Non-malignant and malignant meningioma incidence and survival in the elderly from 2005-2015 using the Central Brain Tumor Registry of the United States

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Abstract

Background

Meningioma incidence increases significantly with age. In the expanding elderly population, we lack complete understanding of population-based trends in meningioma incidence/survival. We provide an updated, comprehensive analysis of meningioma incidence and survival for individuals aged over 65.

Methods

Data were obtained from the Central Brain Tumor Registry of the United States (CBTRUS) from 2005-2015 for non-malignant and malignant meningioma. Age-adjusted incidence rates per 100,000 person-years were analyzed by age, sex, race, ethnicity, location, and treatment modalities. Survival was analyzed using Kaplan-Meier and multivariable Cox proportional hazards models for a subset of CBTRUS data.

Results

Non-malignant meningioma incidence doubled from adults age 65-69 years to adults over age 85 years and was significantly greater in females than males for all ages. Malignant meningioma incidence did not differ by sex for any age grouping. Non-malignant and malignant meningioma incidence was significantly greater in Black populations versus others. Non-malignant meningioma survival was worse with age, in

Black populations, and in males, including when analyzed by five-year age groups. Surgical resection and radiation did not improve survival compared to resection alone in non-malignant meningioma.

Conclusions

This study reports increasing non-malignant meningioma incidence in the elderly, increased incidence in Black populations, and in females. In contrast, malignant meningioma incidence did not differ between sexes. Risk of death was higher for Black individuals and males. Additionally, radiation did not confer a survival advantage when combined with resection for non-malignant meningioma. Thus, we identify clinically relevant discrepancies in meningioma incidence/survival that require further study.

Key Words

Meningioma; incidence; survival; CBTRUS; SEER

Key Points

Meningioma incidence is highest in Black populations, females, and increasingly elderly.

Non-malignant meningioma survival is lowest in Black populations, males, and increasingly elderly.

Adjuvant radiation following surgical resection does not confer a survival advantage in the elderly.

Importance of the Study

Meningioma is the most common primary central nervous system tumor and incidence increases with age. Given the increasing age of the United States population, and the relative paucity of recent nationwide epidemiological reports addressing meningioma specifically in the elderly, we sought to provide an up-to-date, detailed analysis of incidence and survival trends in individuals over age 65 years. We examined non-malignant and malignant meningioma from 2005-2015 using incidence data derived from the Central Brain Tumor Registry of the United States (CBTRUS), which provides data for approximately 99% of the US population. Moreover, we report updated temporal trends in non-malignant and malignant meningioma that potentially shed light on the effect of World Health Organization (WHO) classification changes on incidence over time. We also examine the effects of demographic and clinical factors on survival. This includes the effect of combined resection and radiation, which remains a controversial issue in the treatment of meningioma in the elderly.

Introduction

Meningioma is the most common primary neoplasm of the central nervous system (CNS), accounting for 36.4% of CNS tumors reported from 2010 to 2014.[1] According to a recent study, non-malignant meningioma has an incidence rate of 7.86 per 100,000 people; a rate that has significantly increased from 2004 to 2010, with an annual percentage change (APC) of 3%.[2] A report of atypical, World Health Organization (WHO) grade II meningioma revealed increasing incidence from 2004-2010, with a 3.6% APC.[3] In fact, an estimated 29,320 new meningioma diagnoses are projected in the United States for 2018 alone.[1] Furthermore, there is clear evidence that incidence of meningioma increases with age, with a median age at diagnosis of 66 years old.[1,4] However, few studies have taken a comprehensive approach to the descriptive epidemiology of malignant and non-malignant meningioma in the elderly population.[5,6]

While few studies have addressed the descriptive epidemiology of meningioma in the elderly, many have examined the effects of patient characteristics and treatment modalities on survival.[7,8,17,18,9–16]. Several studies suggest that craniotomy for gross total or subtotal meningioma resection is associated with higher risk of morbidity and mortality in elderly patients when compared to younger cohorts.[10–12] Other studies, however, suggest that there is no association between age and overall survival, but rather between other prognostic factors such as male sex, co-morbidity status, neurological deficits, and performance scales.[13–15] Further analysis suggests comparable mortality rates between elderly and younger patients with meningioma, but a greater number of minor complications and poorer functional outcomes for elderly patients undergoing treatment.[16–18] Thus, there remains a general lack of consensus regarding the association between age and clinical outcomes for elderly patients with meningioma. Therefore, given the increasing life expectancy of the overall population, the concomitant increase in meningioma incidence, and paucity of descriptive epidemiological studies to address trends in this growing at-risk patient cohort,

we aimed to provide an updated comprehensive analysis of meningioma incidence and survival trends specific to the elderly population.

Methods

This study was approved by the University Hospitals Case Medical Center Institutional Review Board. Data were obtained from the Central Brain Tumor Registry of the United States (CBTRUS), which includes incidence data from approximately 99% of the US population. CBTRUS data are derived from 50 state cancer registries and the cancer registry for the District of Columbia. Together, these include 46 National Program of Cancer Registration (NPCR) and five Surveillance Epidemiology and End Results (SEER) central cancer registries.[2] Age-adjusted incidence rates were generated for non-malignant and malignant meningiomas from 2005 to 2015. Non-malignant meningiomas were specified by nine specific ICD-O-3 codes: 9530/0 (Meningioma, NOS), 9530/1 (Meningiomatosis, NOS), 9531/0 (Meningothelial meningioma), 9532/0 (Fibrous meningioma), 9533/0 (Psammomatous meningioma), 9534/0 (Angiomatous meningioma), 9537/0 (Transitional meningioma), 9538/1 (Clear cell meningioma), and 9539/1 (Atypical meningioma, NOS), as previously reported.[1] Malignant meningioma were specified by three ICD-O-3 codes: 9530/3 (Meningioma, malignant), 9538/3 (Papillary meningioma), and 9539/3 (Meningeal sarcomatosis), also as previously reported.[1] Age-adjusted incidence rates were standardized to the 2000 US population[1] and reported per 100,000 population.

Information on patient survival outcomes was derived from SEER data, since NPCR registries do not provide follow-up data to CBTRUS. SEER data were analyzed to generate survival data for both non-malignant and malignant meningiomas from 2005 to 2015. The current SEER registry system consists of 18 registries representing a subset of the population included in the CBTRUS dataset. Of note, NPCR and

SEER dually provide funding for the 18 registries in the SEER subset. According to the US 2000 Census, data pulled from the 18 SEER registries provide population-based information for approximately 28% of the US population.[19,20]

Incidence rates (IRs) and other relevant statistics were calculated using SEER*Stat 8.3.5. Figures were generated using GraphPad Prism 6, Adobe Illustrator and Photoshop, and R statistical software. Statistics were excluded for cells containing fewer than 16 counts as required by NPCR. Age-adjusted incidence rates and 95% confidence intervals were estimated for non-malignant and malignant meningiomas by sex, race, ethnicity, age groupings (65-69, 70-74, 75–79, 80–84, and 85+ years), and tumor location including supratentorial (ICD-O-3 codes: 700, 702-714), infratentorial (716-717), and spine (701, 720-721, 725). Race categories for this study included White, Black, American Indian/Alaskan Native (AIAN), and Asian/Pacific Islander (API). In addition, incidence for Hispanic patients versus non-Hispanic patients was also analyzed. Unknown, unspecified, and other race categories were excluded from race-specific incidence rate comparisons. However, these categories were included in statistics that were not race-specific. Joinpoint Regression Program 4.6.0.0 software was used to compute annual percent change (APC) in incidence rates from 2000 to 2015 to examine trends over time. Joinpoint software selects a minimum number of joinpoints to prohibit statistically significant improvement if one additional joinpoint is added (http://surveillance.cancer.gov/joinpoint).

SEER*Stat was used to generate survival outcomes by age, race, and sex. For survival data, race categories included White, Black, API, and AIAN for non-malignant meningioma. AIAN populations were excluded from malignant meningioma analysis due to insufficient sample size. Survival by age at diagnosis was examined using the age groupings described above. Given that the 18 SEER registries

comprise only 28% of the CBTRUS dataset, an N > 50 was required for group-specific data inclusion to ensure sufficiently stable statistical analyses. Differences in survival were further analyzed in R using Kaplan–Meier and univariable and multivariable Cox proportional hazards models. Survival curves were generated by race, ethnicity, sex, age, tumor location, and treatment modality [gross total resection (GTR), sub-total resection (STR), GTR + radiotherapy (RT), and STR + RT], and compared using the log-rank test. However, for malignant meningioma, RT versus no RT was the only treatment modality we could include in the model, as the sample size was too small (N <50) for statistical analyses pertaining to resection or combined resection and radiation. Adjusted estimates of survival by race, ethnicity, age, tumor location, and treatment modality were also performed in R using a multivariable Cox proportional hazards model. Adjusted estimates included all covariates a priori, regardless of individual significance level.

Results

Non-malignant and Malignant Meningioma Incidence by Age and Sex from 2005-2015 (Figure 1, Supplemental Tables 1-2)

Age-adjusted incidence rates (IR) from 2005-2015 are depicted in Figure 1 by five-year age groups over the age of 65 years for males and females (Fig 1). To note, the overall incidence of non-malignant meningioma increased significantly for each five-year age group, from 23.85 cases per 100,000 in adults age 65-69 years (95% CI: 23.60, 24.11) to 50.33 cases per 100,000 (95% CI: 49.77, 50.89) in individuals over age 85 years. (Supplemental Fig 1A and Supplemental Tables 1-2). The incidence of non-malignant meningioma was also significantly greater in females in every five-year age grouping compared to males in the same age cohort (Fig 1A, Supplemental Table 1). For males and females, from 2005-2009, there was a significant increase in non-malignant meningioma incidence [female APC: 4.69% (95% CI: 3.72,

5.67) p<0.0001, male APC: 4.70% (95% CI: 2.80, 6.64) p=0.0009] (Fig 1B). However, from 2009-2015, there was a significant decrease in incidence in females [APC: -0.85% (95% CI: -1.30, -0.41) p=0.0035], and no significant change in incidence for males [APC: -0.16% (95% CI: -1.01, 0.70) p=0.66]. Additionally, there was a significant increase in non-malignant meningioma incidence in all age groups up to 2008-2009, followed by either no change in incidence or a significant decline in incidence in the case of 65-69 year olds from 2009-2015 (Supplemental Fig 1B).

In malignant meningioma, IR increased for each five-year grouping, though not significantly across all groups (Supplemental Fig 1D, Supplemental Table 2). Contrary to non-malignant meningioma IR, however, malignant meningioma incidence did not significantly differ by sex for any of the five-year age groupings (Fig 1C, Supplemental Table 2). From 2005 to 2015, there was a significant decrease in malignant meningioma incidence in females [APC: -5.45% (95% CI: -8.62, -2.17) p=0.0048] and in males [APC: -2.88% (95% CI: -5.30, -0.39) p=0.0028] (Fig 1D). In most five-year age groups, there was a significant decrease in incidence from 2005-2015 with the exception of 65-69 year olds in whom the decreasing incidence did not reach significance (Supplemental Fig 1F).

Non-malignant and Malignant Meningioma Incidence by Age and Race and Age and Ethnicity from 2005-2015 (Figure 2)

Overall IR for non-malignant meningioma was significantly greater in Black populations [39.7 cases per 100,000 (95% CI: 40.34, 39.07)] compared to all other races, while the overall incidence for AIAN populations was significantly lower than all other races (Supplemental Fig 1C). For every age group, non-malignant meningioma IR was significantly greater in Black populations, and significantly lower in AIAN populations, than all other races (Fig 2A and Supplemental Table 1). From 2005 to 2009, the

incidence of non-malignant meningioma significantly increased in Black and White populations [Black: APC: 7.25% (95% CI: 3.54, 11.10) p=0.0028, White: APC: 4.48% (95% CI: 3.18, 5.81) p=0.0001]. From 2009-2015, however, non-malignant meningioma incidence decreased significantly in these two populations [Black: APC: -2.00% (95% CI: -3.58, -0.39) p=0.022, White: APC: -0.47% (95% CI: -1.08, 0.13)] (Fig 2B). Hispanic populations had significantly higher IR than non-Hispanics for every age group except 65-69 year olds (Fig 2C and Supplemental Table 1). From 2005-2009, the non-malignant meningioma incidence significantly increased in non-Hispanic and Hispanic populations [APC: 4.76% (95% CI: 3.78, 5.74) p<0.0001 vs APC: 3.87% (95% CI: 1.02, 6.80) p=0.016] and decreased significantly in both populations from 2009-2015 [APC: -0.48% (95% CI: -0.93, -0.03) p<0.0001 vs APC: -2.00% (95% CI: -3.23, -0.76) p=0.016] (Fig 2D).

Overall IR for malignant meningioma was significantly greater in Black populations [0.74 cases per 100,000 (95% CI: 0.83, 0.65)] than in White populations [0.45 cases per 100,000 (95% CI: 0.47, 0.43)] (Supplemental Fig 1G). Similar to non-malignant meningioma, IR in Black populations trended higher than in all other races, with a significantly higher IR compared to Whites in 70-79 year olds and 85+ year olds (Fig 2E and Supplemental Table 2). Hispanic populations also trended towards higher IR for malignant meningioma, though no significant differences were identified for any age group (Fig 2G and Supplemental Table 2). From 2005 to 2015, there was a significant decrease in malignant meningioma incidence in Black and White populations [Black: APC: -4.62% (95% CI: -8.20, -0.90) p=0.021, White: APC: -4.47% (95% CI: -6.94, -1.94) p=0.0033], but not in API populations [APC: -3.12% (95% CI: -9.64, 3.87) p=0.33] (Fig 2F). There was also a significant decrease in malignant meningioma incidence in non-Hispanic populations [APC: -4.34% (95% CI: -7.15, -1.44) p=0.0083] but not in Hispanic populations (APC: -4.83% (95% CI: -11.4, 2.24) p=0.15) (Fig 2H). AIAN were excluded from race calculations in malignant meningioma due to insufficient sample size.

Non-malignant and Malignant Meningioma Incidence by Location from 2005-2015 (Figure 3)

The vast majority (95.61%) of non-malignant meningiomas were located in the supratentorial brain regions, with meningiomas of the spine accounting for 4.33% and meningiomas of infratentorial regions accounting for 0.07% (Supplemental Fig 1D). Incidence of spine and supratentorial non-malignant meningioma increased significantly for every five-year increment in age, except for IR of spinal meningiomas in 85+ year olds, which decreased significantly compared to 75-84 year olds [85+: 1.42 (95% CI: 1.32, 1.52) vs 75-79: 1.66 (95% CI: 1.57, 1.75) and 80-84: 1.86 (95% CI: 1.75, 1.96)] (Fig 3A and Supplemental Table 1). From 2005 to 2009, the incidence of supratentorial non-malignant meningioma increased significantly [APC: 4.97% (95% CI: 3.87, 6.08) $p<0.0001$] then declined significantly from 2009-2015 [APC: -0.76% (95% CI: -1.26, -0.26) $p=0.0099$]. In contrast, the incidence of non-malignant spinal meningiomas remained stable over the 11-year study period [APC: -0.21 (95% CI: -0.91, 0.49) $p=0.51$] (Fig 3B, C).

The majority of malignant meningiomas also occurred in supratentorial brain regions (97.16%) (Supplemental Fig 1H). Supratentorial IR increased significantly as age increased while spinal IR trended upwards with advancing age as well (Fig 3C and Supplemental Table 2). Like non-malignant meningiomas, IR of spinal malignant meningiomas decreased, though not significantly, in 85+ populations compared to 75-84 year olds [0.011 (95% CI: 0.005, 0.024) vs 0.02 (95% CI: 0.011, 0.035)] (Fig 3C and Supplemental Table 2). For both spinal and supratentorial malignant meningiomas, incidence rates decreased significantly over time from 2005 to 2015 [Spinal: APC: -9.78% (95% CI: -15.86, -3.27) $p=0.0087$, Supratentorial: APC: -4.27% (95% CI: -6.94, -1.52) $p=0.0068$] (Fig 3D). Infratentorial malignant meningioma was excluded from location analyses due to insufficient sample size.

Non-malignant and Malignant Meningioma Survival by Age, Sex, Race, Ethnicity, Location, Treatment from 2005-2015 (Figure 4 and Table 1)

Kaplan-Meier estimates in non-malignant meningioma showed significant differences in overall survival by age ($p<0.001$), sex ($p<0.001$), race ($p<0.001$), ethnicity ($p<0.001$), location ($p<0.001$), adjuvant radiation treatment ($p<0.001$), surgical resection status ($p=0.045$), and combined surgical resection and radiation treatment ($p=0.018$) (Fig 4A-F). In contrast, age was the only variable that significantly affected survival in malignant meningioma ($p<0.001$) (Fig 4G). Multivariable Cox proportional hazard regression models were used to examine the association of clinical and demographic characteristics with overall survival in non-malignant and malignant meningioma (Table 1). For non-malignant meningioma, after controlling for all other variables in the model, age, sex, race, location, and combined resection and radiation treatment, all significantly affected survival, except for ethnicity ($p = 0.053$). For every increase in five-year age group, the risk of death significantly increased compared to 65-69 year olds. Individuals age 70-74 years had 76% increase in risk of death [HR: 1.76 (95% CI: 1.49, 2.09) $p<0.001$], and age 75-79 years had 2.71 times the risk of death [HR: 2.71 (95% CI: 2.29, 3.22) $p<0.001$] compared to those age 65-69 years. 80-84 year olds had 4.48 times the risk of death [HR: 4.48 (95% CI: 3.76, 5.34) $p<0.001$], and those age 85+ years had 5.91 times the risk of death [HR: 5.91 (95% CI: 4.82, 7.24) $p<0.001$] compared to 65-69 year olds. Compared to females, males had a 42% increased risk of death [HR: 1.42 (95% CI: 1.26, 1.59) $p<0.001$]. Compared to White patients, Black patients had a 21% increased risk of death [HR: 1.21 (95% CI: 1.00, 1.47) $p=0.049$]. Supratentorial location was associated with a 35% increase in risk of death compared to spinal location [HR: 1.35 (95% CI: 1.12, 1.63) $p=0.001$]. When surgery and radiation treatment were combined, GTR+RT and STR+RT were associated with a 57% and 43% increase in risk of death, respectively, compared to GTR alone [HR: 1.57 (95% CI: 1.16, 2.13) $p=0.004$ and HR: 1.43 (95% CI: 1.06, 1.93) $p=0.019$, respectively]. In contrast to the multivariable Cox

proportional hazard for non-malignant meningioma, the only significant difference in survival in malignant meningioma was seen for patients age 85+ years whose risk of death was 2.06 times higher than those age 65-69 years [HR: 2.06 (95% CI: 1.45, 2.94) p<0.001] (Fig 4G) (Table 1). Multivariable Cox proportional hazard models by age group are provided in Supplementary Table 3. There were no clear statistically significant trends by age group for any analyzed variables.

Discussion

Incidence

According to several studies, the incidence of CNS tumors as a whole has decreased over the last 20 years.[2] However, when histology-specific analyses are performed, it is clear that incidence trends are far more heterogeneous.[2,21] Furthermore, examining meningioma incidence and survival in the elderly specifically is necessary given that the median age at diagnosis is 66 years, seven years older than the median age at diagnosis of primary CNS tumors in general.[22] Recent addition of benign and uncertain tumors (ICD-O-3 behavior codes /0 and /1 respectively) to CBTRUS in 2004 has restricted longitudinal study of nationwide incidence and survival trends in non-malignant meningioma.[4] Thus, the purpose of this study was to provide an in-depth update regarding both non-malignant and malignant meningioma incidence and survival in the elderly using the 11-year time-period following the implementation of non-malignant brain tumor collection in cancer registration databases in 2004.

Here, we report that the incidence of non-malignant meningioma increased significantly for every five-year age group from ages 65-69 years (23.85 cases per 100,000 in adults) to 85+ year olds (50.34 cases per 100,000) (Supplemental Fig 1A). Similarly, for malignant meningioma, incidence increased

significantly for every decade compared to the 65-69 year olds (Supplemental Fig 1E). This is in contrast to other CNS tumors such as oligodendrogliomas and anaplastic oligodendrogliomas, whose incidence tends to decrease in the oldest age groups.[23] Interestingly, however, increases in non-malignant meningioma with age parallels increased incidence in glioblastoma despite drastic differences in tumor cell origins, behavior, and molecular profiles.[22] Recent research in glioblastoma and meningioma has highlighted the importance of epigenetic alterations such as DNA methylation patterns in tumorigenesis, which could explain the increased incidence in elderly populations for these two different tumor types.[24–30] It will be necessary to conduct further research to explore this hypothesis and other alternative hypotheses relating to non-epigenetic molecular differences, environmental factors, and other potential contributors.

In addition to increased incidence with age, we also identified a significant female predominance in non-malignant meningioma for every five-year age group studied and a non-significant predominance for malignant meningioma (Fig 1A and C). This finding in our elderly population is in contrast to reports indicating that the incidence of malignant meningioma was higher in males than females.[3,4] These discrepancies are likely due to shorter time-periods studied in previous reports along with differences in methodology for reporting age groupings. We also identified significant differences in meningioma incidence by race and ethnicity (Fig 2A-G). For instance, for every age group, incidence was significantly higher in Black populations, and significantly lower in AIAN populations, compared to other races unlike previously reported incidence rates for oligodendrogliomas and medulloblastomas.[23,31] Similarly, for Hispanics, non-malignant meningioma incidence was significantly higher in all age groups compared to non-Hispanics. Finally, both non-malignant and malignant meningiomas presented overwhelmingly in supratentorial locations, with a small minority presenting in spinal locations (Fig 3A, D).

In a departure from previous reports citing an increased incidence of non-malignant meningioma over the years[2], we find that extension of the study period to 2015 resulted in a more nuanced understanding of temporal trends. In particular, in all categories including sex, age, race, ethnicity, and location, we found that APC increased to 2008 or 2009 and subsequently leveled off or significantly decreased up to 2015. This was true for: 1) males and females, 2) every five-year age groups, 3) Black, White, and non-Hispanic populations, and 4) supratentorial non-malignant meningioma. In contrast, the incidence of spinal non-malignant meningioma remained constant over the 11-year study period. It was previously hypothesized that the increase in non-malignant meningioma was due to the adoption of the 2000 WHO guidelines, and later the 2007 WHO guidelines update, which downgraded cases of meningioma with brain invasion but without anaplasia from grade III (malignant) to grade II or I (non-malignant).[3,32,33] This hypothesis is supported by our findings that incidence generally increased only up to 2009, after which it plateaued or declined. This aligns well with the period after the adoption of the 2007 WHO guidelines during which non-malignant meningioma incidence may have increased simply due to classification changes. This hypothesis is further supported by the observation that supratentorial non-malignant meningioma incidence increased from 2005 to 2009, a location which would be susceptible to reclassification due to brain invasion, compared to the stable incidence of spinal non-malignant meningioma in which brain invasion is not a concern. Future studies should examine temporal trends extending beyond 2015 to determine whether incidence rates remain stable over the next several years. Additionally important to examine are other factors contributing to the high overall incidence of meningioma in the general population, including environmental factors such as ionizing radiation exposure, a known risk factor for meningioma occurrence, group differences in genetic and epigenetic tumorigenic processes, and/or greater detection biases due to increasing access to imaging technologies.[3,4,34]

In keeping with previous reports, the incidence of malignant meningioma decreased over time from 2005 to 2015 in both males and females, Black, White, and non-Hispanic populations, as well as in spinal and supratentorial locations (Fig 1D, 2F-H, 3D). The declines in malignant meningioma could be due to increasingly accurate meningioma reporting by CNS tumor registries thereby shifting meningioma incidence from malignant to non-malignant, as previously discussed.[3,4,35] It is important to note, however, that temporal trends in malignant meningioma diverge from non-malignant incidence given the continued decline up to 2015. Thus, particular attention should be paid to determining the root causes of these disparities in future research.

Survival

Our study also identified several clinical and demographic factors that are associated with decreased survival in non-malignant and malignant meningioma in the elderly US population. For non-malignant meningioma, the study data showed that Black populations, males, and older age groups have a greater risk of death compared to White populations, females, and those age 65-69 years, respectively. It had been previously noted that Black individuals have worse survival than Whites in the general population[36], congruent with our findings in the elderly. As in this study, worse survival in both Black populations and older ages was partially attributed to disparities in access to high-quality neuro-oncologic care.[36,37] However, it is also possible that there are molecular and/or epigenetic differences among races and in aging individuals that contribute to tumor behavior. Interestingly, though the incidence of non-malignant meningioma is greater in elderly females, elderly males had significantly worse survival outcomes. This previously reported dichotomy for spinal meningiomas[38] was confirmed in the present study's much larger patient cohort, highlighting the need for future research to address the disparity between the sexes.

In keeping with the whole cohort survival analyses, five-year age-group specific sub-analyses revealed similar trends towards worsened survival in males, Black populations, supratentorial locations and STR/GTR with RT though statistical significance was only occasionally attained (Supplementary Table 3). It is difficult to ascertain whether statistical significance in certain age groups is indicative of age-specific tumor behavior versus sample size reduction-related increases in estimate uncertainty (ie. increased confidence interval span). Thus, these results should be interpreted with caution and further research conducted to examine the impact of age.

Beyond demographic prognostic factors, we also found that the addition of adjuvant radiation following either GTR or STR resulted in increased risk of death compared to GTR alone despite radiation and GTR improving survival when analyzed independently using the Kaplan-Meier method. Studies in atypical meningioma, which are included in our non-malignant group based on the most recent CBTRUS report classification by ICD-O-3 codes[1], have noted either a trend towards worse outcomes in patients receiving adjuvant radiation[39], or no difference in survival with adjuvant radiation.[40,41] Thus, our findings in the elderly seem to corroborate previous reports in the general population, though these results should be interpreted with caution given the previous studies focus on atypical meningioma alone. Furthermore, conclusions should be reserved until publication of results from ROAM/EORTC-1308: a multi-center randomized controlled trial examining outcomes in patients with atypical meningioma treated with GTR and adjuvant radiation vs GTR and active MRI monitoring for recurrence.[42]

In contrast to non-malignant meningioma, there were no significant differences in malignant meningioma survival by race, sex, location, or radiation therapy. The only two groups with significantly worse survival were the 85+ year-old category, with increasing age being a well-established risk factor for poorer

outcomes[1], likely due to increased risk of complications,[12,13] and males aged 65-69 years old (Supplementary Table 3). Encouragingly for 65-84 year olds, after controlling for other variables in the model, age was not an independent predictor of increased mortality following malignant meningioma diagnosis. This finding may help mitigate fears of surgical treatment for malignant meningioma in elderly individuals based on age alone. Additionally radiation had no significant protective effect in spite of the supporting evidence for its use in anaplastic meningioma.[43,44] However, the supporting literature came from non-controlled and/or reports analyzing small cohorts and thus far has limited definite conclusions. In response to the paucity of Level 1 evidence, a large-scale study is currently underway in Europe to assess the effect of post-resection adjuvant radiation on survival following anaplastic meningioma diagnosis.[45] In the meantime, our results should be interpreted with caution given the insufficient sample size to perform analyses of combined resection and radiation.

Limitations

There are important limitations of epidemiological studies such as this that are noteworthy. First, we chose to classify non-malignant and malignant meningioma according to the ICD-O-3 codes used in the CBTRUS Statistical Report to ensure standardization of comparisons.[1] However, in the literature, meningioma is often grouped according to other factors, such as WHO grade, which does not exactly align with the statistical report's ICD-O-3-based categorization. Second, as is the case with the majority of large-scale epidemiological studies, we were unable to examine incidence and survival trends by molecular signatures of non-malignant and malignant meningioma. In the future, when molecular data collection become more widespread and complete, the epidemiology of tumor behavior will be better addressed. For now, we were able to assess the demographic and clinical factors contributing to incidence from CBTRUS for approximately 99% of the US population, thereby affording us a thorough, in-depth analysis of nationwide trends over the 11 year study period. It is also important to specify that survival

data obtained from SEER only includes 28% of the US population, thereby limiting generalization of survival results to the rest of the US population. Finally, we were unable to include important prognostic factors beyond the demographic and treatment data available in the CBTRUS and SEER registries such as functional status, co-morbid diseases, and performance scales. Future studies should examine the intersection of demographic and function/performance information.

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Figures

Figure 1. (A-D) Age-adjusted incidence rates and annual percent changes (APC) for non-malignant meningioma by A) sex by five-year age groupings, and by B) sex over time from 2005-2015. Age-adjusted incidence rates and annual percent changes (APC) for malignant meningioma by C) sex by five-year age groupings and D) sex over time from 2005-2015. APCs are accompanied by 95% confidence intervals (CI) in parentheses. *Only significant changes in APC are reported in the figures. (CBTRUS 2005-2015)

Figure 2. (A-D) Age-adjusted incidence rates and annual percent changes (APC) for non-malignant meningioma by A) age and race including Black, White, Asian/Pacific Islander (API), and American Indian Alaskan Native (AIAN), B) race over time from 2005-2015, C) age and ethnicity, and D) ethnicity over time from 2005-2015. (E-F) Age-adjusted incidence rates and annual percent changes (APC) for malignant meningioma by E) age and race F) race over time from 2005-2015, G) age and ethnicity, and

H) ethnicity over time from 2005-2015. APCs are accompanied by 95% confidence intervals (CI) in parentheses. *Only significant changes in APC are reported in the figures. (CBTRUS 2005-2015)

Figure 3. (A-B) Age-adjusted incidence rates and annual percent changes (APC) for non-malignant meningioma by A) age and location, and B) location over time from 2005-2015 including supratentorial, infratentorial, and spinal non-malignant meningioma. (C-D) Age-adjusted incidence rates and annual percent changes (APC) for malignant meningioma by C) age and location, and D) location over time from 2005-2015 including supratentorial, infratentorial, and spinal malignant meningioma. APCs are accompanied by 95% confidence intervals (CI) in parentheses. *Only significant changes in APC are reported in the figures. (CBTRUS 2005-2015)

Figure 4. Kaplan-Meier curves depicting variables with significant differences in survival for non-malignant (A-F) and malignant meningioma (G). Significant associations with survival for non-malignant meningioma included A) five-year age groups ($p<0.001$), B) ethnicity ($p<0.001$), C) location ($p<0.001$), D) sex ($p<0.001$), E) race ($p<0.001$), and F) surgical resection/radiation treatment ($p=0.018$). The only significant association with survival for malignant meningioma was G) five-year age groups ($p<0.001$). GTR – gross total resection, STR – subtotal resection, RT – radiation therapy

Table 1. Kaplan-Meier results and multivariable Cox proportional hazard models by race, ethnicity, sex, age, location, radiation, resection, and combined radiation and resection for non-malignant and malignant meningioma.

Non-malignant Meningioma				
Kaplan-Meier Results	**N**	**Median**	**95% CI**	**P-Value**
Race				
White	34,341	88	(85, 89)	<0.001
Black	4,119	73	(68, 77)	
API	3,141	110	(103, 121)	
AIAN	213	104	(84, --)	
Ethnicity				
Spanish-Hispanic-Latino	3,482	106	(98, 115)	<0.001
Non-Spanish-Hispanic Latino	38,625	87	(85, 88)	
Sex				
Male	11,222	71	(69, 75)	<0.001
Female	30,885	94	(92, 96)	
Age				
65-69 years	9,276	--	(--, --)	<0.001
70-74 years	8,655	--	(124, --)	
75-79 years	8,291	92	(89, 96)	
80-84 years	7,377	63	(60, 65)	
85+ years	8,508	32	(31, 33)	
Location				
Supratentorial	40,305	86	(84, 88)	<0.001
Spinal	1,676	--	(119, --)	
Radiation				
No radiation	41,402	88	(86, 89)	<0.001
Radiation	705	125	(90, --)	
Resection				
GTR	2,612	--	(125, --)	0.045
STR	896	--	(113, --)	
Surgery+Radiation				
GTR only	2,522	--	(126, --)	0.018
STR only	778	--	(111, --)	
GTR + RT	90	89	(72, --)	
STR + RT	118	--	(89, --)	
Multivariable Cox Proportional Hazard Model		**Hazard Ratio**	**95% CI**	**P-Value**
Black vs. White*		1.212	(1.001, 1.468)	0.049
API vs. White		0.829	(0.679, 1.012)	0.066
AIAN vs. White		0.794	(0.255, 2.469)	0.690
Hispanic vs. Non-Hispanic		0.821	(0.672, 1.002)	0.053
Male vs. Female*		1.415	(1.263, 1.585)	<0.001
70-74 years vs. 65-69 years*		1.763	(1.487, 2.090)	<0.001

75-79 years vs. 65-69 years*		2.712	(2.287, 3.216)	<0.001
80-84 years vs. 65-69 years*		4.480	(3.758, 5.340)	<0.001
85+ years vs. 65-69 years*		5.911	(4.824, 7.241)	<0.001
Supratentorial vs. Spinal*		1.352	(1.123, 1.628)	0.001
STR Only vs. GTR Only		1.123	(0.986, 1.280)	0.082
GTR and RT vs. GTR Only*		1.569	(1.156, 2.130)	0.004
STR and RT vs. GTR Only*		1.434	(1.062, 1.934)	0.019
Malignant Meningioma				
Kaplan- Meier Results	**N**	**Median**	**95% CI**	**P-Value**
Age				
65-69 years	119	40	(31, 62)	
70-74 years	119	39	(27, 82)	
75-79 years	88	29	(21, 59)	<0.001
80-84 years	77	25	(16, 52)	
85+ years	78	15	(8, 27)	
Multivariable Cox Proportional Hazard Model		**Hazard Ratio**	**95% CI**	**P-Value**
Black vs. White		1.049	(0.751, 1.465)	0.781
API vs. White		0.930	(0.632, 1.370)	0.714
Male vs. Female		1.227	(0.972, 1.549)	0.085
70-74 years vs. 65-69 years		0.906	(0.639, 1.287)	0.583
75-79 years vs. 65-69 years		1.117	(0.777, 1.605)	0.550
80-84 years vs. 65-69 years		1.326	(0.924, 1.903)	0.126
85+ years vs. 65-69 years*		2.061	(1.446, 2.936)	<0.001
Supratentorial vs. Spinal		1.181	(0.579, 2.407)	0.647
Radiation vs. No Radiation		1.019	(0.778, 1.335)	0.890

Abbreviations: API – Asian/Pacific Islander, AIAN – American Indian/Alaska Native, GTR – gross total resection, STR – subtotal resection, RT – radiation therapy

*denotes statistical significance at <0.05 level.

-- denotes that the median was not achieved, indicating survival was greater than 50% at the end of the observation period

Figure 1

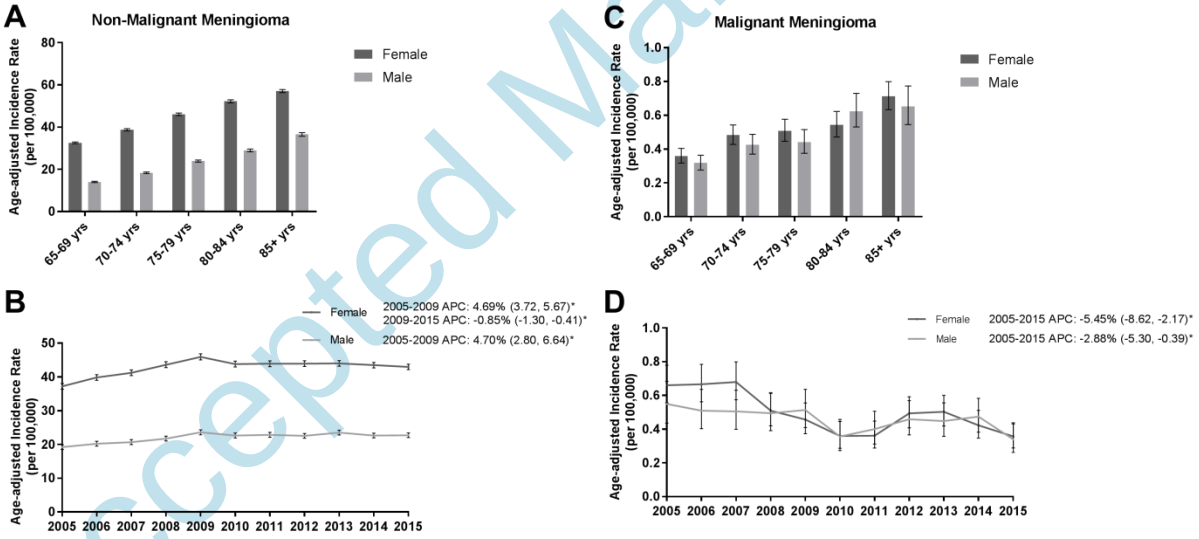

Figure 2

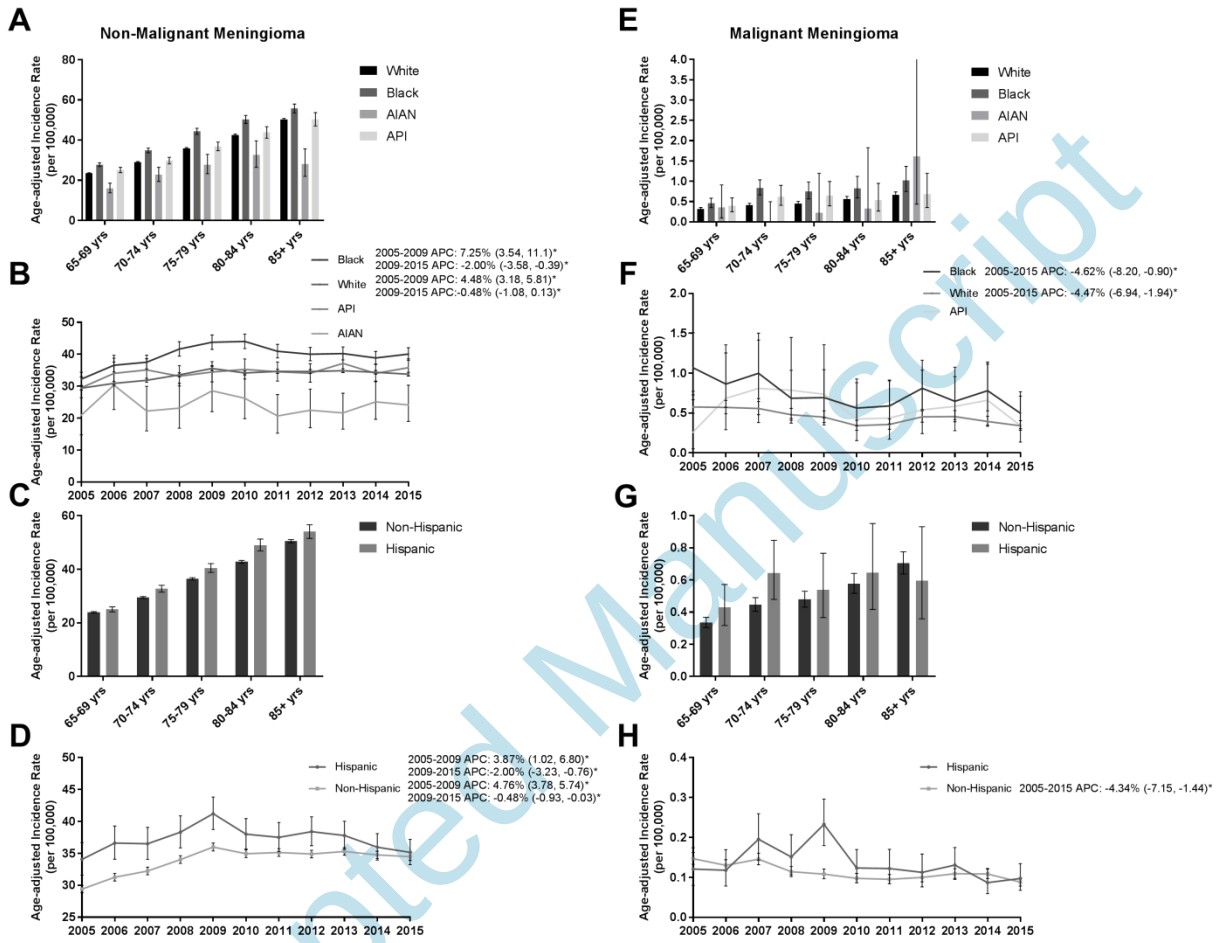

Figure 3

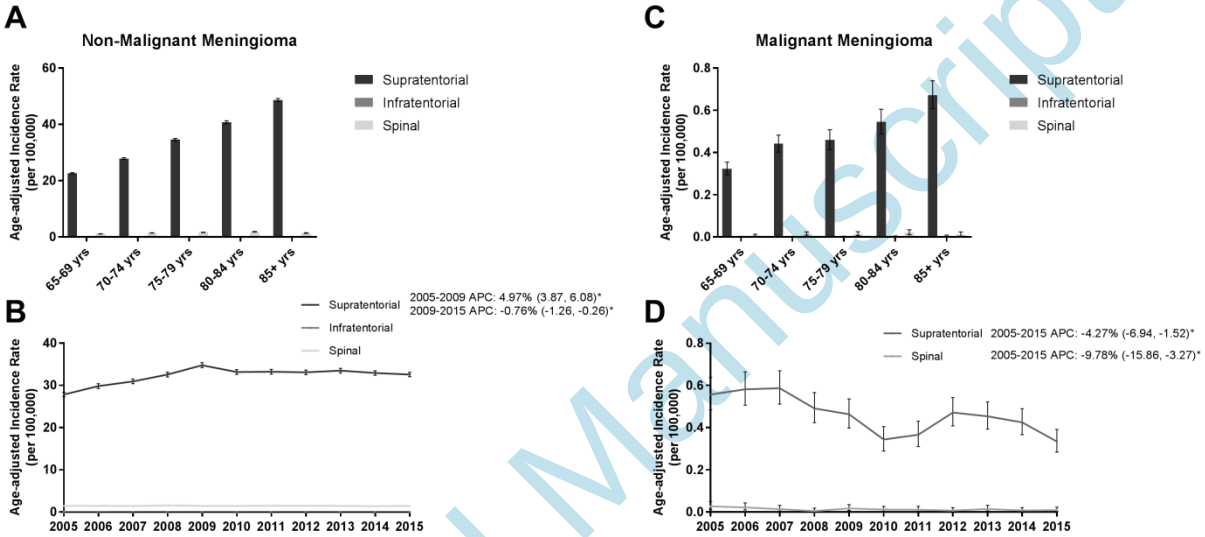

Figure 4