to inconclusive results (27) and may predict more successful candidates for anti-estrogen therapy among those patients diagnosed with meningioma in the future.

Progesterone

The majority of meningiomas (40–100%) possess progesterone receptors (PR), although analyses of the prevalence of these receptors by such factors as age, sex, and histological subtype remain limited. In a series of 70 patients, Hsu et al. (32) reported that women were more likely than men to be PR positive but found no association between age or histological subtype and PR score. Although most meningiomas appear to possess such receptors, the function or role of these receptors is unclear, and large-scale epidemiological studies to examine the correlation between binding and a meaningful biological response or clinical outcome do not exist. However, existing data are suggestive; Hsu et al. (32) observed that benign meningiomas were more likely than malignant to be PR positive (96% versus 40%), with PR status being inversely related to mitotic index and grade and therefore associated with better prognosis. Evidence for the functional role of PRs has been obtained from a number of laboratory analyses including one in vivo study of nude mice implanted with human meningioma (52). In that study, one group of nude mice received 10 mg/kg of the antiprogesterone mifepristone (RU486) daily, whereas the other group received placebo. After 3 months, tumor volume was 154% of baseline in the control group and 25% of baseline in the treated group, demonstrating an inhibitory effect of the drug on meningioma growth. Results such as these point to potential clinical value of accurate knowledge of PR status in meningiomas.

Androgen

Approximately 50% of meningiomas have been noted to express androgen receptors, with tumors from women exhibiting a higher rate than tumors from men. Data suggest that androgen expression positivity rates vary positively with stage (14). Nuclear localization of these receptors suggests their functional relevance, although in vitro studies have produced mixed results (14). As for estrogen receptors and PR, little is known regarding the usefulness of these receptors relative to clinical prediction and treatment.

Head Trauma

Since the time of Harvey Cushing, head trauma has been suggested as a risk factor for meningioma, although the results across studies are not consistent. Although several small case control studies (54, 55) from the early 1980s report an increased risk of meningioma associated with head trauma for both males (OR 1.9, $P = 0.01$) and females (OR 2.0, $P = 0.01$), other studies report no such association (44). 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 8 years, the standardized incidence ratio for meningioma after the first year was 1.2 (95% CI 0.8, 1.7) (34).

Cell Phone Use

The question of whether exposure to electromagnetic fields, particularly in the form of cell phone use, is related to meningioma risk, remains a question of great interest to the general public. Seven papers have been published that examine the association between cell phone use and tumors of the brain (23, 28, 35, 37, 45a, 50, 63). 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. A recent hospital-based case control study from the National Cancer Institute (35) included 197 meningioma cases and reported a meningioma RR of 0.7 (95% CI 0.3, 1.7) associated with cell phone use. Although all of the studies to date support the hypothesis that there is no association between the use of cell phones and tumors of the brain, further study is warranted given the increased prevalence and intensity of exposure to different types of cell phones since the prior studies took place and the fact that few of the studies examined this association specifically for meningiomas. Of note, Swedish investigators of the Interphone study recently reported a significant association between one type of benign brain tumor, acoustic neuroma, and long-term cell phone use (OR, 3.9; 95% CI, 1.6, 9.5) (45a).

Association with Breast Cancer

An association between breast cancer and meningioma has been examined in several studies. A number of explanations have been proposed for this association including common risk factors (particularly those with a hormonal component such as age at menopause or use of OC) or shared genetic predisposition. In a recent small study designed to gather pilot data regarding this second hypothesis, no evidence of mutations in two breast cancer susceptibility genes, BRCA1 and BRCA2, was reported in a series of patients with sporadic meningioma (40). A recent 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 is provided by Custer et al. (17). It is of note that the RRs for the association between breast cancer and meningioma observed across currently existing studies range between 1.5 and 2.0 with the majority statistically significant. Most of these studies are conducted using tumor registry data, and therefore sample sizes are relatively small, and none have been able to examine the association while controlling for risk factors that are likely to be shared by the two tumors, such as pregnancy and menstrual variables as well as the use of exogenous hormones. Therefore, a population-based examination of this association with a large sample size and control of shared risk factors may help to provide a more precise estimate of this association, both across family members as well as within a single individual.

Allergy

Although a number of studies that 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. Two of the larger studies to date, one an international case control study of 331 meningioma cases identified from France, Germany, Sweden, Australia, Canada, and the United States, (68) and the second a hospital-based case control study that included 197 meningiomas (8), found allergy history not to be associated with meningioma.

Genetics

Family History of Meningioma

Within the field of epidemiology, familial aggregation studies are frequently a means to begin to assess a genetic etiology for a given diagnosis. Few studies have examined the relationship between a personal diagnosis of meningioma and a family history of meningioma. Using data from the Swedish Family-Cancer Database, Hemminki et al. (30) reported a statistically significant association between meningioma diagnosis and a parental history of meningioma (standardized incidence ratio 2.5, 95% CI 1.3, 4.3), indicating a familial risk for meningioma tumors. Recent population based surveys (1, 25) suggest that highly penetrant but relatively rare inherited genes may exist for meningioma susceptibility, although it appears at present that these genes may be primarily seen in families with neurofibromatosis 2 (Nf2). In sporadic meningioma, Nf2 is deleted or mutated in up to 50% of cases. In

addition to Nf2, chromosomes 1p, 3p, 6q, 10, and 14q are suspected locations for tumor suppressor genes. Comparative genetic hybridization analyses have revealed gains of chromosomes 12q, 15q, 17q, and 20q, but no specific genes have been identified. In addition to comparative genetic hybridization, researchers, including members of our team, have begun to use microarray or gene expression data to analyze meningiomas (26, 73), although, to date, both the sample size and the number of genes examined are small. In the largest case series examined, 2059 genes were examined in 47 meningiomas (73). In that series, the expression of several groups of genes was found to correlate with tumor grade including growth hormone receptor IGFBP-7, endothelin receptor A, and IGF2 (73).

Given the evidence that only a small proportion of meningioma cases are likely to be attributable to the effects of rare, highly penetrant inherited susceptibility genes, great interest exists in examining the effects of variants in more common, less penetrant genes on meningioma risk as well as the effect on risk of any interaction of these variants with environmental exposures. New methods in genetics and molecular epidemiology allow for the high-throughput processing of thousands of genes in large patient populations with relative ease and low cost. To date, there are few studies involving brain tumor risk and genetic polymorphisms (10, 15, 16, 21, 24, 65a, 72). Only three reports have examined the relationship between certain genetic polymorphisms and meningioma risk (21, 24). As might be expected from the strength of the association between the analogous environmental exposures (i.e., hormones and ionizing radiation), the focus of these studies has been on genes that are involved in steroid biosynthesis, breakdown, or metabolism, and ongoing projects are examining whether variants in DNA repair genes, either alone or accumulated across genes in a pathway, are associated with increased risk of meningioma. The first of these studies examined polymorphisms in glutathione-S-transferase (GSTM1, -P1, -T1) and cytochrome P450 polypeptide 2E1 (20). GSTM1 and GSTT1 code for cytosolic enzymes that are involved in the metabolism of xenobiotics or products of oxidative stress including a number of environmental carcinogens such as the polycyclic aromatic hydrocarbons present in diet and tobacco smoke. cytochrome P450 polypeptide 2E1 is involved in the oxidation of a variety of compounds including steroids, fatty acids, and xenobiotics. With use of data collected from 172 meningioma patients, a borderline statistical significance was noted between the GSTT1 null-type and meningioma risk (OR 1.5, 95% CI 1.0, 2.3). Of note, the association appeared to be stronger for younger patients than old, although this difference was not statistically significant. A second study including 48 meningioma patients and 412 control subjects reported similar findings, with an OR of 3.6 (95% CI 1.8, 6.9) comparing GSTT1 null with positive (24). More recently, data from the TINEA CAPITAS study revealed an association between variants in DNA repair genes and meningioma risk, as well as a modification in the association by radiation exposure (65a). The future examination of genes potentially involved in meningioma risk such as DNA repair, cell cycle, or steroid hormone metabolism genes and their association with environmental risk factors including exposure to ionizing radiation or exogenous and endogenous hormones represents a exciting new area of meningioma research.

Directions for Future Studies

The study of risk factors for intracranial meningioma remains a challenging and largely unexplored field. The known risk factors of genetic predisposition and high-dose radiation exposures account for a small proportion of cases. Although a role for hormones is likely given the sex distribution of meningiomas, little specific or consistent data exist on hormonal risk factors. Tools from the field of epidemiology may be used to collect appropriate subject data from well-defined source populations in an effort to identify risk factors both for the overall group of meningioma patients as well as for specific subgroups. High-quality follow-up data of sufficient time period 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 genetic information such as DNA polymorphism and microarray data. The collection of microarray data allows one the opportunity to assess the expression levels for thousands of genes simultaneously. Molecular classification techniques based on machine learning algorithms applied to microarray data have been shown to have statistical and clinical relevance (49, 51, 53, 76). These data may be used to classify tumors into prognostic groups and to explore gene function and pathways within a set of tumors. Molecular genetic analyses in general show great promise with respect to the classification and treatment of brain tumors; for example, oligodendrogliomas exhibit completely different response to chemotherapy based on the presence or absence of alleles on chromosomes 1p and 19q. No reports exist to date of such work in meningioma; one of the most promising roles for such an analysis is in the classification of meningiomas into risk categories with respect to eventual outcome or response to treatment.

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 OC 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 (65a). Given the large numbers of subjects needed to study such gene–environment interactions, collaborative, possibly multicenter efforts between a variety of researchers will be needed, including experts from such fields as neurosurgery, epidemiology, genetics, statistics, and neuropathology. The study of brain tumors is a greatly underserved area of medical research. Recent House and Senate Appropriations Committees recognize this paucity of knowledge and have

made recommendations to increase attention to brain tumor research. Thus, the current era represents a key time and opportunity in the United States for the study of meningioma given this mandate as well as new legislation recently passed by Congress to include the collection of "benign" tumors such as meningioma in the Public Health Service Act within cancer registries for the first time.

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COMMENTS

This is a valuable contribution regarding the epidemiology of meningioma. This tumor continues to be a great challenge for all of neurosurgery. This article presents a very thorough review of the current state of the art with regard to statistics on incidence, survival, and many of the epidemiological factors implicated in the pathogenesis and prognosis of the tumor. It is a shame that all of the extensive work regarding the hormonal attributes of meningiomas has not resulted in a major advance in the management of these lesions. It remains food for thought, and the material in this review certainly helps individual investigators put the tumor and the many factors that

play a role in its management into perspective. I hope we can be optimistic that molecular genetics will ultimately provide some clues that will result in improved outcomes for our patients with meningioma.

Edward R. Laws, Jr.
Charlottesville, Virginia

This is a nice review of current information regarding the potential causes for meningiomas. The presentation is informative and relevant for neurosurgeons. Although conclusions are difficult because of the lack of confirmatory data, this report reminds us that even benign tumors are the result of genetic mutations. A larger study, properly constructed to try to answer the question "Where did my tumor come from?," would be welcomed, as patients frequently ask. Hopefully, this report will serve as a stimulus for this work to be completed.

Joseph M. Piepmeier
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This well-written and comprehensive overview of epidemiological risk factors that promote or favor the development of meningioma incites thought on several levels. The authors point out a number of opportunities for epidemiological study as they characterize which data are available, and which are missing, from current knowledge of risk factors affecting meningioma incidence. As the authors point out, the link between previous ionizing irradiation and meningioma genesis is well established. A hormonal influence has also long been proposed, based on the greater incidence of these tumors in women and on the well-known tumor growth invoked during the later stages of pregnancy. However, even after several decades of research into the role of estrogens and progestins in initiating or stimulating meningioma growth, the data remain weak. Here, a brief discussion is given that implies a possible role for estrogen receptors, but, in truth, these are not ubiquitously expressed and estrogen receptor blockade has never proven useful in a clinical setting. Although meningiomas are replete with progesterone receptors, they respond poorly to antiprogestational agents and conflicting results have been obtained as to the function of these receptors in cultured cells. Hormone replacement therapy in women does give an excess relative risk for meningioma, but testosterone levels in men have never been correlated with meningioma risk despite the presence of nearly as many androgen receptors as progesterone receptors. Thus, our understanding of hormonal influences is incomplete and somewhat chaotic. I would propose that it is somewhat simplistic to assume that progesterone is the key hormone explaining the behavior of meningiomas during pregnancy and their higher incidence in women. Pregnancy induces a legion of other physiological changes that one might implicate in the stimulation of meningioma growth: as just one example, insulin-like growth factor-I (which is known to be a powerful stimulant to meningioma growth both in vitro and in vivo) rises significantly during the third trimester, when meningiomas grow most significantly (1). Progesterone may simply be a cofactor for another hormone, enabling its action rather than driving growth directly. Even the oft-suggested link between carcinoma of the breast and meningioma seems to be shaky, and population-based studies are needed to conclusively show whether the association is based on shared hormonal factors, shared oncogenetic mechanisms, or simply the shared higher incidence of these two tumors in women. The authors are right to suggest that environmental factors such as those discussed here should be correlated with genetic data (e.g., gene function relating to steroid processing or deoxyribonucleic acid repair) for optimal understanding, but given that our understanding of those environmental factors is foggy at best, we need to establish much more conclusively which are important (and which not) before we invest too much energy in such correlations. Cell phones seem not to cause meningiomas, ionizing irradiation does, and defects in the *NF2* gene cause meningiomas. But, multiple mechanisms are at play, and we remain otherwise uncertain of much of what causes a meningioma to take root, what causes its cells to divide, and what causes its occasional transformation to the anaplastic phenotype.

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