Neuro-Oncology Advances
2(1), 1–8, 2020 | doi:10.1093/noajnl/vdaa135 | Advance Access date 10 October 2020

Epidemiology of vestibular schwannoma in the United States, 2004–2016

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Abstract

Background. Vestibular schwannomas (VS) are nonmalignant tumors of the eighth cranial nerve and are the most common nonmalignant nerve sheath tumor. This study provides the most comprehensive and current analysis of VS epidemiology in the United States.

Methods. Incidence data were obtained from the Central Brain Tumor Registry of the United States, from 2004 to 2016 for VS. Age-adjusted incidence rates (AAIRs), rate ratios (AAIRRs), and prevalence ratios (AAPRs) per 100 000 were analyzed by age, sex, race and ethnicity, and laterality. Additional analyses were performed to assess differences in treatment, laterality, and diagnostic confirmation.

Results. Incidence of VS was highest among adults (aged 65–74 years, AAIR: 3.18, 95% confidence interval [CI]: 3.15–3.25). However, there was a much higher distribution of bilateral tumors compared to unilateral in children aged 0–19 years (28.5% vs 1.0%, $P < .001$). VS incidence was highest among white non-Hispanics (AAIR:1.30, 95% CI: 1.29–1. 31) and lowest among black non-Hispanics. Incidence of radiographically confirmed VS increased from 2004 to 2016 (annual percent change: 1.64, 95% CI: 0.15–3.16, $P = .03$). For treatment, 40.1% received surgery, while only 23.7% received radiation. There were an estimated 44 762 prevalent cases of VS in 2016 (AAPR: 12.17, 95% CI: 12.06–12.29).

Conclusions. VS incidence and prevalence are highest among adults and white non-Hispanics. Bilateral VS was more common among children. There was an increase of radiographically confirmed VS over time. A higher proportion of patients received surgical treatment than radiotherapy. Population-based statistics provide healthcare professionals with vital information regarding disease burden and help improve patient care.

Key Points

- Vestibular schwannoma incidence was highest among white non-Hispanics (AAIR: 1.30, 95% CI: 1.29–1. 31) and lowest among black non-Hispanics.
- Incidence of vestibular schwannoma was highest among adults (aged 65–74 years, AAIR: 3.18, 95% CI: 3.15–3.25).
- Overall, there was a higher distribution of bilateral tumors compared to unilateral in children aged 0–19 (28.5% vs 1.0%, $P < .001$) from 2004 to 2016.

Importance of the Study

Vestibular schwannomas (VSs) are the most common nonmalignant nerve sheath tumor. While rarely fatal, VS diagnoses are associated with various comorbidities, such as hearing loss, tinnitus, and vertigo. Population-based studies provide the healthcare community with important information on disease occurrence and burden and help guide patient care. This is the most current and comprehensive study on primary VS in the United States, providing age-adjusted incidence and prevalence rates for age, sex, race, and laterality, as well as statistics on diagnostic confirmation and treatment patterns.

Vestibular schwannomas (VSs) are nonmalignant tumors of the eighth cranial nerve. VS, previously known as acoustic neuroma, is the most common nonmalignant nerve sheath tumor (97.5%) and the third most common nonmalignant primary brain tumor (12.3%), after meningioma and tumors of the pituitary.[1,2] While rarely fatal, VS can cause physical impairment such as hearing loss, tinnitus, disequilibrium, and vertigo.[3] Management options include serial observation to determine growth or intervention (microsurgical resection or use of radiation therapy) in cases of persistent growth or upfront larger size of the tumor. These decisions are complex and should be undertaken after extensive counseling of patients and caregivers in a multidisciplinary fashion.[3]

Prior epidemiological studies assessing the incidence of VS were not comprehensive as they evaluated either a smaller sample population or a shorter timeframe.[4–7] We provide an up-to-date epidemiological study that evaluates the incidence and prevalence of VS by demographic and histological factors, utilizing data from the Central Brain Tumor Registry of the United States (CBTRUS) for diagnosis years 2004–2016. Population-based statistics provide researchers and healthcare professionals with vital information regarding the burden of the disease and help inform patient care and prognosis.

Methods

CBTRUS, which receives data in collaboration with the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) and the National Cancer Institute's Survival, Epidemiology, and Ends Results Program (SEER), is the largest population-based registry focused exclusively on primary brain and other central nervous system tumors in the United States, covering the entire US population.[1]

First-sequence, microscopically or histologically confirmed cases of VS diagnosed between 2004 and 2016 were identified using *the International Classification of Diseases for Oncology, Third Edition* (ICD-O-3) histology and morphology code 9560/0 (Neurilemoma, NOS), and primary site code C72.4 (acoustic nerve). Only Neurilemoma, NOS found in the acoustic nerve can be labeled VS.

Age-adjusted incidence rates (AAIRs) and rate ratios (AAIRRs) per 100 000 persons were generated for age, sex, race, ethnicity, histology, and laterality with 95% confidence intervals (95% CIs). Annual percent change (APC) was calculated to assess incidence trends. Age-adjusted prevalence rates (AAPRs) per 100 000 persons for 2016 were estimated for age, sex, and race based on the Zheng et al.'s complete prevalence methodology, using incidence data provided by CBTRUS and survival data from the NPCR United States Cancer Statistics Survival Dataset which includes data from 43 NPCR registries for the years 2004–2015.[8,9] Proportions were calculated to evaluate the distribution of histologic confirmation, surgical treatment, and radiation therapy. This dataset provides population-based survival information for approximately 93% of the US population for the years 2004–2015 and is a subset of the data used for the incidence calculations.

SEER*Stat (version 8.3.6) was used to generate all incidence rates and incidence rate ratios. Incidence trends were assessed using Joinpoint Regression Program (version 4.7.0; http://surveillance.cancer.gov/joinpoint). All incidence rates were age-adjusted and standardized to the 2000 US population to adjust for differences in age distribution. Ninety-five percent (95%) CIs were calculated using the method described in the work of Tiwari et al.[10] Chi-square tests were performed to assess differences in proportions. Prevalence analyses and figures were generated using R Software (version 3.5.2).

Results

Overall, from 2004 to 2016, there were 49 869 cases of VS with an AAIR of 1.14 (1.13–1.15) per 100 000. The majority of tumors were unilateral (99.2%) and occurred mostly in white, non-Hispanics (82.7%), with a slight female predominance (52.6%; Table 1). There were notable differences in age distribution based on laterality, with a significantly larger proportion of children aged 0–19 years with bilateral VS (28.5% vs 1.0%, $P < .001$; Figure 1).

There was a prominent difference in age distribution by diagnostic confirmation and treatment. A significantly higher proportion of elderly patients had radiographically confirmed tumors (65–74 years: 24.8%, 75+ years: 15.5%) compared to microscopic confirmed tumors (65–74 years: 12.3%, 75+ years: 3.2%, $P < .001$). There were also fewer elderly patients who received surgery (65–74 years: 23.0%, 75+ years: 9.6%; $P < .001$; Figure 2). For all patients, the primary treatment following diagnosis was either surgery (40.1%) or radiation therapy (23.7%; Supplementary Figure 1). Though most patients

Table 1. Frequency and Age-Adjusted Incidence of Primary Vestibular Schwannoma, by Demographic and Histological Factors: CBTRUS 2004–2016

	Frequency, *n* (%)	Age-Adjusted Incidence Rate (95% CI)	Age-Adjusted Incidence Rate Ratio (95% CI)
Overall	49 869 (100)	1.14 (1.13–1.15)	
Age (years)			
0–19	606 (1.2)	0.055 (0.051–0.06)	Ref
20–44	9742 (19.5)	0.75 (0.73–0.76)	13.58 (12.50–14.76)
45–54	11 462 (23.0)	1.99 (1.95–2.02)	36.02 (33.19–39.15)
55–64	13 634 (27.3)	2.88 (2.83–2.92)	52.19 (48.10–56.71)
65–74	9513 (19.1)	3.18 (3.12–3.25)	57.77 (53.21–62.83)
75+	4912 (9.8)	2.05 (1.99–2.11)	37.16 (34.15–40.50)
Sex			
Male	23 636 (47.4)	1.13 (1.12–1.15)	Ref
Female	26 233 (52.6)	1.15 (1.14–1.17)	1.02 (1.00–1.03)
Race and ethnicity			
White non-Hispanic	40 350 (82.7)	1.30 (1.29–1.31)	Ref
American Indian/Alaska native non-Hispanic	252 (0.5)	0.81 (0.71–0.92)	0.62 (0.55–0.71)
Asian or Pacific Islander non-Hispanic	2206 (4.5)	1.05 (1.00–1.09)	0.80 (0.77–0.84)
Black non-Hispanic	2210 (4.5)	0.46 (0.44–0.48)	0.36 (0.34–0.37)
Hispanic	3775 (7.7)	0.80 (0.77–0.83)	0.61 (0.59–0.64)
Laterality			
Unilateral	48 393 (99.2)	1.11 (1.1–1.12)	Ref
Bilateral	414 (0.8)	0.01 (0.009–0.011)	0.009 (0.008–0.01)

Ref indicated the reference group for the age-adjusted incidence rate ratios.

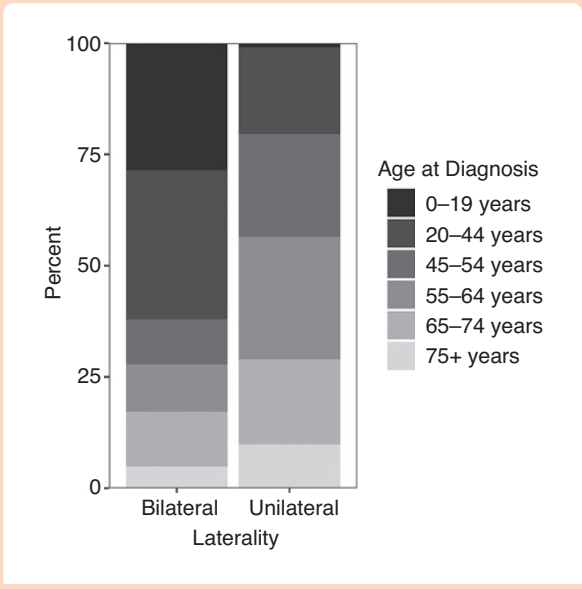

Figure 1. Age at diagnosis of primary vestibular schwannoma stratified by laterality, CBTRUS 2004–2016.

received either surgery or radiation, only 1.8% of patients received both.

VS was most common in adults, with incidence per 100 000 being highest among those aged 65–74 years (AAIR: 3.18, 95% CI: 3.15–3.25) and 55–64 years (AAIR: 2.88, 95% CI: 2.83–2.92). VS was much less common in children, with those aged 0–19 years having an AAIR of 0.06 per 100 000 (95% CI: 0.05–0.06; Figure 3). Incidence in males (AAIR: 1.13, 95% CI: 1.12–1.15) and females (AAIR: 1.15, 95% CI: 1.14–1.17) did not differ significantly (AAIRR: 1.02, 95% CI: 1.00–1.03, P = .072). Among race and ethnic subgroups, VS incidence was highest among white non-Hispanics (AAIR: 1.30, 95% CI: 1. 29–1. 31) followed by Asian or Pacific Islanders (AAIR: 1.05, 95% CI: 1.00–1.09). Black non-Hispanics had the lowest incidence (AAIR: 0.46, 95% CI: 0.44–0.48; Table 1, Figure 3).

Incidence of VS was relatively stable from 2004 to 2016, showing no overall change over time (APC: –0.07, 95% CI: –1.02 to 0.88, P = .87) or among demographic factors. Though there were notable trends based on the diagnostic confirmation, with decreased incidence of VS diagnosed through microscopic confirmation over time (APC: –2.08, 95% CI: –2.78 to –1.38, P < .001), and increased incidence of VS diagnosed through radiographic

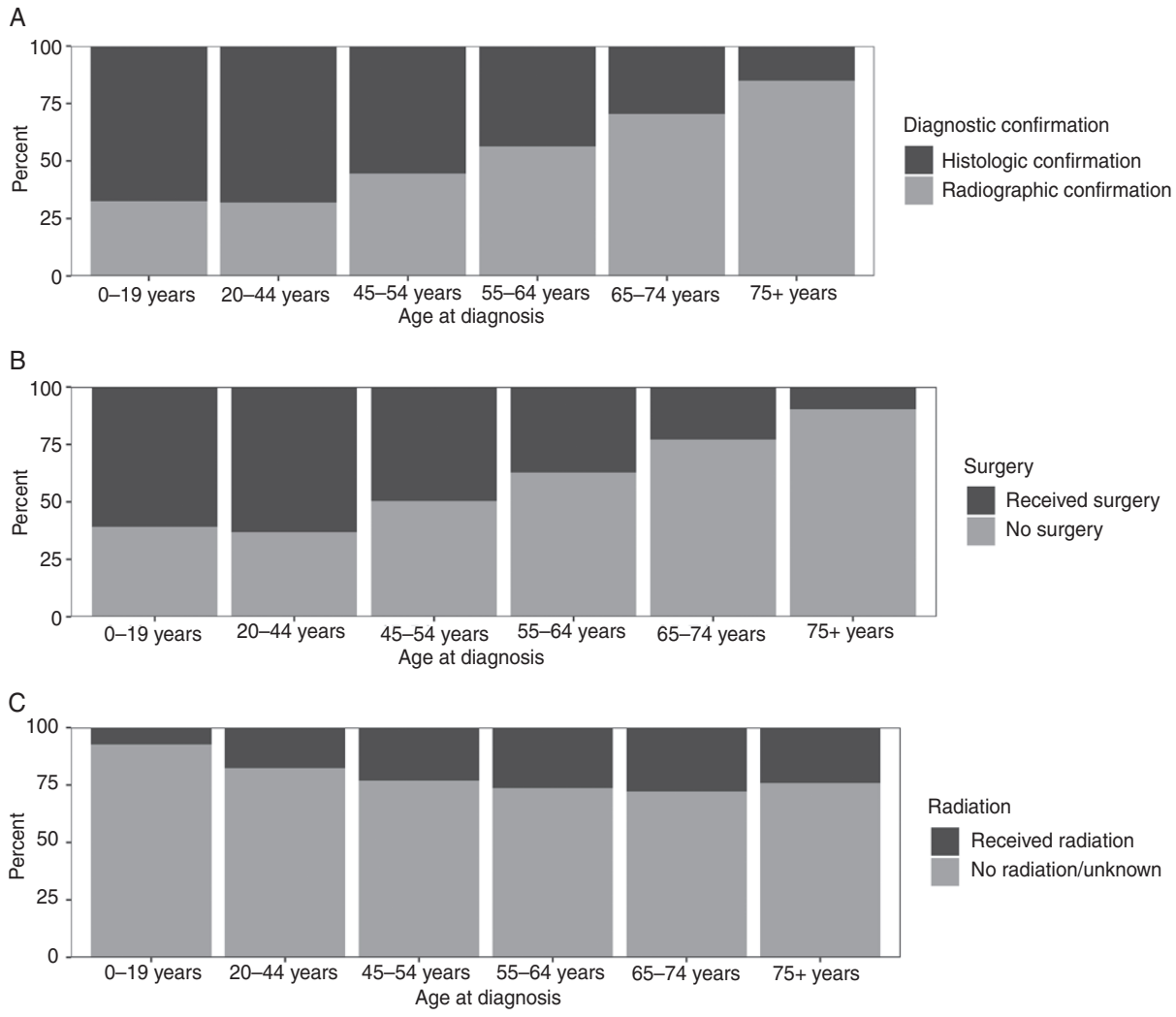

Figure 2. Age at diagnosis of primary vestibular schwannoma stratified by (A) diagnostic confirmation, (B) surgery, and (C) radiation, CBTRUS 2004–2016.

confirmation (APC: 1.64, 95% CI: 0.15–3.16, P = .03; Figure 4).

There were an estimated 44 762 prevalent cases of VS in 2016, with an overall AAPR of 12.17 per 100 000 (95% CI: 12.06–12.29). Highest prevalence occurred in those aged 64–74 years (AAPR: 41.43, 95% CI: 40.67–42.10) and in white non-Hispanics (AAPR 9.71, 95% CI: 9.60–9.81; Table 2).

Discussion

This is the first known study to estimate the prevalence of VS using complete US data. Our current and comprehensive study covers approximately 100% of the US population and provides important national age-adjusted incidence, incidence trends, and prevalence rates along with information on patterns of treatment of VS. A 2006 study by Propp et al.[7] used data from the existing CBTRUS database at the time, which consisted of only 11state cancer registries, in addition to the Los Angeles County Cancer Surveillance Program, representing just 20% of the US population. This study also used data collected between 1975 and 1998, prior to the implementation of the Benign Brain Tumor Cancer Registries Amendment Act in 2004, that led to CBTRUS expanding to include all central (50 states and the District of Columbia) cancer registries and greater accuracy in the collection of these tumors.[11] Kshettry et al.[5] published a study using comprehensive CBTRUS data from 2004 to 2010, but did not perform analyses on laterality or treatment patterns. Therefore, the current study includes the largest, most up-to-date dataset with additional analyses of incidence trends, prevalence, laterality, and treatment patterns.

The AAIR from 2004 to 2016 was 1.14 per 100 000 with the highest incidence of VS occurring in older adults aged 65–74 years. Our results were similar to those of 2 other series using SEER data over a similar time period.

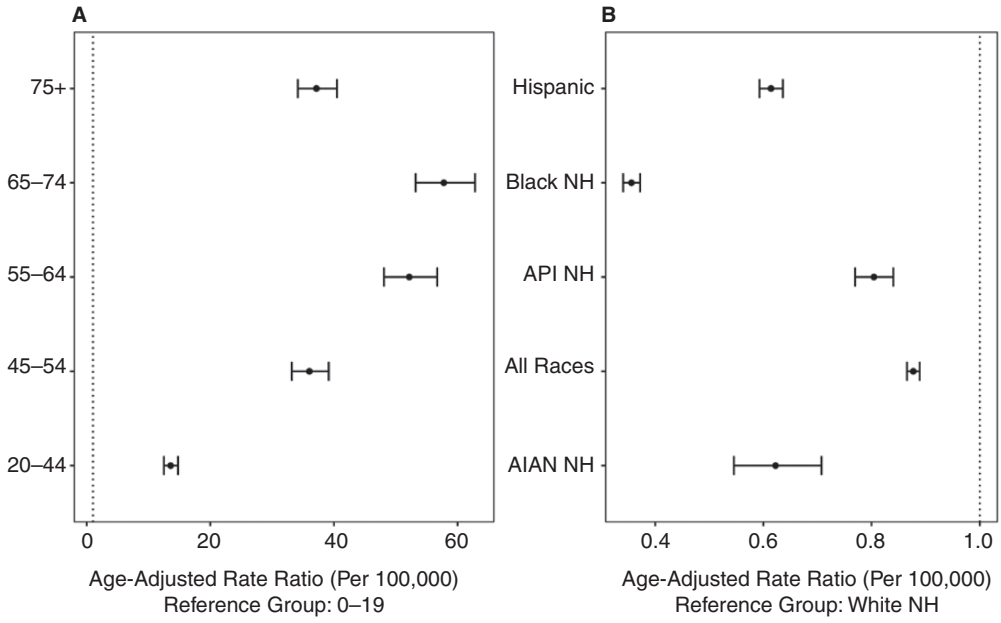

Figure 3. Age-adjusted incidence rate ratios per 100 000 with 95% CI by (A) age at diagnosis and (B) race and ethnicity for primary vestibular schwannoma, CBTRUS 2004–2016.

Carlson et al.[12] showed a VS incidence of 1.1 per 100 000 (range 1.03–1.21) for patients diagnosed from 2004 to 2011. In their study, the AAIR also increased with age. The AAIR was 0.75 for patients aged 20–44 years compared to 2.88 for 55–64 years and 3.18 for 65–74 years. In a state series from 2006 to 2016, Marinelli et al.[2] showed similar trends of incidence of VS increasing with age but they found a much higher incidence in their older adults. Incidence ranged from a low of 0.4–2.0 per 100 000 for patients aged 20–39 years to 9.9–11.1 in patients aged 50–69 years. Patients 70 years and older displayed the highest incidence rates of any age group at 20.6 per 100 000.[2] While both our studies showed a gradual increase with age, the difference in the higher variability and incidence for patients at least 70 years noted in the Marinelli study could potentially be due to differences in sample size. There were 10 and 15 cases for patients aged 60–69 and at least 70 years old, respectively, representing a single county in Minnesota for the Marinelli analysis. Our study using nation-wide data identified 9513 and 4912 cases for patients aged 65–74 and at least 75 years old, respectively, and thus with significantly larger numbers may better capture the national incidence more uniformly.

VSs demonstrate variability in growth with about 40% of tumors shows no clinically significant changes over time. Tumors that do grow also demonstrate a relatively slow-growing profile with an average growth rate of approximately 1–3 mm/year.[13] Increasing incidence and prevalence of VS with age could result from biological factors important to tumorigenesis and growth as well as diagnostic biases as older patients are more likely to have imaging due to unrelated conditions (ie, MRI), leading to an incidental diagnosis of VS. In support of the latter, almost a quarter of all sporadic VS in a recent report were diagnosed incidentally after individuals obtained head imaging for unrelated indications.[2] Various mutations in the neurofibromatosis-2 (NF2) gene are seen in both familial and non-familial VS cases.[14] Although important, NF2 loss alone is not considered sufficient and VS formation likely requires additional mutational events in other genes.[15] Accumulation of necessary genetic mutations to initiate the formation of VS requires time, and as with other tumorigenesis processes, is much more likely to occur later in life. Finally, VSs are in general relatively slow-growing tumors with an average growth rate of approximately 1–3 mm/year and are thus, expected to become symptomatic and therefore diagnosed much later in life.[16]

VS management varies and can include observation, surgery, or radiation. Better understanding of the natural history of VS over the past 2 decades has resulted in more patients being managed using observation and surveillance testing, with treatment including surgery and/or radiation reserved for those who demonstrate progressive tumor growth and/or hearing loss.[13] When analyzing patterns of care over time, the rate of surveillance has increased from approximately 15% in 2004 to more than 35% by 2014, indicating a preference for this management in the modern era where imaging surveillance is easily accessible.[13] While about 75% of patients may have minimal growth with surveillance over a course of a year, there is still a potential risk of gradual hearing loss despite minimal growth.[17] Common treatments for symptomatic patients include surgery and radiation therapy. In our series, 40.1% of patients received surgery, 23.7% of patients received radiation therapy, though overall only 1.8% of patients received a combination of both treatment types. Numbers in

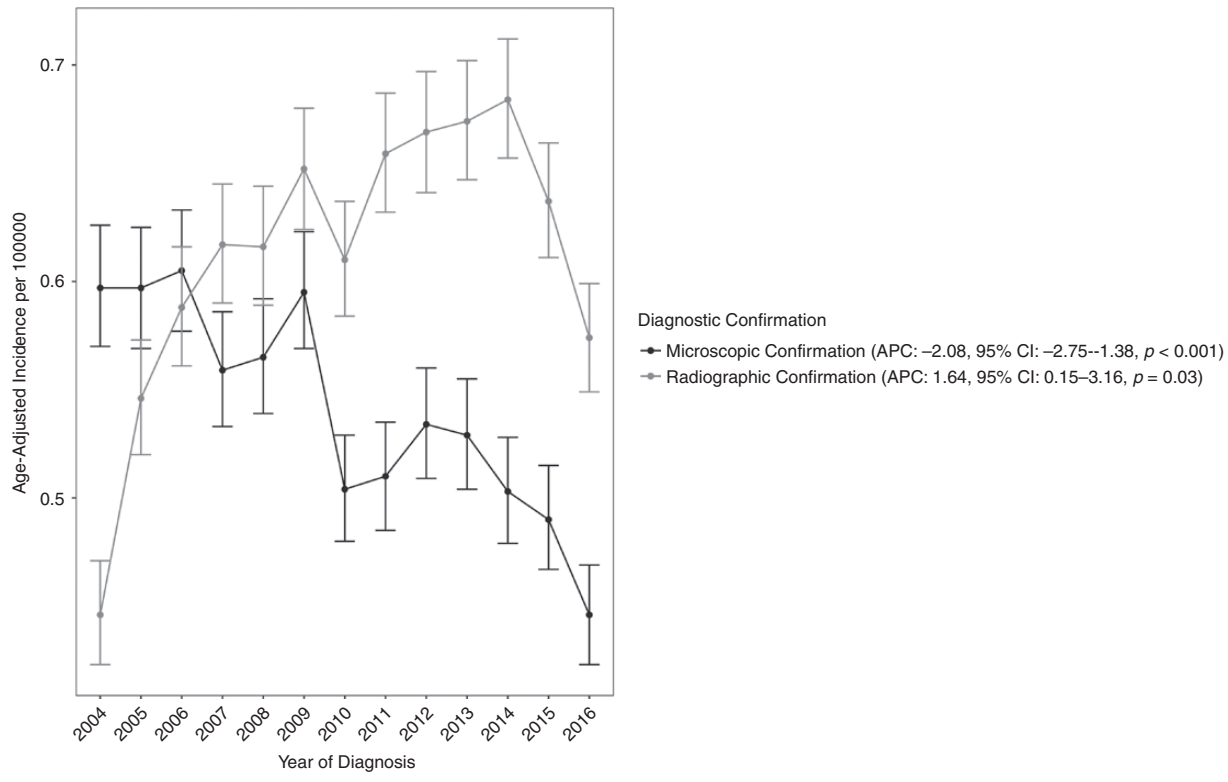

Figure 4. Age-adjusted incidence rates per 100 000 with 95% CI by diagnostic confirmation over time for primary vestibular schwannoma, CBTRUS 2004–2016.

this report are similar to those from the National Cancer Database (NCDB), a clinical oncology database sourced from hospital registry data, over a similar time period (2004–2014).[18]The percentage of patients observed, treated with surgery, or treated with radiation as the first management was 27.3%, 39.5%, and 30.2%, respectively.[13] For smaller tumors confined to the internal auditory canal or minimal extension in the cerebellopontine angle, management options are varied and include observation, radiation, or hearing preservation microsurgery.[19] Radiation techniques have evolved over time with greater availability of stereotactic radiosurgery (SRS), a form of focused precision high-dose therapy done in 1–5 fractions, which offers excellent long-term local control of over 90% of these tumors with minimal side effects.[20,21] SRS treatment has variable hearing preservation rates with factors influenced by initial baseline hearing and time,[22] though one series noted high rates of almost 90% at 1 year, 68% by 5 years, and 51% at 10 years.[23] In addition, in select cases SRS treatment may be more cost-effective.[20,24] For larger lesions that are not amenable to SRS, fractionated therapy with either protons or new forms of photon therapy such as intensity-modulated therapy or volumetric modulated arc therapy has been shown to have good efficacy in tumor control.[25,26]

We identified 414 patients with bilateral VSs at diagnosis, accounting for 0.8% of the total study population. Though, among these bilateral patients, there was a significantly larger proportion of children aged 0–19, compared to unilateral cases (28.5% vs 1.0%, $P < .001$). The presence of bilateral VSs is considered pathognomonic for the diagnosis of NF2, a disease caused by the autosomal dominant loss of the tumor-suppressor protein, merlin.[20] Approximately 5% of all patients newly diagnosed with VS have NF2. Patients with NF2 have an increased incidence of tumors involving the brain and spinal cord including VSs, meningiomas, and ependymomas.[27] A hallmark of NF2 is the development of VS and other tumors at a young age, often in childhood, consistent with our findings. Although bilateral VS is pathognomonic for NF2, and more than 90% of patients diagnosed with NF2 will develop bilateral VS by age 30, and up to 20% of patients with NF2 present only with unilateral VS suggesting that we are significantly underestimating the diagnosis of NF2 in this population by relying solely on the presence of bilateral VS at presentation.[27–29]

Lastly, our data show a higher incidence among white patients with an AAIR of 1.3 per 100 000 and a low AAIR among other races with the lowest rate among black patients at 0.46 per 100 000. Our cohort was 82.7% white non-Hispanic, and only 4.5% black non-Hispanic and 4.5% Asian non-Hispanic. Our distribution of lower incidence among non-white rates is similar to other registry data such as SEER and NCDB. One SEER series shows the median annual incidence of disease was lowest among black (0.43 per 100 000 persons) and Hispanic populations (0.45 per

Table 2. Age-Adjusted Prevalence of Primary Vestibular Schwannoma, by Demographic Factors for 2016

	Estimated Frequency	Age-Adjusted Prevalence Rate (95% CI)
Overall	44 762	12.17 (12.06–12.29)
Age (years)		
0–19	244.0	0.29 (0.26–0.33)
20–44	6011.1	6.14 (5.98–6.3)
45–54	8010.3	18.41 (18–18.82)
55–64	12 834.9	30.76 (30.23–31.3)
65–74	11 801.3	41.43 (40.67–42.19)
75+	5574.7	39.26 (38.23–40.3)
Sex		
Male	21 045.5	12.08 (11.91–12.25)
Female	23 430.3	12.31 (12.15–12.47)
Race and ethnicity		
White non-Hispanic	35 756.3	9.71 (9.6–9.81)
Black non-Hispanic	1973.6	0.54 (0.52–0.57)
American Indian/ Alaskan native non-Hispanic	231.6	0.07 (0.06–0.08)
Asian or Pacific Islander non-Hispanic	2054.8	0.58 (0.55–0.61)
Hispanic	3446.2	0.99 (0.96–1.03)

100 000 persons) and, in contrast, highest among whites similar to our cohort.[30] An NCDB-based study identified a similar racial distribution with the largest demographic being white at 87.7%, and only 4.4% black and 3.0% Asian.[13] The demographic distribution was also mirrored in the prevalence among the races. The age-adjusted prevalence was 9.71 per 100 000 for white, while only 0.54 for black and 0.58 for Asian. While our data are consistent with multiple other registry sources, they do not exclude the possibility that the findings reflect a possible element of ascertainment bias in identifying VSs in certain racial or ethnic groups.[31] Regarding prevalence, the overall prevalence was 12.17 per 100 000 in our study. In other series, the asymptomatic incidental VS was 7.5 per 100 000.[32] Additionally, asymptomatic incidental VS prevalence was also 10–11 cases per 100 000 for patients older than 20 years of age in a series by Lin et al.[33]

Our study has limitations that are inherent to studies using registry databases. These include the limited data available on the detailed treatment techniques of surgery and radiation therapy after diagnosis. As treatment can also be driven by tumor size and clinical presentation such as hearing loss, our study was limited by the lack of available clinical data on these 2 factors. Similarly, there were also limited data on therapy trends over time. In spite of this, our study provides for a large national cohort of cross-sectional percentage of patients treated with the various treatment management strategies. Additional correlating clinical information was limited including informative medical correlates such as the presence of NF2. While we did not have genetic information available, the presence of bilateral VSs is distinctly characteristic of patients with NF2.

In conclusion, our series is one of the largest cohorts to assess nationally the age-adjusted incidence and prevalence and treatment patterns of VS in the most recent decade. We also have identified one of the largest series of bilateral VS and the incidence nationally. These results provide researchers and healthcare professionals with vital information regarding the burden of this disease and help inform patient prognosis and care.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Advances* online.

Keywords

brain tumors | CBTRUS | epidemiology | vestibular schwannoma

Funding

Funding for CBTRUS was provided by the Centers for Disease Control and Prevention (CDC) under Contract No. 75D30119C06056, the American Brain Tumor Association, The Sontag Foundation, Novocure, the Musella Foundation, National Brain Tumor Society, the Pediatric Brain Tumor Foundation, the Uncle Kory Foundation, the Zelda Dorin Tetenbaum Memorial Fund, as well as private and in-kind donations. Contents are solely the responsibility of the authors and do not necessarily represent the official views of the CDC.

Conflict of interest statement. There are no conflicts of interest or disclosures to report.

Authorship statement. Study conception and design: G.C., N.P., and J.S.B.S.; data generation: G.C., K.T., K.W., and N.P.; data analysis and interpretation: G.C., D.N.Y., M.K., N.M., and J.S.B.S.; preparation and critical revision of the manuscript: all authors.

References

1. Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012–2016. *Neuro Oncol*. 2019;21(Suppl 5):v1–v100.

2. Marinelli JP, Lohse CM, Carlson ML. Incidence of vestibular schwannoma over the past half-century: a population-based study of Olmsted County, Minnesota. *Otolaryngol Head Neck Surg.* 2018;159(4):717–723.
3. Goldbrunner R, Weller M, Regis J, et al. EANO guideline on the diagnosis and treatment of vestibular schwannoma. *Neuro Oncol.* 2020;22(1):31–45.
4. Reznitsky M, Petersen MMBS, West N, Stangerup SE, Cayé-Thomasen P. Epidemiology of vestibular schwannomas—prospective 40-year data from an unselected national cohort. *Clin Epidemiol.* 2019;11:981–986.
5. Kshettry VR, Hsieh JK, Ostrom QT, Kruchko C, Barnholtz-Sloan JS. Incidence of vestibular schwannomas in the United States. *J Neurooncol.* 2015;124(2):223–228.
6. Marinelli JP, Lohse CM, Grossardt BR, Lane JI, Carlson ML. Rising incidence of sporadic vestibular schwannoma: true biological shift versus simply greater detection. *Otol Neurotol.* 2020;41(6):813–847.
7. Propp JM, McCarthy BJ, Davis FG, Preston-Martin S. Descriptive epidemiology of vestibular schwannomas. *Neuro Oncol.* 2006;8(1):1–11.
8. Zheng S, Cherniack AD, Dewal N, et al.; Cancer Genome Atlas Research Network. Comprehensive pan-genomic characterization of adrenocortical carcinoma. *Cancer Cell.* 2016;29(5):723–736.
9. Hoffman RM, Stone SN, Espey D, Potosky AL. Differences between men with screening-detected versus clinically diagnosed prostate cancers in the USA. *BMC Cancer.* 2005;5:27.
10. Tiwari RC, Clegg LX, Zou Z. Efficient interval estimation for age-adjusted cancer rates. *Stat Methods Med Res.* 2006;15(6):547–569.
11. McCarthy BJ, Kruchko C, Dolecek TA. The impact of the Benign Brain Tumor Cancer Registries Amendment Act (Public Law 107–260) on nonmalignant brain and central nervous system tumor incidence trends. *J Registry Manag.* 2013;40(1):32–35.
12. Carlson ML, Habermann EB, Wagie AE, et al. The changing landscape of vestibular schwannoma management in the united states—a shift toward conservatism. *Otolaryngol Head Neck Surg.* 2015;153(3):440–446.
13. Torres Maldonado S, Naples JG, Fathy R, et al. Recent trends in vestibular schwannoma management: an 11-year analysis of the National cancer database. *Otolaryngol Head Neck Surg.* 2019;161(1):137–143.
14. Hexter AT, Evans DG. The genetics of vestibular schwannoma. *Curr Otorhinolaryngol Rep.* 2014;2:226–234.
15. Woods R, Friedman JM, Evans DG, Baser ME, Joe H. Exploring the "two-hit hypothesis" in NF2: tests of two-hit and three-hit models of vestibular schwannoma development. *Genet Epidemiol.* 2003;24(4):265–272.
16. Paldor I, Chen AS, Kaye AH. Growth rate of vestibular schwannoma. *J Clin Neurosci.* 2016;32:1–8.
17. Miller LE, Brant JA, Chen J, Kaufman AC, Ruckenstein MJ. Hearing and quality of life over time in vestibular schwannoma patients: observation compared to stereotactic radiosurgery. *Otol Neurotol.* 2019;40(8):1094–1100.
18. Johansson JE, Andrén O, Andersson SO, et al. Natural history of early, localized prostate cancer. *JAMA.* 2004;291(22):2713–2719.
19. Deberge S, Meyer A, Le Pabic E, Peigne L, Morandi X, Godey B. Quality of life in the management of small vestibular schwannomas: observation, radiotherapy and microsurgery. *Clin Otolaryngol.* 2018;43(6):1478–1486.
20. Boari N, Bailo M, Gagliardi F, et al. Gamma Knife radiosurgery for vestibular schwannoma: clinical results at long-term follow-up in a series of 379 patients. *J Neurosurg.* 2014;121(Suppl):123–142.
21. Mahboubi H, Sahyouni R, Moshtaghi O, et al. CyberKnife for treatment of vestibular schwannoma: a meta-analysis. *Otolaryngol Head Neck Surg.* 2017;157(1):7–15.
22. Roos DE, Potter AE, Zacest AC. Hearing preservation after low dose linac radiosurgery for acoustic neuroma depends on initial hearing and time. *Radiother Oncol.* 2011;101(3):420–424.
23. Johnson S, Kano H, Faramand A, et al. Predicting hearing outcomes before primary radiosurgery for vestibular schwannomas. *J Neurosurg.* 2019:1–7.
24. Schnurman Z, Golfinos JG, Epstein D, et al. Comparing costs of microsurgical resection and stereotactic radiosurgery for vestibular schwannoma. *J Neurosurg.* 2018;131(5):1–10.
25. Barnes CJ, Bush DA, Grove RI, Loredo LN, Slater JD. Fractionated proton beam therapy for acoustic neuromas: tumor control and hearing preservation. *Int J Part Ther.* 2018;4(4):28–36.
26. Fuss M, Salter BJ, Sadeghi A, Vollmer DG, Hevezi JM, Herman TS. Fractionated stereotactic intensity-modulated radiotherapy (FS-IMRT) for small acoustic neuromas. *Med Dosim.* 2002;27(2):147–154.
27. Parry DM, Eldridge R, Kaiser-Kupfer MI, Bouzas EA, Pikus A, Patronas N. Neurofibromatosis 2 (NF2): clinical characteristics of 63 affected individuals and clinical evidence for heterogeneity. *Am J Med Genet.* 1994;52(4):450–461.
28. Mautner VF, Lindenau M, Baser ME, et al. The neuroimaging and clinical spectrum of neurofibromatosis 2. *Neurosurgery.* 1996;38(5):880–885; discussion 885–886.
29. Evans DG, Lye R, Neary W, et al. Probability of bilateral disease in people presenting with a unilateral vestibular schwannoma. *J Neurol Neurosurg Psychiatry.* 1999;66(6):764–767.
30. Carlson ML, Marston AP, Glasgow AE, et al. Racial differences in vestibular schwannoma. *Laryngoscope.* 2016;126(9):2128–2133.
31. Clegg LX, Reichman ME, Hankey BF, et al. Quality of race, Hispanic ethnicity, and immigrant status in population-based cancer registry data: implications for health disparity studies. *Cancer Causes Control.* 2007;18(2):177–187.
32. Marinelli JP, Grossardt BR, Lohse CM, Carlson ML. Prevalence of sporadic vestibular schwannoma: reconciling temporal bone, radiologic, and population-based studies. *Otol Neurotol.* 2019;40(3):384–390.
33. Lin D, Hegarty JL, Fischbein NJ, Jackler RK. The prevalence of "incidental" acoustic neuroma. *Arch Otolaryngol Head Neck Surg.* 2005;131(3):241–244.