Hunting for the Causes of Meningioma—Obesity Is a Suspect

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Abstract

In this issue of the journal, Michaud and colleagues report a 48% increased risk of meningioma in obese individuals compared with individuals with a normal body mass index (BMI). This large prospective cohort study adds weight to the suggested link between BMI and meningioma, thus contributing to the growing number of cancer sites likely associated with body fatness. Although the exact mechanisms underlying the BMI–meningioma link are unclear, possible mediators include hormonal factors, immunologic response, and levels of insulin or insulin-like growth factors, each of which has been implicated by various levels of evidence in meningioma risk. Understanding the relationships between body fatness, height, and hormonal and immunologic factors could provide important clues to the etiology of meningioma and may have implications for the early detection and prevention of these tumors. *Cancer Prev Res; 4(9); 1353–5. ©2011 AACR.*

Autopsy series and imaging studies for conditions other than meningioma suggest that more than 2% of the general population is likely to have asymptomatic meningioma (1, 2), but only a small fraction of this population-wide prevalence is clinically detected. Even so, recent statistics indicate that brain and nervous system meningiomas are now the most commonly reported type of brain tumor in the United States (3). Although generally histologically benign, these tumors can produce significant morbidity including focal or generalized seizure disorders, neurologic deficits, and neuropsychological decline as a result of their intracranial location (4). Therefore, identifying ways to prevent clinically relevant tumors is important.

Until recently, the study of meningioma has faced a number of impediments. Because meningiomas are relatively rare, accruing a large enough number of cases for sufficiently powered studies has been difficult. Reporting meningioma to population-based cancer or brain tumor registries varies internationally and was not mandatory in the United States until January 2004, when the Benign Brain Tumor Cancer Registries Amendment Act (Public Law 107–260) took effect. Older data are thus subject to incomplete reporting and selection biases. Even with routine reporting of meningioma, there remains a potential for detection bias because of the presence of asymptomatic cases in the population. Given the difficulties in studying these tumors, it is not entirely surprising that their only

established risk factors to date are possession of rare mutations, particularly in the neurofibromatosis gene (*NF2*; ref. 5), and exposure to moderate-to-high doses of ionizing radiation (6–9).

In this issue of the journal, Michaud and colleagues (10) report a 48% increased risk of meningioma in obese individuals [body mass index (BMI) $\geq$ 30 kg/m^2] compared with individuals with a normal BMI of 20 to 24.9 kg/m^2 (HR = 1.48, 95% CI: 0.98–2.23). They also observed a 71% increase in meningioma among men and women in the top quartile of waist circumference (HR = 1.71, 95% CI: 1.08–2.73). A few key points make these results particularly noteworthy. First, body fatness was measured before knowing the disease status, thus eliminating the possibility that the results reflect postdisease changes in body fatness or that the association may be due to differences in reporting between cases or controls. Second, unlike many studies that rely on self-reported data, Michaud and colleagues report on measured values of height, weight, and waist circumference. Last, the magnitude of the BMI–meningioma association is very consistent with previous prospective studies that observed a 40% to 60% increase in meningioma in individuals with the highest versus the lowest BMIs (11, 12) and is also consistent with positive meningioma associations with BMI at time of diagnosis in a hospital-based case–control study (13) and with BMI prior to symptomatic meningioma in a community-based case–control study (although this association was not statistically significant; ref. 14).

Novel to the study of Michaud and colleagues is the association with waist circumference. Although attenuated after controlling for BMI in this analysis (suggesting that BMI was a more powerful predictor in this dataset), waist circumference could prove to be an independent measure of risk in future studies and thus add to the predictive power of BMI alone. Together with the other evidence

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published to date, the results of this measurement-based prospective study by Michaud and colleagues indicate that a positive association between BMI and meningioma is highly likely. Meningioma thus joins the growing number of cancers which are probably associated with body fatness, including cancers of the breast (postmenopausal), esophagus, pancreas, colorectum, endometrium, and kidney (15, 16). Data for other cancers, including prostate and lung cancer, remain inconclusive (15).

If this risk association proves to be true, the number of meningioma cases attributable to obesity is likely to be much greater than the number attributable to the confirmed, but rare, risk factors of genetic syndromes and ionizing radiation, given the growing prevalence of obesity worldwide (17). One can imagine several factors that might drive this association, including circulating levels of sex steroid hormones (including estradiol, progesterone, and testosterone), inflammatory response factors, and insulin, insulin-like growth factor 1 (IGF-1), and associated binding proteins (18).

Women are twice as likely as men to develop meningioma, and estrogen and progesterone receptors are found in some meningiomas, suggesting a role for female hormones in its etiology (19, 20). Furthermore, several reports have indicated a possible association between meningioma and breast cancer (21, 22). It is tempting to link the obesity–meningioma association to the female predominance, as suggested by Michaud and colleagues (10). Certainly, higher BMI has been associated with significant increases in levels of estrone, estradiol, and free estradiol, which have in turn been linked with postmenopausal breast cancer (23). Unlike breast cancer, however, for which epidemiologic studies indicate an increased risk with reported higher lifetime exposure to estrogen (measured by factors such as early menarche and late menopause; ref. 24), epidemiologic studies have shown inconsistent relationships for meningioma with age at menarche or menopause and with use of hormone replacement therapy or oral contraceptives (25). Any potential relationship between BMI, hormones, and meningioma is thus unlikely to be straightforward.

Even if the relationship between BMI and meningioma involves mediation by hormonal factors, other factors likely are also involved. Obese individuals are subject to a low-grade chronic inflammatory state (26, 27). Adipocytes (fat cells) are known to produce proinflammatory factors (28), and obese individuals have elevated concentrations of circulating TNF-α, interleukin (IL)-6, and C-reactive protein compared with lean BMI individuals (15, 29). Could the association between meningioma and BMI thus somehow be related to immunity? Again, there is no obvious link. Genetic polymorphisms related to innate immunity have been associated with risk of meningioma in a small case–control study (30), and subjects with meningioma in a large case–control study had lower serum immunoglobulin E and were 36% less likely than controls to report a history of physician-diagnosed allergy (31). However, neither of these observations directly addresses the issue of BMI and so it is unclear if these results are relevant to the BMI association. A further mechanism that is often invoked to explain the association between BMI and cancer is the modulating effect of insulin and IGFs. Overexpression of the *IGF1*, *IGF2*, and *IGF1R* genes has been observed in meningioma (32), and higher levels of serum IGF-1 have been positively associated with risk of cancers of the breast, colon, and prostate (18). However, the question of whether serum IGF-1 levels are associated with risk of meningioma remains to be addressed.

Although endowed with several strengths, the multicenter study by Michaud and colleagues also has the limitation that its different study sites measured BMI and waist circumference in slightly different ways. Although the investigators attempted to correct for differences in measurement by statistical adjustment, some differences inevitably remained and may have attenuated risk estimates. The question of the relevant time period of the risk exposure is also pertinent. Weight, waist circumference, and height all change through the course of lifetime of an individual, and Michaud and colleagues used measured data for body dimensions/weight for all participants at study baseline (used in the primary risk analysis) but only self-reported body size/weight data at age 20 (used in a secondary risk analysis) for a subset of this population. They found no increase in risk of meningioma with BMI at age 20. It is unclear, however, whether the lack of risk reflected a true null association with early-life BMI, a lower power to detect an association, or misclassification of self-reported early-life measures. A study with more cases of meningioma (vs. only 203 cases in the study by Michaud and colleagues) and measurements at multiple time points would be needed to better define the shape and magnitude of the dose–response curve and to address questions of temporality.

Anthropometric measures (to a lesser extent) and other factors such as hormonal factors or allergic conditions (to a greater extent) are subject to measurement error, particularly when self-reported or measured at one time point, whereas common germline genetic variation can generally be measured with much greater reliability and accuracy. Meningioma risk likely has a genetic component, given the following facts: Individuals with rare mutations in the *NF2* gene are predisposed to meningioma (33); a 2- to 3-fold higher meningioma risk has been reported for individuals with a family history (34, 35); a single-nucleotide polymorphism in the gene coding for breast cancer susceptibility gene 1 (BRCA1)-interacting protein 1 (*BRIP1*) has been associated with risk of meningioma (36); and most recently results of a genome-wide association study of meningioma indicate that the rs11012732 locus near the *MLLT10* gene is strongly associated with risk of meningioma (37). Future high-throughput genotyping studies along with follow-up efforts on the functional significance of identified variants will likely provide new insights into relevant risk pathways.

In conclusion, BMI is a strong suspect in the development of meningioma. Understanding the mechanisms underlying the relationship between BMI and meningioma could provide important clues to the etiology of this disease. If 2% or more of the population do indeed have an asymptomatic meningioma (1, 2), what causes growth and/or clinical manifestations in the small fraction of individuals who are diagnosed? Large studies examining individual and joint effects of body fatness, serum markers, genetic factors, and other potential risk factors will help address this question and could have implications for meningioma prevention through maintenance of normal body weight and/or for meningioma early detection (e.g., using serum biomarkers).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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