

Meningiomas: causes and risk factors

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✓Meningiomas are among the most common primary intracranial tumors. Although the vast majority of these tumors are considered histologically benign, the incidence of complications can be high. Few studies have investigated the causes and risk factors for meningioma; this review highlights the current state of knowledge. Gaining a better understanding of the origin of this disease is essential so that treatments and outcomes can be improved and prevention strategies can be developed. (DOI: 10.3171/FOC-07/10/E2)

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MENINGIOMAS account for 30% of all primary brain tumor diagnoses in adults in the United States.⁹ The overall age-adjusted incidence rate is 4.52 per 100,000.⁹ Although age-adjusted incidence rates are reportedly similar across racial groups, the incidence in women is approximately twice that in men (Table 1).⁹ The incidence increases with increasing age, peaking in the seventh and eighth decades of life; these tumors are very rare in children (Fig. 1).⁹ It is currently estimated that 83% of all meningiomas are microscopically confirmed.³⁶ The incidence of both diagnostically and nondiagnostically confirmed meningiomas increased between 1985 and 1999;³⁶ on average the incidence of nondiagnostically confirmed meningiomas increased significantly at 4.1% per year (95% CI 2.5–5.6) potentially reflecting both the increased use of improved imaging techniques such as MR imaging and increased numbers of meningiomas treated with observation or primary radiotherapy rather than through surgical intervention. A similar statistically significant difference in the average annual percent change was not seen for diagnostically confirmed meningiomas.³⁶

The vast majority of meningiomas are considered histologically benign (92.8%); only 2.2% are defined as uncertain or atypical, and 5% as malignant.⁹ Five-year survival rates are high for this tumor type (reported to be anywhere from 70 to 95%)^{60,77,94} and therefore the estimated population prevalence (number of individuals living with this tumor) is relatively high, 50.4 per 100,000.¹⁵ Long survival times coupled with potentially significant neurocognitive and physical deficits could lead to significant medical costs over time. The estimated average years of potential life lost

in persons with meningiomas is 13 years, providing further evidence of the long-term burden of this disease.¹¹⁰

Causes and Risk Factors

In addition to increasing age, the most consistent factor associated with risk of meningioma is exposure to ionizing radiation; many other environmental, lifestyle and genetic risk factors have been studied with inconclusive results.¹² Some of the factors that have been studied are endogenous and exogenous hormone use,^{11,13,33,41,49,51,97,113} cell phone use,^{10,28,30,31,40,42,46,55,65,100} and genetic variants or polymorphisms.^{16,17,19,48,57,58,71,93,102} Other risk factors have included preexisting conditions (such as diabetes, hypertension, and epilepsy),^{6,61,96,98,101} occupational lead exposure,^{2,66,81,106,112} personal hair dye use,^{5,18,80} radio frequency/microwave electromagnetic field exposure,^{4,23,108} cigarette smoking,^{38,51,61,70,75,76,78,89} head trauma,^{39,53,73} and allergies.^{6,96,99} For most of these factors, either no significant association or inconsistent associations with meningioma risk have been reported. Many of these studies have had small sample sizes, short follow-up times, and differences in eligibility criteria and exposure measurement, making reproducibility across studies difficult.

Ionizing Radiation

The strongest evidence to date for an increased risk of meningioma is exposure to ionizing radiation. Studies of ionizing radiation have focused on the tinea capitis cohort in Israel,^{62,84,91,92} atomic bomb survivors,^{79,85,90,103,104,109} and patients with exposures in medical and occupational settings (diagnostic or therapeutic radiation).^{43,54,69,74–76,78,83,88} The strongest evidence for high-dose radiation exposure in the development of meningiomas comes from individuals who underwent therapeutic radiation treatment to the head or neck for neoplastic conditions,^{1,32,35,56,63,67,69,87,105} whereas

Abbreviations used in this paper: CI = confidence interval; HRT = hormone replacement therapy; MR = magnetic resonance; NF2 = neurofibromatosis Type 2; OR = odds ratio.

the strongest evidence for low-dose radiation exposure comes from the tinea capitis cohort studies.^{62,84,91,92} Studies of meningioma risk in atomic bomb survivors who received moderate to high doses of radiation—depending on their distance from the hypocenter of the bomb explosion—are less consistent,^{79,90,104} as is evidence from diagnostic radiation exposure from dental x-ray studies.^{54,74–76, 78,83,88,95} The latency periods for meningiomas arising after radiation show a trend towards diminishing latency period with increasing radiation dose; 35.2 years for low-dose (< 10 Gy), 26.1 for moderate dose (10–20 Gy), and 19.5 years for high-dose (> 20 Gy).³² In addition, the age at diagnosis decreases with increasing radiation dose and there is a stronger tendency toward the presence of multiple tumors with a greater likelihood of being atypical or malignant.^{87,105}

Between 1948 and 1960, approximately 20,000 new immigrants to Israel (mostly children) received low-dose cranial radiation for the treatment of tinea capitis, a fungal infection of the scalp.^{62,64} The largest cohort with long-term follow-up from this population includes approximately 11,000 patients who received radiation and an equal number of matched individuals who did not receive radiation. The patients who received radiation were individually matched by age, sex, country of birth, and year of immigration, with a sibling group that did not receive radiation.⁹¹ Munk et al.⁶⁴ were the first to report an association between irradiation for tinea capitis and meningioma; the authors of subsequent studies have shown that irradiated individuals had a 9.5-fold increased risk (95% CI 3.5–25.7) of developing meningioma compared with individuals who did not undergo radiation^{84,91} over a 20- to 30-year period. The interplay between genetic predisposition and exposure to ionizing radiation was examined in this cohort to further refine estimates of meningioma risk. In particular, the role of genes involved in DNA repair and cell cycle pathways was examined. Sadetzki et al.⁹³ showed that variants in the cell cycle control gene *Ki-Ras* and DNA repair gene *ERCC2* were associated with an increased risk of meningioma in the entire cohort (*Ki-Ras* OR [95% CI] 1.76 [1.07–1.92]; *ERCC2* OR [95% CI] 1.68 [1.00–2.84]). Additionally they showed that there was a significant interaction between radiation status and variants in two other cell cycle control genes, *cyclin D1* and *p16*, having an interactive, inverse effect on development of meningiomas (that is, a decreased risk) in individuals who received radiation compared with those who did not. Interestingly, in the entire cohort meningiomas developed in fewer than 1% of individuals who received radiation, supporting the idea that there are other factors (environmental, lifestyle, and/or genetic) that modify tumorigenesis after low-dose irradiation.²¹ A recent follow-up study in this cohort and their families supports the idea that inherited genetic susceptibility may increase the risk of developing meningioma after receiving radiation.²¹ Patients who had undergone radiation and subsequently developed a meningioma were more likely to have relatives affected with cancers at other irradiated sites compared with 5% of the group that did not receive radiation (p = 0.04). Hence, inheriting specific risk variants at key genes for tumorigenesis may make one more susceptible to the chromosome damaging effects of radiation, adversely affecting the risk of meningioma development.

Atomic bomb survivors from Hiroshima and Nagasaki

TABLE 1
Age-adjusted incidence rate of meningiomas by sex and race/ethnicity*

Sex or Race/Ethnicity	Total No. of Cases	Age-Adjusted Incidence Rate†
all individuals	19,190	4.52
w/ benign & malignant tumors		
men	5,112	2.75
women	14,075	6.01
Whites	16,486	4.44
Blacks	1,762	4.44
Hispanics of any race	1,807	4.61
White Hispanics	1,656	4.54
non-Hispanics of any race	17,383	4.53
White non-Hispanics	14,830	4.46
Black, non-Hispanics	1,728	4.58
w/ benign tumors only		
men	4,778	2.57
women	13,458	5.75
w/ malignant tumors only		
men	334	0.18
women	617	0.26

* Data based on the 1998–2002 CBTRUS report. Racial/ethnic categories are those used by the census.

† Incidence rates are per 100,000 person-years and are age-adjusted to the 2000 US Standard Population.

have been studied for risk of multiple different cancer types following radiation exposure from the bomb blasts.^{79,85, 90,103,104,109} Radiation exposure in these individuals was moderate to high depending on how close they were to the hypocenter of the blast. Seyama et al.¹⁰³ initially reported an increased risk of all brain tumor types in male survivors who received high-dose levels of radiation exposure, however a follow-up study in this same cohort, which included an additional 12 years of follow-up, showed no significant increase in radiation-associated brain tumor risk.¹⁰⁹ More recently, two studies have shown an association between increased brain tumor risk (specifically meningiomas) and proximity to the hypocenter of the blast. Risk was increased in those individuals closest to the blast hypocenter who received the highest radiation doses.^{90,104} The most recent study of this cohort, with follow-up through 1995, showed a statistically significant dose-related increased excess risk for all brain tumors combined.⁷⁹ These studies provide further evidence for an association between high-dose radiation exposure and overall risk of a brain tumor, regardless of age at exposure. Further follow-up in this population is necessary to completely quantify lifetime risks for brain tumors and to fully evaluate the lifetime risk of developing specific histological tumor types.

Individuals receiving high-dose therapeutic radiation treatment to the head or neck for neoplastic conditions have also been shown to have an increased risk of developing a meningioma.^{1,32,35,56,63,67,69,87,92,105} Multiple studies have shown that age at high-dose therapeutic radiation treatment is directly correlated with tumor latency; the younger the age at irradiation, the shorter the latency period to meningioma formation.^{32,56,92} These and additional studies have shown that many of these individuals develop multiple meningiomas, that a higher proportion of these tumors tend to be atypical or malignant than would be expected and that these

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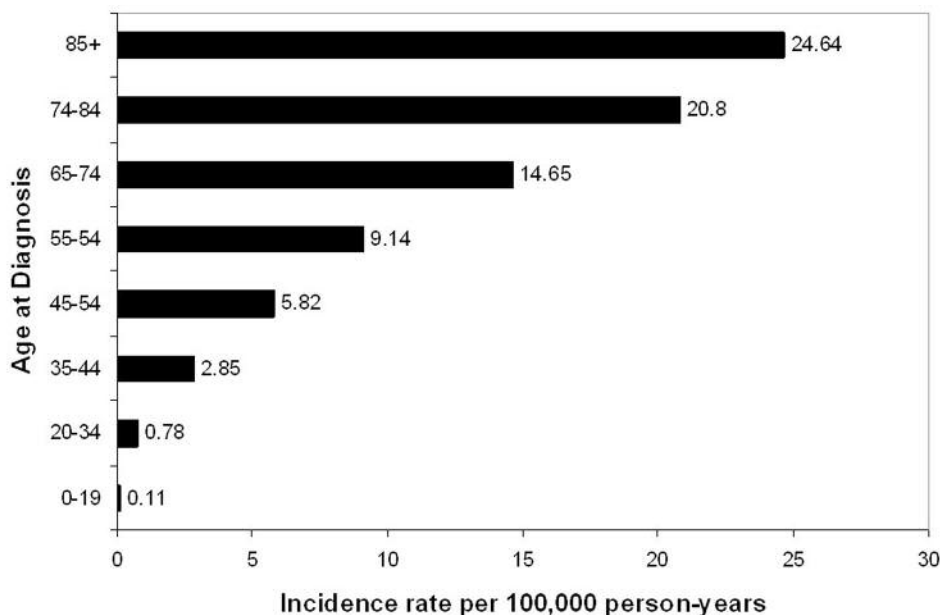


FIG. 1. Bar graph illustrating the incidence rates of meningioma (benign and malignant combined) according to patient age at diagnosis. Data based on the report of the Central Brain Tumor Registry of the United States from 1998 to 2002.

tumors have an increased recurrence rate.^{1,63,86,105} The most recent evidence for increased risk of development of meningiomas following high-dose therapeutic radiation treatment comes from studies of childhood cancer survivors.^{35,67} In one cohort of 14,361 5-year survivors of multiple different types of childhood cancer (The Childhood Cancer Survivor Study), radiation exposure was associated with a 9.94-fold increased risk of meningioma (95% CI 2.17–45.6), with a median latency period of 17 years and a 6.78-fold increased risk of glioma (95% CI 1.54–29.7), with a median latency period of 9 years. In another study of 2169 survivors of childhood acute lymphoblastic leukemia, meningiomas developed in 14% of individuals, with an estimated latency period of 20.6 years (95% CI 12.6–31.7). The estimated standardized incidence ratio for development of a CNS tumor following cranial and craniospinal radiation compared to the general US population was increased by 45.8-fold (95% CI 26.0–64.2), while those who did not receive radiation had an increased risk of 4.3-fold (95% CI 0.1–24.0). Taken together these studies provide strong evidence for an increased risk for long-term development of secondary meningiomas after high-dose therapeutic radiation to the head and neck.

The primary source of diagnostic ionizing radiation to the head and neck for individuals in the United States is from diagnostic dental x-ray studies. In particular, full-mouth series and panoramic dental radiographs use radiation beam conversion points that include parts of the meninges. Initial studies in Los Angeles, California showed that individuals who had repeated full-mouth dental x-ray exposure, particularly before the age of 20 or before 1945, were at a four-fold increased risk of developing a meningioma (p value < 0.01).^{74–76,78} However, studies conducted in populations outside the United States did not confirm these results.^{83,88,95} The authors of the most recent study of this exposure in the United States found that there was an

increased risk of meningiomas associated with dental x-ray exposure (OR [95% CI] 2.06 [1.03–4.17]), but only for full-mouth series that were performed at least 20 years ago when the radiation exposure was much greater than it is currently.⁵⁴ Taken together, these studies imply that the radiation exposure obtained from diagnostic dental radiographs could be associated with meningioma risk, but with a long latency period of at least two decades. Other types of diagnostic x-ray studies, such as computed tomography scans, have not yet been studied on a large enough scale to form conclusive results.

Hormones

Given the predominance of meningiomas in women compared with men, the presence of hormone expression in some tumors, the possibility of an association with breast cancer, as well as reported changes in tumor size during pregnancy, the menstrual cycle, and menopause, the authors of a number of studies have focused on the relationship between hormones and meningioma risk.^{11,13,33,41,49,51,97,113}

In studies of exogenous hormone exposure, researchers have looked at the risk of meningioma associated with the use of oral contraceptives and HRT in both pre- and postmenopausal women.^{11,13,33,41,51,113} Overall, the data currently reveal no evidence for an association between oral contraceptive use and meningioma risk but do suggest a possible association with the use of HRT.¹¹ Wigertz and colleagues¹¹³ found a significantly increased risk of meningiomas in postmenopausal women in Sweden who had ever used HRT (OR [95% CI] 1.7 [1.0–2.8]), confirming earlier findings by Jhavar and colleagues⁴¹ within the Nurses Health Study. It should be noted that despite these reports, not all studies have supported an association between HRT use and meningiomas.¹³ Larger studies that examine the rela-

tionship between exogenous hormone use and meningioma risk by hormone receptor subtype and by hormone composition (opposed compared with unopposed estrogen, for example) using a larger patient cohort are needed.

In the studies of endogenous hormone exposure, researchers have looked at the risk of meningioma associated with menopausal status, parity, ever having been pregnant, and age at menarche.^{33,41,49,51,97} A decreased risk of meningiomas in menopausal women has been reported⁹⁷ (OR [95% CI] 0.58 [0.18–1.90]) but was not confirmed in later studies.^{33,51} Lee and colleagues⁵¹ recently reported a decreased risk associated with having been pregnant at least once (OR [95% CI] 0.4 [0.2–0.8]); an association that was stronger with increasing number of pregnancies. However this finding has not been supported by other studies of the same factor.^{41,49} Jhawar and associates⁴¹ demonstrated that women older than 14 at the beginning of menarche were at an increased risk (OR 95% CI 1.97 [1.06–3.66]) of developing a meningioma compared with women in whom menarche occurred before age 12, adjusting for hormone use and menopause status. However, other studies of age at menarche show no significantly increased or decreased risk for meningioma development.^{33,51} In conclusion, these studies do not provide strong evidence for an association between endogenous hormone exposure and an increased risk of meningioma.

The possible relationship between breast cancer and meningiomas is scientifically intriguing. A recent study using data from the Washington State Cancer Registry¹⁴ showed that the risk of meningioma among women with breast cancer and the risk of breast cancer among women with meningioma was elevated; however, it is unclear whether the relationship is due to shared risk factors. This study involved very small numbers of women with both cancer types; this topic would benefit from study in a larger population where information is also available on other environmental, lifestyle and genetic factors.

Multiple studies have also investigated the presence of various hormone receptors (estrogen, progesterone, and/or androgen) in meningiomas to try to explain the female predominance of this tumor.^{7,8,45,59,86} The majority of benign meningiomas express the progesterone receptor (~ 60–90%),^{37,45,59,86} whereas most meningiomas do not express estrogen and androgen receptors.^{7,45,59} Multiple studies have shown the prognostic significance of the presence of progesterone receptors for recurrence status and recurrence-free and progression-free survival.^{20,37,72,86,107} Specifically Hsu et al.³⁷ showed in a multivariate analysis that individuals with a combination of zero nuclei staining positive for the progesterone receptor, a mitotic index greater than six, and malignant histopathological characteristics had the shortest period of progression-free survival compared to other individuals with meningiomas; hence showing that the presence of the progesterone receptor is a favorable prognostic indicator of recurrence.

How the expression of these hormone receptors in these tumors would translate into better therapeutic treatments for meningiomas remains unclear; the results from studies of antiestrogen and antiprogestosterone agents have been equivocal. One study of tamoxifen (an antiestrogen therapy) as a chemotherapy for meningiomas, was too inconclusive to enable a definite recommendation about its use in this patient population.²² Authors of other studies have re-

ported using an antiprogestosterone (RU-486) chemotherapeutic agent to treat patients with meningiomas, but only minor radiographic tumor regression was observed in about 25% of patients.^{24,25}

Cell Phone Use

Although public interest in the topic remains high, to date little evidence exists to suggest an association between cell phone use and the risk of meningioma.⁴⁷ Multiple studies have been performed in United States,^{40,65} European, and Israeli populations including the Interphone case-control study of cell phones and brain tumor risk.^{10,28,30,31,42,44,46,55,100} None of these studies found a significant association between cell phone use and meningioma risk. However, inconsistent findings have been reported for an increased risk of acoustic neuroma,^{27–29} some types of high-grade gliomas^{10,29} and long-term cell phone usage (> 10 years).^{27,29,46} Follow-up time in the majority of these studies is relatively short and measurements of cell phone exposure vary between studies, therefore further long-term study of cell phone exposure may be warranted.

Genetics

The majority of meningiomas are sporadic tumors; patients with sporadic lesions have no family history of any kind of brain tumor. Known inherited genetic syndromes that predispose to meningioma development are few and rare. Meningioma is observed in patients with NF2, a rare autosomal dominant disorder caused by germline mutations in the *NF2* gene on 22q12 (US incidence: 1 per 30,000–40,000 persons).³ However, there are probably many genes other than *NF2* involved in familial meningioma. Excess familial risk of meningioma has been reported in Swedish families without any evidence of NF2 in whom there was a significant association between meningioma diagnosis and parental history of a meningioma (standardized incidence ratio [95% CI] 3.06 [1.84–4.79]).³⁴ In addition, in the tinea capitis cohort from Israel, the patients with meningiomas who had received radiation were more likely than those who did not to have family members affected with radiation-induced cancers, highlighting a potential inherited genetic susceptibility. Interestingly, approximately 50% of all sporadic meningiomas are also believed to harbor mutations in the *NF2* gene or genetic losses that include the 22q12 chromosomal band.^{26,52,82} Additionally, sporadic meningiomas reveal a host of other chromosomal losses (1p, 6q, 10, 14q, and 18q) and gains (1q, 9q, 12q, 15q, 17q, and 20q), many associated with tumor grade.^{50,68,111}

A number of researchers have examined the relationship between specific genetic variants and meningioma risk, focusing on genes involved in DNA repair, cell cycle regulation, detoxification, and hormone metabolic pathways.^{16,17,19,48,57,58,71,93,102} The majority of these studies have focused on variants in the *GST* and *CYP450* genes, which are genes involved in metabolism and detoxification of exogenous and endogenous carcinogens.^{16,17,19,48,71,102} Results from these six studies were generally consistent, finding few significant associations with variants in these genes and an increased risk of meningioma. Authors of three of these stud-

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ies found a significantly increased risk of meningioma associated with having the *GSTT1* null genotype compared to those with the *GSTT1* positive genotype (~ 1.5 to 3.5-fold increased risk).^{17,19,48} In one of these studies a significant increased risk for meningioma was found to be associated with having the *GSTM3* *B/*B genotype (OR [95% CI] 3.6 [1.3–9.8]).¹⁶ The remaining two studies found no significant associations between meningioma risk and variants at various *GST* or *CYP450* genes.^{71,102}

The remaining three studies focused on the most well-known tumor suppressor gene, *TP53*,^{57,58} and on DNA repair and cell cycle control genes.⁹³ Malmer et al.⁵⁷ studied three variants in *TP53* and found that overall there was no associated increased risk of meningioma for any of the individual variants or for combinations of these variants. However when restricting the analysis to individuals with a family history of cancer, the association between a specific variant combination (CC-CG-CC) and meningioma risk was a 5.69-fold increase (95% CI 1.81–17.96) and glioma risk was a 3.62-fold increase (95% CI 1.05–12.48). In a follow-up study, Malmer and colleagues⁵⁸ again studied the same three *TP53* variants and also five *ATM* variants, the gene responsible for regulating cellular response to DNA damage. They showed that a specific combination of variants in the *ATM* gene was significantly increased in patients with meningiomas (33.8%) compared with control participants (30.3%; p value = 0.03), while a different combination was significantly decreased in patients with meningiomas (36.1%) compared with control participants (40.7%; p-value = 0.009). Sadetzki et al.⁹³ showed that variants in *Ki-RAS* and *ERCC2* were each associated with an approximately 2-fold increased risk of meningioma. Although these studies have yielded interesting results, a more formal large-scale, population-based study will be needed to fully assess the role of genes in the risk of meningioma development, incorporating information on various environmental and lifestyle factors.

Conclusions and Future Directions

Other than increasing age, the most consistently confirmed risk factor for meningioma is ionizing radiation exposure, despite the fact that many other environmental, lifestyle, and genetic risk factors have been studied with inconclusive results. Further studies are needed that fully integrate environmental exposure and lifestyle information with genetics, but for these studies to be scientifically meaningful they will require large sample sizes, rigorous long-term follow-up, and high-quality measurement of environmental exposure and lifestyle factors.

Recent legislation, Public Law 107-260 “The Benign Brain Tumor Cancer Registries Amendment,” which went into effect January 1, 2004 now requires all state-wide cancer registries to collect incidence information on all newly diagnosed benign brain tumors in addition to the information they already collect on newly diagnosed malignant brain tumors. The Surveillance, Epidemiology, and End Results program of the National Cancer Institute has voluntarily agreed to collect these data. This information will provide a valuable resource not only for calculating more reliable incidence and survival rates, but also as a mechanism to identify individuals for epidemiologic and other types of research studies. In fact, the National Cancer In-

stitute has recently funded the first multicenter case-control study¹² to investigate environmental and genetic risk factors as well as quality of life and long-term outcomes for patients with meningiomas, utilizing cancer registry resources in five states to identify eligible individuals (<http://www.brainsciencefoundation.org> and <http://www.meningiomommas.org>). We hope that these and other studies will move forward the investigation of causes and risk factors for this understudied disease.

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