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Incidence and survival of benign, borderline, and malignant meningioma patients in the United States from 2004 to 2018

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Abstract

Meningioma is the most common primary central nervous system tumor, and its incidence is increasing. A systematic epidemiological and clinical analysis is required to better estimate its public health impact and understand its prognostic factors. Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2018 for all types of meningiomas without an age restriction. Age-adjusted incidence rates (IRs) and 95% confidence intervals were estimated according to sex, age, race, ethnicity, and tumor location. Kaplan-Meier analysis and multivariate Cox proportional hazard models were used to analyze the overall survival (OS). The competing risk regression model of Fine-Gray was used to analyze cause-specific survival. Data from a total of 109 660 meningioma patients were analyzed. A majority of patients were older than 60 years, and only 0.41% of patients were 0-19 years. The meningioma IRs were higher in females, Black, and non-Hispanic patients than in males, White, and Hispanic patients, respectively, and IRs increased with age. The ratio of IRs for females to males was 2.1 and also increased with age, peaking at 3.6 in the 45-49-year-old group. Older and male patients with all types of meningiomas, Black patients with benign and borderline meningiomas, and patients with larger borderline and malignant meningiomas showed poorer prognosis. For all meningioma types, surgical resection improved survival. The reported incidence rates and survival trends covered all demographics and subtypes of meningiomas. Older age, male sex, Black race, and tumor size may be important prognostic factors for meningioma cases, and tumor resection can substantially improve survival among meningioma patients.

KEYWORDS
incidence, meningioma, SEER program, survival

What's new?

The incidence of meningioma, the most common primary central nervous system tumor, is increasing. A systematic epidemiological and clinical analysis is needed to better estimate its public health impact and understand its prognostic factors. Here, using the Surveillance,

Abbreviations: AIAN, American Indian/Alaska Native; APC, annual percentage change; API, Asian/Pacific Islander; CI, confidence interval; CNS, central nervous system; GTR, gross total resection; HR, hazard ratio; ICD-O-3, International Classification of Diseases for Oncology, Third Edition; IR, incidence rate; NS, no surgery; OS, overall survival; RT, radiotherapy; SEER, Surveillance, Epidemiology, and End Results; SHR, subdistribution hazard ratio; STR, subtotal resection; TIMP3, tissue inhibitor of metalloproteinase 3; TP73, tumor protein 73; WHO, World Health Organization.

Epidemiology, and End Results (SEER) database in the United States, the authors performed a systematic review of the incidence and survival trends of meningioma, covering all demographics and all tumor subtypes. Older age, male sex, Black race, and tumor size may be important prognostic factors for meningioma cases, and tumor resection can substantially improve survival among meningioma patients.

1 | INTRODUCTION

Meningioma is the most common primary central nervous system (CNS) tumor, accounting for 38.3% of all types of CNS tumors and 54.5% of nonmalignant CNS tumors reported from 2013 to 2017 in the United States, with an incidence rate (IR) of 8.81 per 100 000 person-years.[1] Females are more likely to be affected by nonmalignant meningioma than males.[1-5] Meningiomas are mainly intracranial, and only approximately 10% are spinal.[6-9] They are most common in the elderly population, with a higher frequency in individuals over 65 years of age,[10] and rare in children, accounting for 0.4% to 4.1% of all childhood tumors.[11] Because the risk of meningioma increases considerably with age, the healthcare burden related to meningioma will continue to climb as the population ages. Despite its prevalence as a CNS tumor, epidemiological studies of meningioma are rare compared to other types of CNS tumors. Moreover, these studies are either limited to patients over 65 years old,[12] only investigated the incidence of World Health Organization (WHO) Grades II and III meningiomas,[13] or analyzed only hospital cohorts or otherwise selected patient samples.[14-16] To date, none of them have covered broad demographics or different subtypes of meningioma.

Studies have identified various prognostic factors associated with the prognosis of meningioma patients, including patient characteristics and treatment modalities.[15,17-27] In addition to WHO grade, age and extent of resection represent vital prognostic factors.[28] Multivariate analysis has shown that age <40 years, male sex, subtotal resection (STR), and a high mitotic index are all independently associated with shorter progression-free survival.[29] Other studies, however, reported that age was not associated with overall survival (OS), but other factors, such as male sex, comorbidity status, neurological impairments, and performance scales affected the prognosis.[17,22,24] Therefore, considering the poor prognosis of some types of meningiomas and their increasing prevalence, a systematic epidemiological and clinical analysis was still needed for neuro-oncologists and health policymakers to better estimate its public health impact, understand its prognostic factors, and thereby take action accordingly.

The Surveillance, Epidemiology, and End Results (SEER) Program is an authoritative source of information on cancer incidence and survival in the United States.[30] SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 48.0% of the US population.[30] SEER-supported cancer registries report almost all incident cases coded as in situ (nonmalignant) and invasive (malignant; primary site only) according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3).[30] They sought to document the best method for confirmation of a cancer diagnosis, including histopathology, radiology, and clinical confirmation, as reported at any time in the patient's medical history.[30] In the present study, we utilized the SEER registry and performed a comprehensive analysis of raw data from meningioma patients collected from 2004 to 2018 in the United States. Our study provides a thorough review of the incidence and survival trends of all subtypes of meningioma in the population.

2 | METHODS

2.1 | Data collection

We used the SEER Database "Incidence-SEER Research Data, 18 Registries Plus, Nov 2020 Sub (2000-2018)" to search for meningioma cases from 2004 to 2018 without an age restriction. Because benign and borderline CNS tumors have been identified in the SEER program since 2004, this year was selected as the cut-off year. When setting the screening criteria ("selection" part of the software SEER-Stat), we only selected clear or specific items for demographic details (age, sex, race, and ethnicity), clinical characteristics (tumor location and size), and treatment details. The subjects with unspecified or missing items, not primary or first tumor were not included. Together, our selection criteria produced a cohort of 109 660 patients.

2.2 | Variables and population analysis

Age-adjusted incidence rates (IRs) and 95% confidence intervals (CIs) were estimated for meningiomas from 2004 to 2018 according to patient sex, age, race, ethnicity, and tumor location. Benign meningiomas were identified according to the following seven ICD-O-3 codes: 9530/0, 9530/1, 9531/0, 9532/0, 9533/0, 9534/0, and 9537/0. Borderline meningiomas were identified by the following two ICD-O-3 codes: 9538/1 and 9539/1. Malignant meningiomas were identified by the following three ICD-O-3 codes: 9530/3, 9538/3, and 9539/3. We divided all subjects into age groups based on 5-year intervals. Race categories included Black, White, American Indian/Alaska Native (AIAN), and Asian/Pacific Islander (API). Ethnicity categories included Hispanic and non-Hispanic. Cases of tumors at supratentorial (ICD-O-3 codes 700, 702-714), infratentorial (716-717), and spine (701, 720-721, 725) locations were analyzed. Unspecified, and other categories were not included in the IR comparisons. The 2000 US population is the standard population commonly used for calculating age-adjusted rates, so age-adjusted IRs were standardized to the

2000 US population and reported per 100 000 population in our study. IRs were calculated using SEERStat 8.4.0. To characterize trends in meningioma IRs from 2004 to 2018, Annual Percent Change (APC) was calculated by Joinpoint Regression Program 4.6.0.0 software. The permutation test was performed for APCs, statistical significance was set at $P < .05$, and only APCs with significant differences were shown in the figures. All figures were generated using GraphPad Prism 7.0.

2.3 | Survival analysis

Survival analyses were performed for all cases of meningiomas reported from 2004 to 2018 by sex, age, race, ethnicity, tumor location, tumor size, treatment modality. The categories of sex, race, ethnicity, and tumor location were the same for IR analysis. We used five age groups (0-19 years, 20-39 years, 40-59 years, 60-79 years, and 80+ years) and two tumor size groups (<3 cm and ≥3 cm). The treatment modality was grouped based on SEER site-specific coding guidelines into the following five subgroups: no treatment (No), STR, gross total resection (GTR), STR + Radiotherapy (RT) and GTR + RT. Due to limited sample sizes, AIAN and infratentorial meningiomas were excluded from the survival analyses for borderline and malignant meningiomas. To calculate the OS in separate groups, Kaplan-Meier model was used in our study, and differences between groups were examined using the log-rank test. To investigate the independent prognostic factors associated with OS, multivariate Cox proportional hazard models were used to determine hazard ratios (HRs) and 95% CIs. For competing risk analysis, cumulative incidence of tumor-related death was computed for each factor after accounting for death of other causes. Competing risk regression model of Fine-Gray was used to estimate the subdistribution hazard ratio (SHR) and 95% CIs. $P < .05$ was considered statistically significant. IBM SPSS Statistics 25, R Statistical Software and SAS Software were used for data analyses.

3 | RESULTS

3.1 | Baseline patient characteristics

Data from a total of 109 660 patients were analyzed. Table 1 presents the baseline characteristics and treatment outcomes of these patients. We found that 95.4% of the patients had benign meningiomas, 3.6% had borderline meningiomas, and 1.0% had malignant meningiomas. Of meningioma with documented WHO grade (7740 cases), 79.4% of meningioma were WHO Grade I, 18.7% were WHO Grade II, and 1.9% were WHO Grade III. The largest age group was 60-79 years, with 48 856 (44.6%) patients, followed by 40-59 years with 31 586 (28.8%) patients and 80+ years with 22 487 (20.5%) patients. There were more female patients than male patients (females: 81 192, 74.04%; male: 28 468, 25.96%) with a female to male ratio of 2.85:1. Interestingly, this ratio varied among patients with tumors of different WHO grades: 2.98:1 for Grade I, 1.33:1 for Grade II, and 1.26:1 for Grade III. A majority of patients were White (87 188, 79.5%), followed by Black (12 872, 11.7%) and API (8867, 8.1%). Overall, 89.1% of patients (97 649) were non-Hispanic. Regarding tumor location, most cases were supratentorial (105 314, 96.0%). Most benign tumors were <3 cm in size (60 989, 70.5%), but most borderline (2779, 84.7%) and malignant tumors (626, 77.9%) were ≥3 cm. Most patients with benign tumors did not undergo surgical or RT treatment (69 079, 66.04%), whereas most patients with borderline and malignant tumors did surgery (borderline: 3459, 88.1%; malignant: 834, 73.5%). In addition, 23.3% of borderline and 32.4% of malignant meningioma patients performed surgery and RT.

3.2 | IRs of benign, borderline and malignant meningiomas from 2004 to 2018

3.2.1 | Incidence by age and sex

The age-adjusted IRs for the different meningioma types from 2004 to 2018 are shown in Figure 1. For benign meningioma, the IR increased significantly with each 5-year age group increase, from 0.11 cases per 100 000 in population (95% CI: 0.06-0.26) at age 0-19 years to 64.28 cases per 100 000 (95% CI: 62.56-66.15) at age 85+ years for females, and from 0.10 cases per 100 000 in population (95% CI: 0.06-0.24) at age 0-19 years to 39.71 cases per 100 000 (95% CI: 37.85-41.88) at age 85+ years for males (Figure 1A). For borderline meningioma, the IRs in females and males increased with age but then peaked and gradually decreased. The peak IRs were 1.35 cases per 100 000 (95% CI: 1.16-1.55) for females in the 70-74-year-old group and 1.28 cases per 100 000 (95% CI: 1.06-1.55) for males in the 75-79-year-old group (Figure 1C). For malignant meningioma, the IR increased significantly for each 5-year age group, from 0.006 cases per 100 000 in population at age 0-19 years (95% CI: 0.001-0.057) to 0.539 cases per 100 000 (95% CI: 0.391-0.789) in age 85+ years. Both IRs for females and males were higher than 0.2 cases per 100 000 beyond age 60 years (Figure 1E). The female to male ratio of the IRs for benign meningiomas increased with age, reaching a peak ratio of 3.6 in the 45-49-year-old group and then decreased with age (Figure 1G). Unlike the benign meningioma, IRs for borderline and malignant meningiomas did not differ significantly by sex for any 5-year age group.

For both males and females, a significant increase in the IR of benign meningioma occurred between 2004 and 2009 (female APC: 5.5% [95% CI: 3.9-7.2], $P < .001$; male APC: 5.6% [95% CI: 3.6-7.6], $P < .001$; Figure 1B). However, from 2009 to 2018, the growth rate slowed (female APC: 1.1% [95% CI: 1.8-3.9], $P = .003$; male APC: 0.9% [95% CI: 1.7-2.6], $P = .028$; Figure 1B). For borderline meningioma, from 2004 to 2018, the IR in females continued to increase significantly (APC: 5.6% [95% CI: 4.6-6.6], $P < .001$). The IR in males showed a similar trend from 2004 to 2018 (APC: 4.2% [95% CI: 3.2-5.3], $P < .001$; Figure 1D). For malignant meningioma, the IR in females showed a significant decrease from 2004 to 2018

TABLE 1 Patient baseline characteristics

		Benign		Borderline		Malignant		In total	
		Number	%	Number	%	Number	%	Number	%
In total	109 660	104 596	95.38	3927	3.58	1137	1.04	109 660	100
Age	00-19 y	379	0.36	61	1.55	14	1.23	454	0.41
	20–39 y	5743	5.49	443	11.28	91	8.00	6277	5.72
	40–59 y	29 892	28.58	1379	35.12	315	27.70	31 586	28.80
	60–79 y	46 602	44.55	1728	44.00	526	46.26	48 856	44.55
	80+ y	21 980	21.01	316	8.05	191	16.80	22 487	20.51
Sex	Female	78 318	74.88	2239	57.02	635	55.85	81 192	74.04
	Male	26 278	25.12	1688	42.98	502	44.15	28 468	25.96
Race	White	83 442	79.78	2923	74.43	823	72.38	87 188	79.51
	Black	12 141	11.61	553	14.08	178	15.66	12 872	11.74
	AIAN	705	0.67	21	0.53	7	0.62	733	0.67
	API	8308	7.94	430	10.95	129	11.35	8867	8.09
Ethnicity	Hispanic	11 426	10.92	434	11.05	151	13.28	12 011	10.95
	Non-Hispanic	93 170	89.08	3493	88.95	986	86.72	97 649	89.05
Site	Supratentorial	100 398	95.99	3820	97.28	1096	96.39	105 314	96.04
	Infratentorial	51	0.05	2	0.05	6	0.53	59	0.05
	Spinal	4147	3.96	105	2.67	35	3.08	4287	3.91
Size	<3 cm	73 688	70.45	601	15.30	251	22.14	61 669	68.02
	≥3 cm	30 908	29.55	3326	84.70	886	77.86	28 992	31.98
Treatment	No	69 075	66.04	467	11.88	301	26.47	69 845	63.69
	STR	13 211	12.63	905	23.05	180	15.86	14 298	13.04
	GTR	20 103	19.22	1641	41.78	287	25.26	22 027	20.09
	STR + RT	1193	1.14	384	9.79	138	12.11	1718	1.57
	GTR + RT	1004	0.96	530	13.50	231	20.30	1765	1.61

(APC: −4.7% [95% CI: −7.1 to −2.3], $P = .001$; Figure 1F). For males, the incidence also showed a declining trend but the decrease was not statistically significant (Figure 1F).

3.2.2 | Incidence by age and race

For benign meningioma, overall IR was significantly higher for the Black population (20.81 cases per 100 000 [95% CI: 19.59-22.08]) than for all other races, while the overall incidence for the AIAN population was significantly lower than for all other races (11.13 cases per 100 000 [95% CI: 8.46-14.45]; Figure 2A). Like that for benign meningioma, the IRs for borderline and malignant meningiomas were also significantly higher for the Black population (borderline: 0.81 cases per 100 000 [95% CI: 0.59-1.09]; malignant: 0.33 cases per 100 000 [95% CI: 0.19-0.53]) than those for the White population (borderline: 0.56 cases per 100 000 [95% CI: 0.50-0.64]; malignant: 0.19 cases per 100 000 [95% CI: 0.15-0.23]; Figure 2C,E).

For benign meningioma, from 2004 to 2009, the incidence increased significantly for Black and White populations (Black: APC: 5.7% [95% CI: 3.7-7.8], $P < .001$; White: APC: 5.6% [95% CI: 3.7-7.5], $P < .001$). From 2009 to 2018, the IR continued to increase, but the rate of increase slowed in the White population (White: APC: 1.0% [95% CI: 0.2-1.7], $P = .014$). For the AIAN and API populations, the IR increased significantly from 2004 to 2018 (AIAN: APC: 3.1% [95% CI: 0.9-5.3], $P = .009$; API: APC: 1.2% [95% CI: 0.5-2.0], $P = .004$; Figure 2B). For borderline meningioma, the IRs for the White, Black, and API populations increased significantly from 2004 to 2018 (White: APC: 4.9% [95% CI: 4.3-5.5], $P < .001$; Black: APC: 6.0% [95% CI: 3.5-8.6], $P < .001$; API: APC: 2.4% [95% CI: 0.5-4.3], $P = .017$; Figure 2D). By contrast, the IR of malignant meningioma decreased significantly during the same period for both the White and Black populations (White: APC: −2.9% [95% CI: −4.8 to −0.9], $P = .008$; Black: APC: −7.4% [95% CI: −10.8 to −3.9], $P = .001$), and that for the API population showed a declining but statistically insignificant trend (Figure 2F).

3.2.3 | Incidence by age and ethnicity

For benign meningioma, the overall IR was significantly greater in the non-Hispanic population (18.21 cases per 100 000 [95% CI:

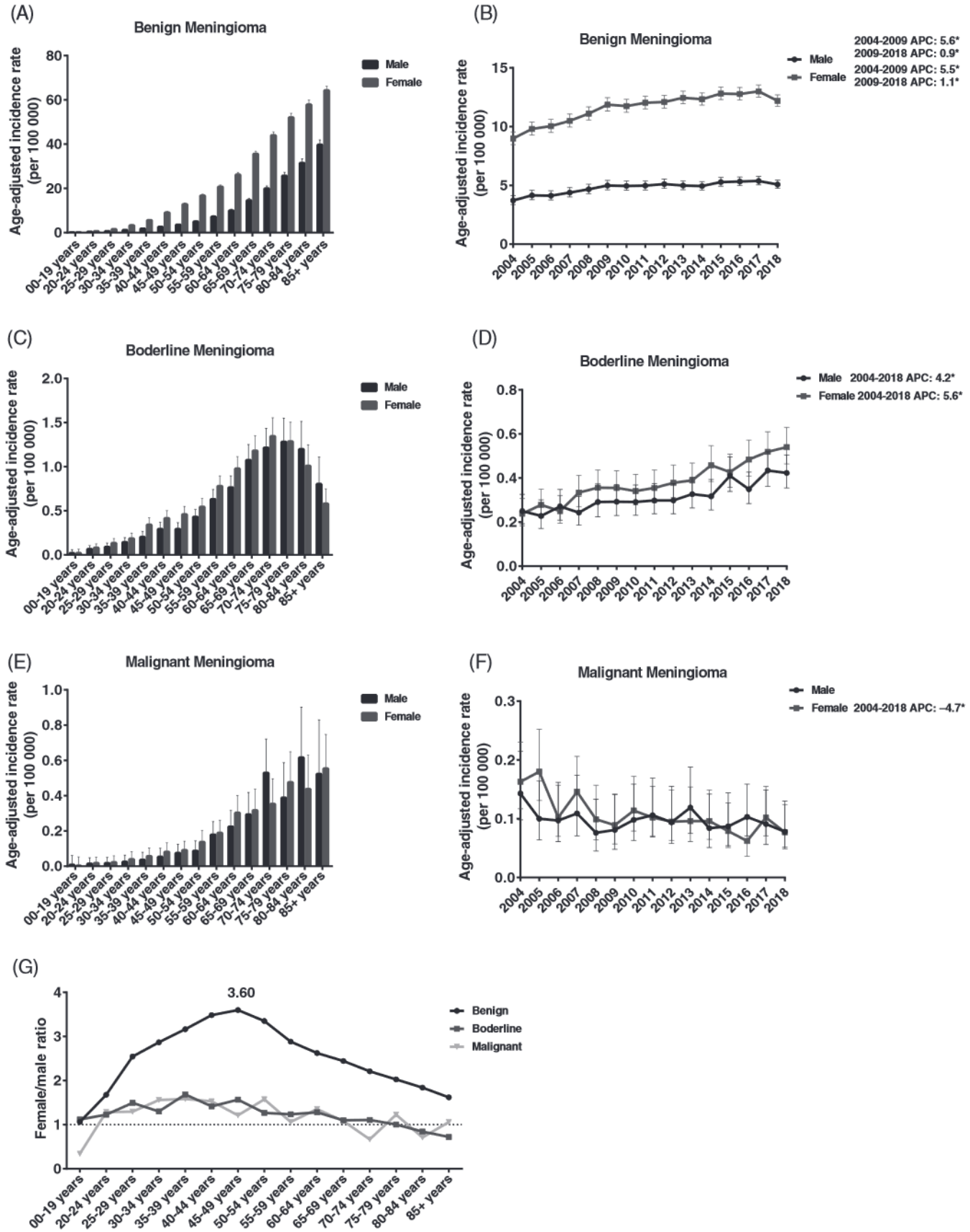

FIGURE 1 Age-adjusted incidence rates (IRs) and annual percent changes (APCs) by age and sex. IRs by sex and by 5-year age intervals (A, C, and E), APCs by sex over time from 2004 to 2018 (B, D, and F). (A and B) Benign meningioma; (C and D) borderline meningioma; (E and F) malignant meningioma. (G) The female to male ratio curve of the IRs by age. *Only show APCs that are significantly different at the $P < .05$ level

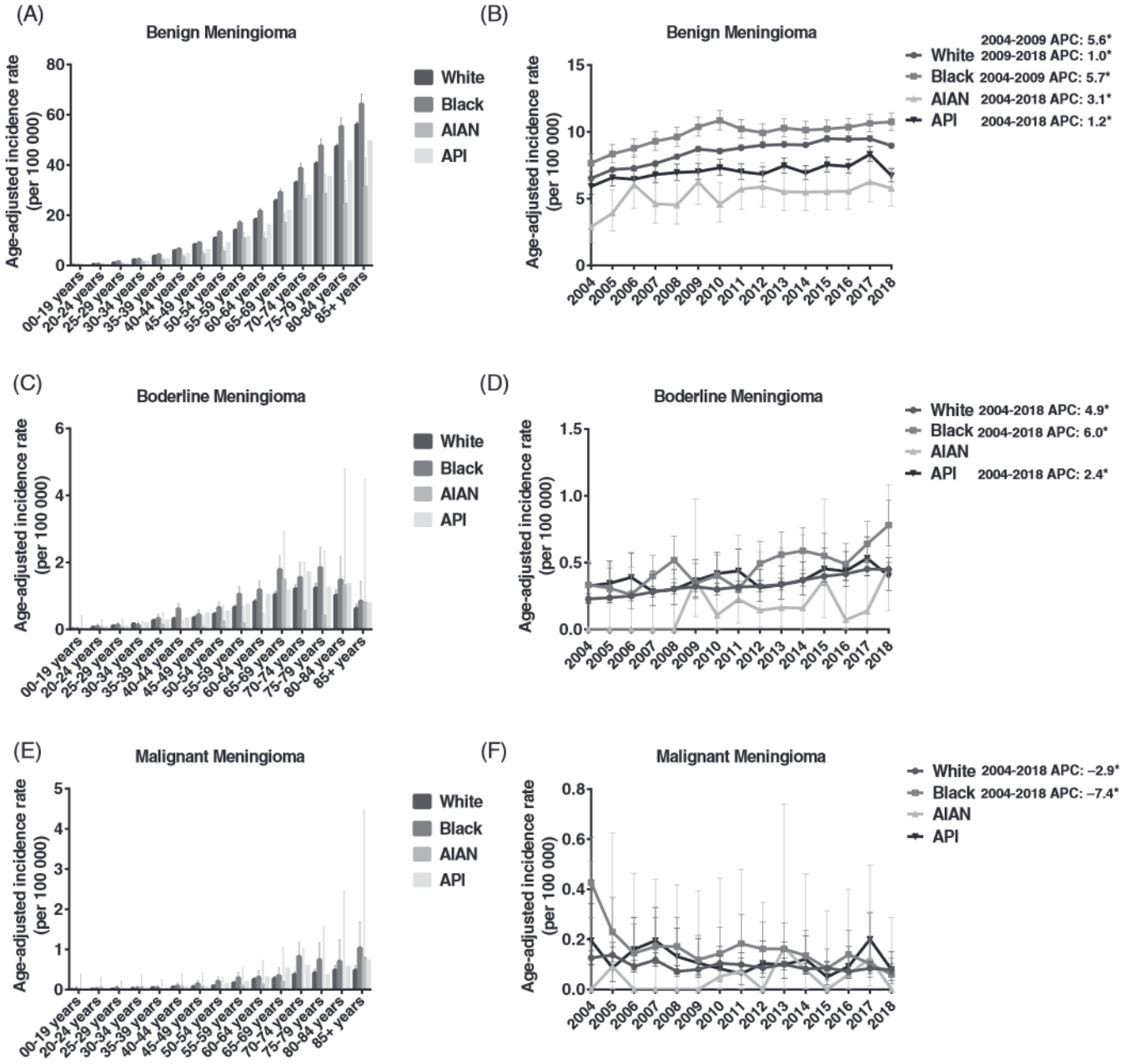

FIGURE 2 Age-adjusted incidence rates (IRs) and annual percent changes (APCs) by age and race. IRs by race and by 5-year age intervals (A, C, and E), APCs by race over time from 2004 to 2018 (B, D, and F). (A and B) benign meningioma; (C and D) borderline meningioma; (E and F) malignant meningioma. Races including White, Black, American Indian Alaskan Native (AIAN), and Asian/Pacific Islander (API). *Only show APCs that are significantly different at the $P < .05$ level

17.85-18.59]) than in the Hispanic population (15.13 cases per 100 000 [95% CI: 14.21-16.11]; Figure 3A). Similar to benign meningioma, the IRs for borderline and malignant meningiomas were significantly higher in the non-Hispanic population (borderline: 0.61 cases per 100 000 [95% CI: 0.55-0.69]; malignant: 0.21 cases per 100 000 [95% CI: 0.17-0.25]) than those in the Hispanic population (borderline: 0.46 cases per 100 000 [95% CI: 0.32-0.65]; malignant: 0.19 cases per 100 000 [95% CI: 0.10-0.33]; Figure 3C,E).

From 2004 to 2009, the IR of benign meningioma increased significantly in the non-Hispanic population (APC: 5.5% [95% CI: 3.9-7.1], $P < .001$), and the trend continued from 2009 to 2018 (APC: 0.9% [95% CI: 0.3-1.6], $P = .007$). Similar to that in the non-Hispanic population, the IR of benign meningioma in the Hispanic population also increased significantly from 2004 to 2018 (APC: 1.6% [95% CI: 0.6-2.6], $P = .003$; Figure 3B). For borderline meningioma, the IRs in both the non-Hispanic and Hispanic groups increased significantly from 2004 to 2018 (non-Hispanic: APC: 5.4% [95% CI: 4.8-6.1], $P < .001$; Hispanic: APC: 1.7% [95% CI: 0.3-3.0], $P = .02$; Figure 3D). For malignant meningioma, the IR significantly decreased from 2004 to 2018 in the non-Hispanic population (APC: −4.3%

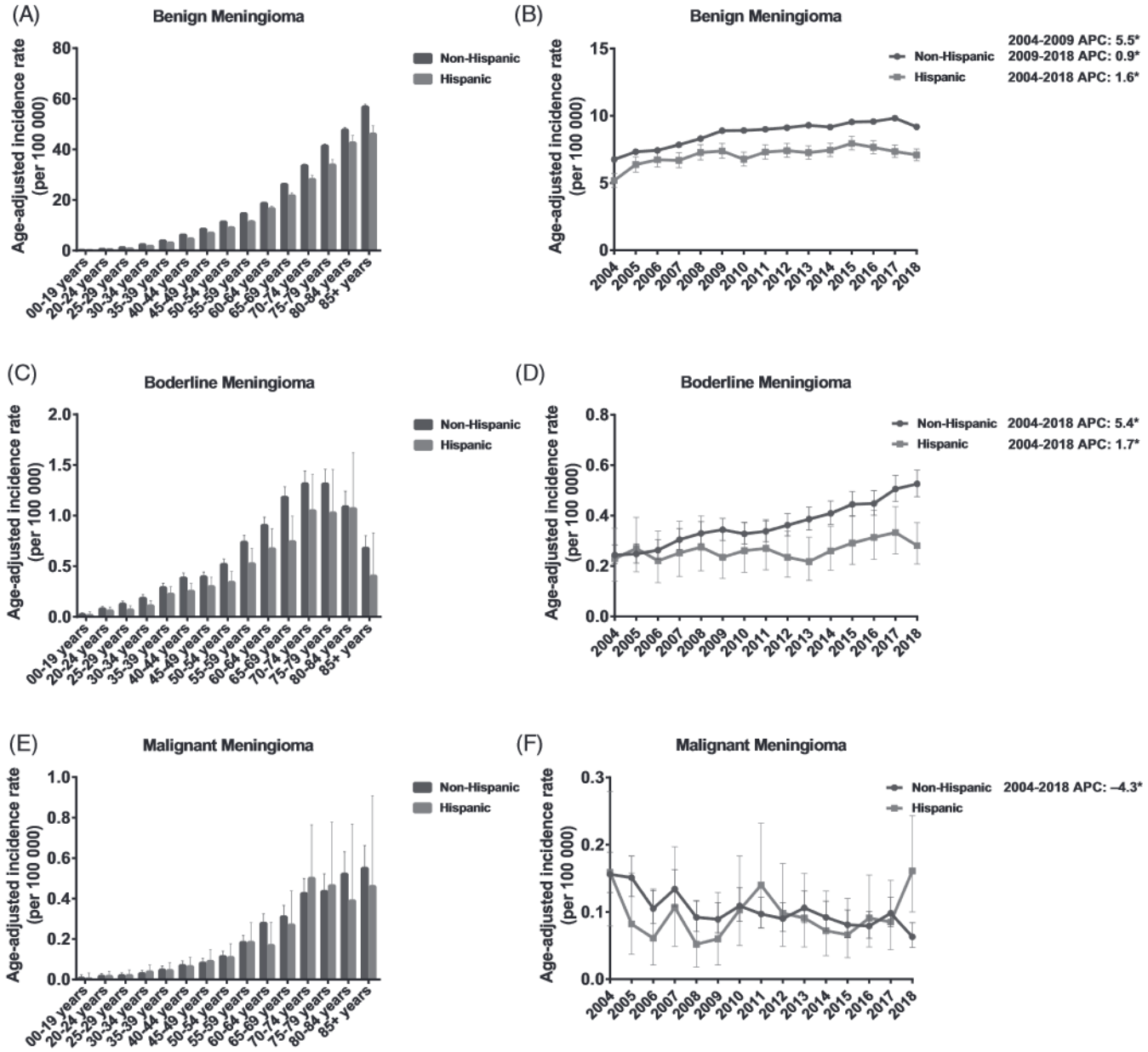

FIGURE 3 Age-adjusted incidence rates (IRs) and annual percent changes (APCs) by age and ethnicity. IRs by ethnicity and by 5-year age intervals (A, C, and E), APCs by ethnicity over time from 2004 to 2018 (B, D, and F). (A and B) Benign meningioma; (C and D) borderline meningioma; (E and F) malignant meningioma. *Only show APCs that are significantly different at the $P < .05$ level

[95% CI: −6.1 to −2.4], $P < .001$), but not in the Hispanic population (Figure 3F).

3.2.4 | Incidence by age and tumor location

Regarding the location of the tumors, most were located in supratentorial region (105 314, 96.0%). Some were located in the spinal region (4287, 3.9%), and meningiomas in infratentorial regions accounted for less than 0.1% of all cases. For supratentorial benign and malignant meningiomas, the IRs increased significantly with every 5-year increment in age and reached peak values at age 85+ years (benign: 54.62 cases per 100 000 [95% CI: 53.28-56.06]; malignant: 0.53 cases per 100 000 [95% CI: 0.40-0.78]; Figure 4A,E). For borderline supratentorial meningioma, the IR increased to a peak at 70-74 years (0.64 cases per 100 00 [95% CI: 0.52-0.88]) and then decreased gradually (Figure 4C). For spinal meningioma, the IRs for all three types of meningioma increased with age and then decreased after reaching a peak. The peak age ranges varied though (80-84 years for benign, 75-79 years for borderline, and 70-74 years for malignant meningioma; Figure 4A,C,E).

From 2004 to 2009, the IR of benign supratentorial meningioma increased significantly (APC: 5.6% [95% CI: 4.0-7.3], $P < .001$), and it continued increasing significantly from 2009 to 2018

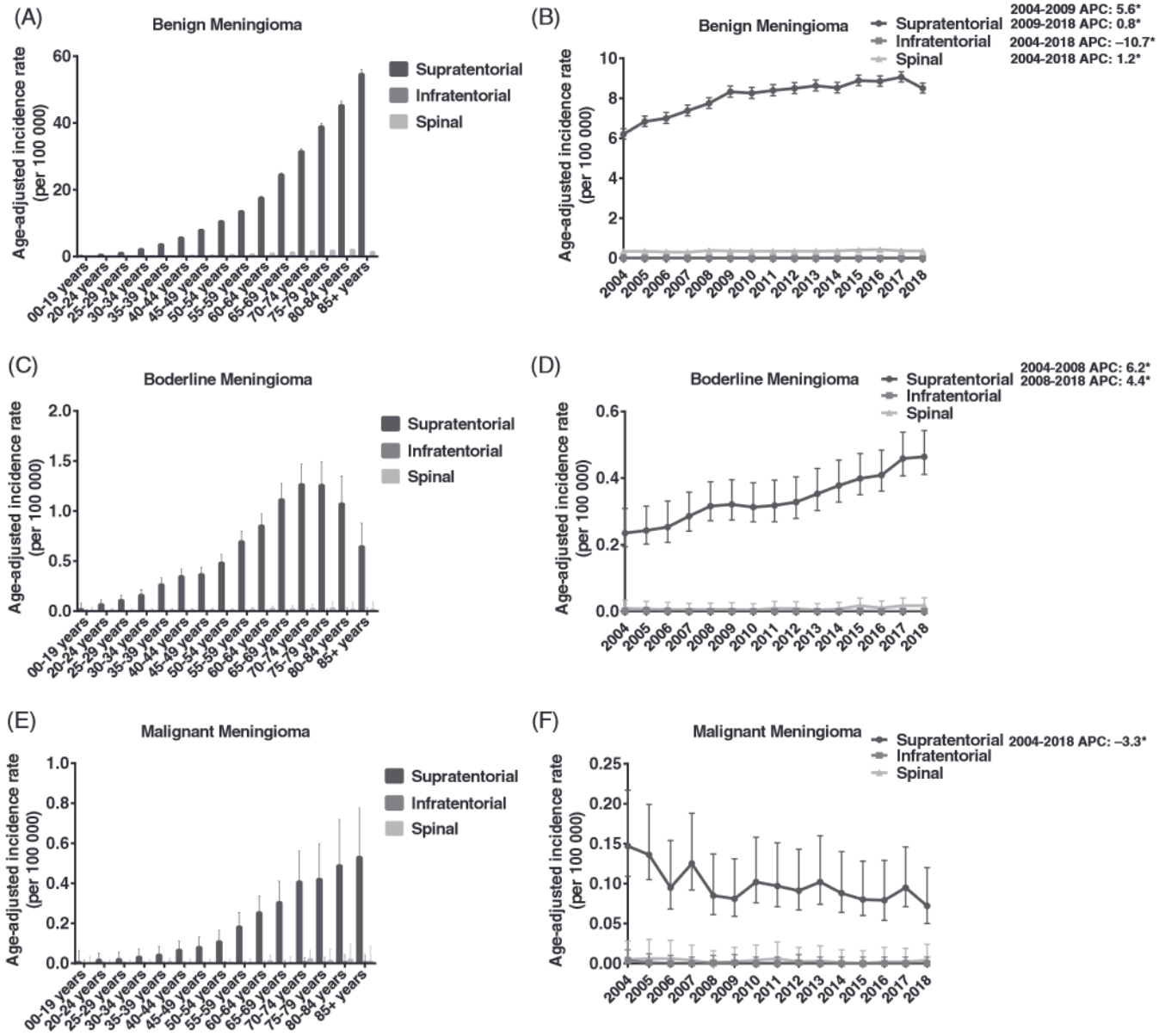

FIGURE 4 Age-adjusted incidence rates (IRs) and annual percent changes (APCs) by age and tumor location. IRs by tumor location and by 5-year age intervals (A, C, and E), APCs by tumor location over time from 2004 to 2018 (B, D, and F). (A and B) Benign meningioma; (C and D) borderline meningioma; (E and F) malignant meningioma. Tumor locations including supratentorial, infratentorial, and spinal. *Only show APCs that are significantly different at the $P < .05$ level

(APC: 0.8% [95% CI: 0.2-1.4], $P = .02$). By contrast, the IR of infratentorial meningioma decreased significantly from 2004 to 2018 (APC: −10.7% [95% CI: −17.2, to −3.6], $P = .007$; Figure 4B). Similar to that of benign supratentorial meningioma, the IR of borderline meningioma increased significantly between 2004 and 2008 (APC: 6.2% [95% CI: 2.3-10.3], $P = .005$) as well as 2008 and 2018 (APC: 4.4% [95% CI: 3.4-5.4], $P < .001$; Figure 4D). Unlike the IRs of benign and borderline supratentorial meningioma, the IR of malignant meningioma decreased significantly from 2004 to 2018 (APC: −3.3% [95% CI: −5.1 to −1.5], $P = .002$; Figure 4F).

3.3 | OS of patients with benign, borderline and malignant meningioma according to age, sex, race, ethnicity, tumor location, tumor size and treatment modality from 2004 to 2018

3.3.1 | OS by Kaplan-Meier analysis

Kaplan-Meier analysis showed significant differences in OS for benign meningioma by age ($P < .0001$), sex ($P < .0001$), race ($P < .0001$), ethnicity ($P < .0001$), tumor location ($P < .0001$), and treatment modality ($P < .0001$), but tumor size had little effect on OS (Figure 5A). For

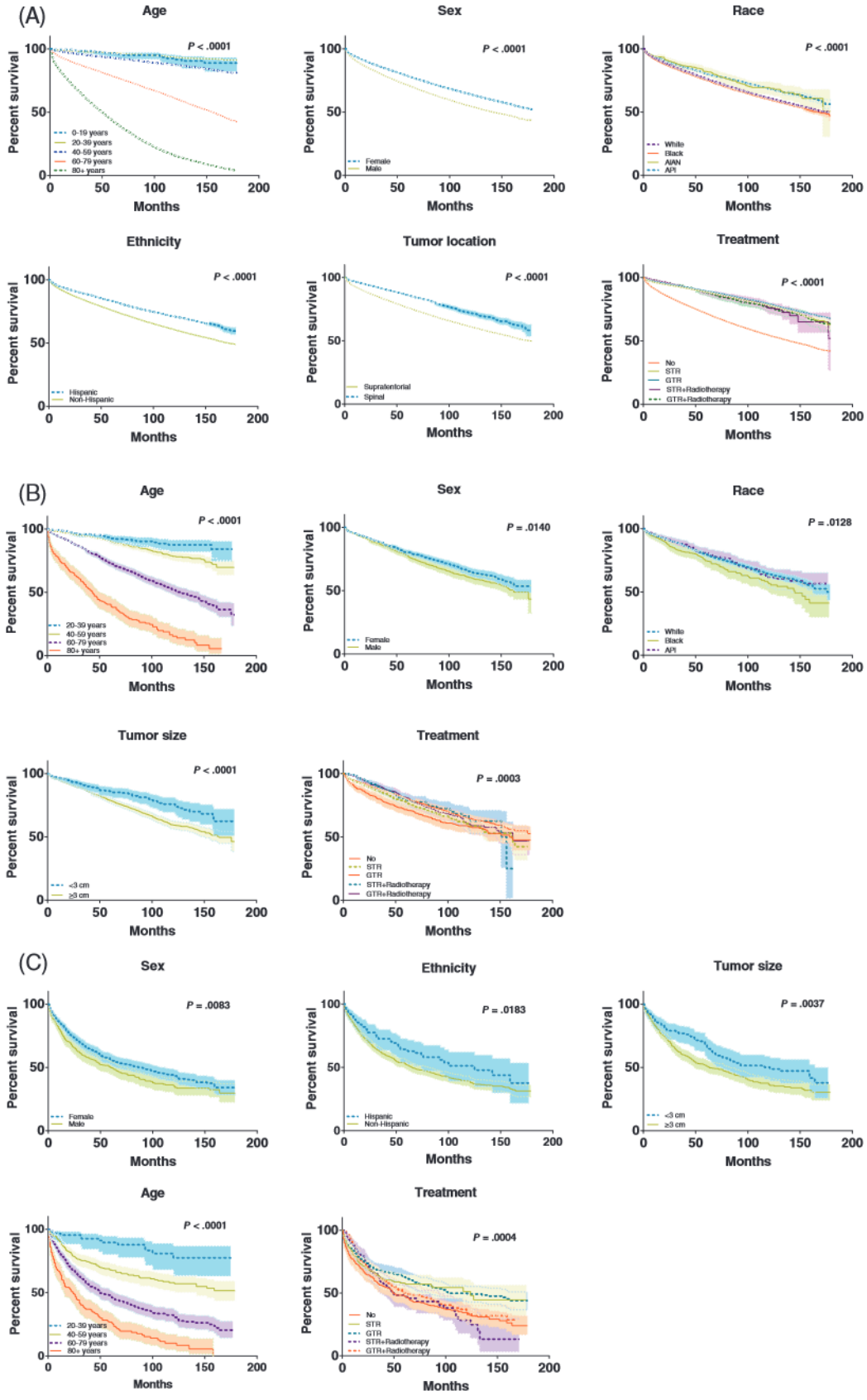

FIGURE 5 Kaplan-Meier analysis by age, sex, race, ethnicity, tumor location, tumor size and treatment modality. (A) Benign meningioma; (B) borderline meningioma; (C) malignant meningioma. *Only show significant differences in overall survival at the $P < .05$ level

borderline meningioma, significant differences in OS were observed according to age ($P < .0001$), sex ($P = .0140$), race ($P = .0128$), tumor size ($P < .0001$), and treatment modality ($P = .0003$), but not ethnicity (Figure 5B). For malignant meningioma, significant differences in OS were observed according to age ($P < .0001$), sex ($P = .0083$), ethnicity ($P = .0183$), tumor size ($P = .0037$), and treatment modality ($P = .0004$), but race and tumor location did not show an effect on OS (Figure 5C). Median survivals and 95% CIs of each group are shown in Supplementary Table 1.

3.3.2 | Factors associated with OS based on multivariable Cox proportional hazards models

Next, we investigated the associations between clinical and demographic variables and OS of patients with benign, borderline, and malignant meningiomas using multivariable Cox proportional hazards regression models (Figure 6B and Supplementary Table 1). After controlling for different factors, the model showed that the following factors had a significant impact on OS among benign meningioma patients: age, sex, race, ethnicity, tumor location, tumor size, and treatment modality (Figure 6B and Supplementary Table 1). The risk of death increases 3.35 times for every 20-year increase in patient age (HR: 3.35 [95% CI: 3.29-3.41], $P < .001$). Compared to females, males had a 41.3% greater risk of death (HR: 1.41 [95% CI: 1.38-1.45], $P < .001$). Black patients had a 27.4% higher risk of mortality (HR: 1.27 [95% CI: 1.23-1.32], $P < .001$) than White patients, but the API population had a 13.3% lower risk of mortality (HR: 0.87 [95% CI: 0.83-0.91], $P < .001$) than White patients. Compared to Hispanic patients, non-Hispanic patients had a 10.6% higher mortality risk (HR: 1.11 [95% CI: 1.06-1.56], $P < .001$). Patients with a spinal tumor had a 15.2% lower risk of death (HR: 0.85 [95% CI: 0.79-0.91], $P < .001$) compared to patients with a supratentorial tumor. Patients with a large tumor (≥3 cm) had a 39.2% higher risk of death (HR: 1.39 [95% CI: 1.35-1.43], $P < .001$) than patients with a small tumor (<3 cm). STR and GTR operations reduced the death risk by 59.5% and 62.0%, respectively (STR: HR: 0.41 [95% CI: 0.39-0.42], $P < .001$; GTR: HR: 0.38 [95% CI: 0.37-0.39], $P < .001$). In addition, STR + RT and GTR + RT reduced the death risk by 64.5% and 59.4%, respectively (STR + RT: HR: 0.36 [95% CI: 0.31-0.41], $P < .001$; GTR + RT: HR: 0.41 [95% CI: 0.36-0.46], $P < .001$).

For borderline meningioma, age, sex, race, ethnicity, tumor location, tumor size and treatment modality had a significant effect on OS according to the model (Figure 6B and Supplementary Table 1). The risk of death increases 2.78 times for every 20-year increase in patient age (HR: 2.78 [95% CI: 2.53-3.05], $P < .001$). Males had a 14.3% greater risk of death (HR: 1.14 [95% CI: 1.00-1.30], $P = .045$) than females. Black patients had a 58.2% higher risk of death (HR: 1.58 [95% CI: 1.32-1.90], $P < .001$) than White patients. Compared to that of Hispanic patients, non-Hispanic had a 28.0% lower risk of death (HR: 0.720 [95% CI: 0.580-0.893], $P = .003$). Spinal tumor location was associated with a 47.9% lower risk of death compared to supratentorial tumor location (HR: 0.52 [95% CI: 0.28-0.98], $P = .043$). Patients with a large tumor (≥3 cm) had a 43.9% higher death risk (HR: 1.44 [95% CI: 1.13-1.84], $P = .004$) than patients with a small tumor (<3 cm). STR and GTR operations reduced the death risk by 16.0% and 29.8%, respectively (STR: HR: 0.84 [95% CI: 0.71-1.00], $P = .047$; GTR: HR: 0.70 [95% CI: 0.60-0.82], $P < .001$). In addition, STR + RT and GTR + RT reduced the death risk by 40.0% and 34.5%, respectively (STR + RT: HR: 0.60 [95% CI: 0.47-0.77], $P < .001$; GTR + RT: HR: 0.66 [95% CI: 0.53-0.81], $P < .001$).

Age, sex, tumor size, and treatment modality significantly affected OS for malignant meningioma patients, but race, ethnicity, and tumor location had little effect (Figure 6B and Supplementary Table 1). The risk of death increases 2.06 times for every 20-year increase in patient age (HR: 2.06 [95% CI: 1.85-2.28], $P < .001$). Males had a 36.4% higher death risk (HR: 1.36 [95% CI: 1.53-1.61], $P < .001$) than females. Patients with a large tumor (≥3 cm) had a 40.6% higher risk of death (HR: 1.41 [95% CI: 1.07-1.85], $P = .014$) than those with a small tumor (<3 cm). Patients who underwent STR or GTR had a 31.1% or 43.8% lower death risk (STR: HR: 0.69 [95% CI: 0.54-0.88], $P = .003$; GTR: HR: 0.56 [95% CI: 0.51-0.77], $P < .001$) than those who did not receive treatment. In addition, GTR + RT reduced the death risk by 26.9% (GTR + RT: HR: 0.73 [95% CI: 0.59-0.91], $P = .004$).

3.4 | Cause-specific survival of patients with malignant meningioma according to age, sex, race, ethnicity, tumor location, tumor size and treatment modality from 2004 to 2018

At data collection, 446 malignant meningioma patients (39.2%) were dead of their meningioma, and there was no benign or borderline meningioma patient dead recorded contribute to meningioma. We performed an analysis of the cumulative incidence of meningioma-related death and death of other causes, results showed that there was an obvious difference (Supplementary Figure 1A). In addition, the cumulative risk of malignant meningioma related death at 1 year, 5 years and 10 years respectively was 14.2% [95% CI: 12.2-16.4], 33.7% [95% CI: 30.7-36.9] and 40.1% [95% CI: 36.6-43.7]. For malignant meningioma, significant differences in case-specific survival were observed according to age ($P < .0001$), sex ($P = .015$), tumor size ($P < .0001$), and treatment modality ($P = .0027$), but race, ethnicity and tumor location did not show an effect on case-specific survival (Figure 6A).

The SHRs of the risk for meningioma-related death after competing risk analysis are shown in Figure 6C and Supplementary Table 2. In the Fine-Gray competing risk regression for meningioma cause-specific survival, following factors had a significant impact on case-specific survival among malignant meningioma patients: age, sex, tumor size, and treatment modality. The risk of death increases by 14% for every 20-year increase in patient age (HR: 1.14 [95% CI: 1.11-1.18], $P < .001$). Compared to females, males had a 26.5% greater risk of death (HR: 1.27 [95% CI: 1.17-1.36], $P = .015$). Patients with a large tumor (≥3 cm) had a 2.09 times higher risk of death (HR:

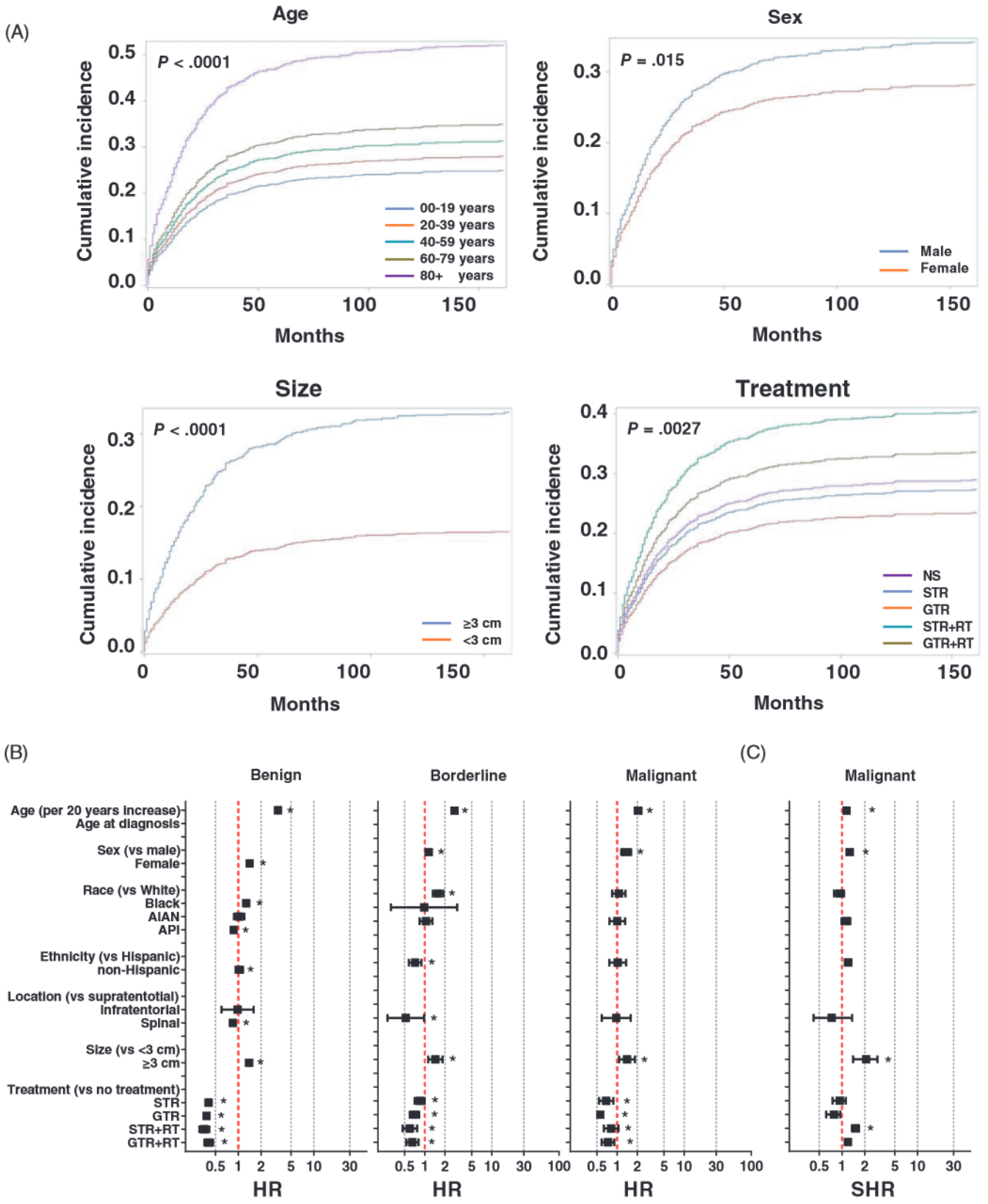

FIGURE 6 Cumulative incidences curves and hazard ratios for each of the features of the survival model. (A) Cumulative incidences curves by age, sex, tumor size and treatment modality for malignant meningioma; (B) multivariable Cox regression survival analysis for benign, borderline and malignant meningioma; (C) competing risk regression survival analysis for malignant meningioma. *Represents significant differences at the $P < .05$ level

2.09 [95% CI: 1.40-2.94], $P = .002$) than patients with a small tumor (<3 cm). Interestingly, patients who underwent STR + RT had a 51.1% higher death risk (STR + RT: HR: 1.51 [95% CI: 1.35-1.67], $P = .001$) than those who did not receive surgical or radiotherapy treatment.

4 | DISCUSSION

4.1 | Incidence

In our study, we analyzed data from a total of 109 660 patients and found that 95.4% of the patients had benign meningioma, 3.6% had borderline meningioma, and 1.0% had malignant meningioma, which was consistent with previous reports.[16,31] Quinn et al described 159 038 meningioma patients in the United States from 2013 to 2017, and the percentages of nonmalignant and malignant meningioma were similar to those in our study (157 288 [98.9%] nonmalignant and 1750 [1.1%] malignant).[1] Notably, both our study and that by Quinn et al. employed ICD-O-3 codes to define meningioma, which differs from the WHO classification that has been widely used in the literature.[1] Of meningioma with documented WHO grade in our study, 79.4% of meningioma were WHO Grade I, 18.7% were WHO Grade II, and 1.9% were WHO Grade III. Therefore, it is critical to pay attention to disparities in meningioma epidemiological data produced according to different standards, and there is an urgent need for scientists to create a consistent and trustworthy categorization standard for meningiomas.

We found IRs increased with age and the majority of patients were older than 60 years, indicating that age may be a risk factor for meningioma. Recently, studies have highlighted epigenetic mechanisms, such as the change in DNA methylation patterns in cancer, that may explain the higher frequency of meningioma in aged populations.[16,32-35] In addition, we found that the ratio of meningioma IRs for females to males was 2.1:1, and it increased with age, reaching a peak of 3.6 in the 45-49-year-old group and then decreasing in older populations (Figure 1G). However, in any 5-year age group, the IRs of borderline and malignant meningioma did not differ substantially by sex. According to CBTRUS data, the prevalence of nonmalignant meningiomas was 2.3 times higher in females than in males.[1] In that study, the female-to-male incidence rate ratios were highest in those of 35-54 years old, where the female IR was 3.29 times higher.[1] In the present study, we pinpointed the peak ratio between 45 and 49 years. Maybe unknown sex-related factors play an important role, further studies are needed to explore the mechanism.[31]

We also analyzed the IRs of meningiomas according to tumor location and found that 96.0% of patients had supratentorial tumors, and infratentorial meningiomas were extremely rare, accounting for less than 0.1%. In their study, Quinn et al reported that the majority of meningiomas (80.6%) were found in the cerebral meninges, with 4.2% in the spinal meninges and 14.5% having no specific meningeal site indicated.[1] In the present study, we did not include patients with an unknown tumor location, and the IRs of supratentorial and spinal meningiomas were quite similar between their study and ours.

Furthermore, we studied the changes in the IRs of various types of meningiomas in different populations from 2004 to 2018. We observed an increasing incidence for both benign and borderline meningiomas from 2004 to 2018, but malignant meningioma showed a decreasing trend overall during the same time period. In addition, we found that the APC grew until 2008 or 2009 with all variables, including sex, age, race, ethnicity, and location, and then leveled out or even fell until 2018. Instances of meningiomas with brain invasion but no anaplasia were downgraded from WHO III to WHO II or I according to the updated guidelines published in 2000 and 2007,[13,36,37] suggesting that some trend may be due to the classification guideline modifications. Interestingly, we observed that the IR decreased for the first time in 2017-2018, and if this trend continues, it may support this hypothesis. However, other factors, including the aging of the population, improvements in health services and diagnostic technologies, changes in the classification of tumor codes reported by the registry, and an increase in the incidence of histological confirmation could possibly explain these trends.

Therefore, based on a large meningioma database, we updated the prevalence of different types of meningiomas by using two classification systems (ICD-O-3 and WHO). Then we found majority of patients are old people, especially older than 60 years old. Next, we found that ratio of meningioma IRs for females to males increased with age and reaching a peak of 3.6 in the 45-49-year-old group. We also identified an increase in the frequency of benign and borderline meningioma over time, but the APC grew until 2008 or 2009 and then leveled out or even fell until 2018.

4.2 | Survival

Our study discovered a number of demographic and clinical characteristics associated with a worse survival rate in patients with meningiomas in the United States from 2004 to 2018. For all subtypes of meningioma, older age was a major risk factor for worse prognosis. In addition, males and the Black population showed poorer survival rates. Quinn et al. also reported that Black patients had worse survival than White among elderly patients.[1] Robert A. et al studied trends in mortality for Black and White populations in the United States from 1900 to 2010.[38] And they stated several explanations for the worse survival of Black population, including social and environmental factors, such as education, employment, poverty, sanitation; biological and behavioral factors, such as hypertension, cholesterol levels, cigarette smoking, and diet; and preventive and therapeutic interventions and access to them, such as vaccination, hypertension screening, and treatment of cardiovascular disease. Many of these factors may also contribute the worse survival of Black meningioma patients, such as late access to neuro-oncologic care. However, molecular or epigenetic differences among races may also contribute to tumor behavior. Further studies are needed to dissect the mechanisms underlying these differences.

We also investigated the effect of tumor location on OS. We found that patients with supratentorial meningioma had a greater risk

of death than those with a spinal tumor, but this was only observed in patients with benign meningioma and not in those with borderline or malignant tumors. Other research has found that tumors located in the cerebral convexity had a better prognosis than tumors located elsewhere (parasagittal, falx, skull base).[39] This effect is likely due to the proximity of critical structures such as the superior sagittal sinus in the falx/parasagittal location, the cranial nerves, brainstem, and venous sinuses in the posterior fossa/cranial base locations.[40]

Kaplan-Meier survival analysis indicated that patients with benign meningioma did not show significant differences in OS according to the size of the tumor. However, patients with borderline and malignant meningiomas showed substantial differences in OS, and patients with larger tumors (≥3 cm) had a higher mortality risk than those with smaller tumors (<3 cm). Moreover, the results of Multivariable Cox proportional hazards regression models showed that tumor size significantly affected survival of all types of meningioma patients, which was consistent with previous reports, indicating that tumor size is one of the most important prognostic factors affecting tumor recurrence and patient survival.[40-44] Further studies are needed to confirm the prognostic effect of tumor size in these patients.

The present study demonstrated that treatment modality could affect OS substantially in patients with benign, borderline, or malignant meningiomas. We further analyzed the differences in the effect of No, STR and GTR on OS (Supplementary Figure 2). Our analysis showed that in benign meningioma, there were significant differences between any two of the three surgical types, GTR patients surviving longer than STR, and STR patients surviving longer than NS patients. For borderline meningioma, we observed a significant survival difference between GTR and STR, but not between STR and NS. For malignant meningioma, we observed a significant difference in survival between STR and NS but not between GTR and STR. Furthermore, we also compared overall survival of surgery alone and surgery + RT, results showed that GTR + RT in malignant meningioma result in increase of death significantly compare to GTR alone, others without significant difference.

Since meningioma patients generally have a good prognosis and long survival, it is necessary to analyze the data using a competing risks analysis to avoid the limitations of traditional overall survival analysis, which include the risk of death from causes other than the tumor. For example, our previous analysis suggested that the overall survival of patients was related to age and sex. However, it could also be an increase in age-related diseases as the patient ages, or a male-related disease, which leads to the death of the patient. We overcome this bias by evaluating parameters in the context of tumor-related death, and the results imply that the influence of age or sex on survival is attributable to tumor-specific features. Interestingly, we also identified the cause-specific survival was affected by age, sex, tumor size and treatment modality, which was the same to overall survival analysis. In addition, we also compared cause-specific survival of surgery alone and surgery + RT, results showed that addition of RT in malignant meningioma result in increase of death significantly compare to STR or GTR alone (Supplementary Figure 1B). Similarly, several studies in meningioma based on CBTRUS or SEER have noted either a trend toward worse outcomes in patients receiving adjuvant radiation or no difference in survival with adjuvant radiation.[12,40] There could be several reasons, such as the SEER database does not specify which type of radiotherapy is given, whether it is adjuvant or salvage radiotherapy. Or, because it is a retrospective study, clinicians tend to select patients with high-grade, not total resected or highly recurrent meningiomas for radiotherapy. Therefore, it is necessary to design a multicenter prospective study in the future, using the same radiotherapy modality and dose, to clearly compare whether adjuvant radiotherapy can benefit patients with STR or GTR.

In meningiomas, many genetic and epigenetic abnormalities have been found that are significantly linked to prognosis, and might be used as therapeutic targets. With the development of global methylation analysis, researchers realized that epigenetic signatures or methylation-based classification of meningioma have strong clinical associations with the prognosis and even more accurate than traditional WHO classification.[33,45] Sahm et al analyzed DNA methylation profiles of 497 meningioma samples and distinguished six distinct methylation classes associated with typical mutational, cytogenetic, and gene expression patterns, which has a higher power for predicting tumor recurrence and prognosis than the WHO classification.[33] Olar et al also clustered meningioma into two distinct subgroups by DNA methylation analysis, which were correlated to meningioma recurrence.[34] There are also some genes with abnormal methylation associate with tumorigenesis, such as tumor protein 73 (TP73) and tissue inhibitor of metalloproteinase 3 (TIMP3).[46] The methylation of TP73 promoter occurs in 7% of meningioma, mostly in atypical and anaplastic meningioma.[47] Forty percent of anaplastic meningioma have TIMP3 hypermethylation, and it correlates to shorter time to recurrence.[47] Furthermore, methylation of PDCD1 and IGF2BP1 has been linked to an enhanced malignant potential and an aggressive phenotype.[48] The characterization of aggressive meningioma at the molecular level may aid in stratifying patients into distinct recurrence risk groups and guiding therapy to more aggressive techniques for those with greater risk factors for recurrence. In the future, it is hoped that the DNA methylation profiles of patients can be included in the SEER database, which is important for predicting patient outcomes.

5 | LIMITATIONS

This retrospective study based on SEER database has several limitations. Firstly, the database is based on the US population, the discoveries may not be able to be applied to populations in other countries. Also, there are some limitations related to the undetailed information of the database. For instance, only the cerebral meninges or spinal meninges were recorded about the location of the meningioma, there was no detailed location or adjacent tissue, such as whether it invaded the venous sinus or not, whether it was at the skull base or not. For surgical resection, the commonly used Simpson grading was not used. In addition, there are some differences between the ICD-O-3 codes we used and the WHO classification normally used in the literature. In terms of adjuvant therapy, the mode or dose of radiotherapy is

unclear, and the information on the use of chemotherapy drugs in some patients is incomplete.

6 | CONCLUSION

The present study provides a thorough review of the incidence of meningiomas and survival trends among patients according to all demographics. Despite there were several limitations, we were able to demonstrate that older age, male sex, Black race, and tumor size may be important prognostic factors. Our results also indicate that tumor resection can improve survival substantially in meningioma patients. For future studies, it is necessary to design a multicenter prospective study, to clearly compare whether adjuvant radiotherapy can benefit patients with STR or GTR. Furthermore, we should not only perform analyses based on demographic and clinical factors in the future, but also investigate molecular signatures, such as epigenetic alterations or genetic mutations in meningiomas.

AUTHOR CONTRIBUTIONS

Study design: Junguo Cao. *Data collection*: Junguo Cao, Weijia Yan, Guihong Li and Zhixin Zhan. *Data analysis/interpretation*: Junguo Cao and Weijia Yan. *Figure preparation*: Junguo Cao, Hong Yan and Xinyu Hong. *Manuscript drafting*: Junguo Cao. *Reviewing/editing manuscript*: Junguo Cao, Hong Yan and Xinyu Hong. All the work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

Only publicly available data were used in our study, and data sources and handling of these data are described in the Materials and Methods. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

Cases were collected from the SEER database and were analyzed anonymously; therefore, no additional informed consent was required.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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