

Future of Testicular Germ Cell Tumor Incidence in the United States: Forecast Through 2026

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BACKGROUND: Testicular germ cell tumors (TGCTs) are rare tumors in the general population but are the most commonly occurring malignancy among males between ages 15 and 44 years in the United States (US). Although non-Hispanic whites (NHWs) have the highest incidence in the US, rates among Hispanics have increased the most in recent years. To forecast what these incidence rates may be in the future, an analysis of TGCT incidence in the Surveillance, Epidemiology, and End Results program and the National Program of Cancer Registries was conducted. **METHODS:** TGCT incidence data among males ages 15 to 59 years for the years 1999 to 2012 were obtained from 39 US cancer registries. Incidence rates through 2026 were forecast using age-period-cohort models stratified by race/ethnicity, histology (seminoma, nonseminoma), and age. **RESULTS:** Between 1999 and 2012, TGCT incidence rates, both overall and by histology, were highest among NHWs, followed by Hispanics, Asian/Pacific Islanders, and non-Hispanic blacks. Between 2013 and 2026, rates among Hispanics were forecast to increase annually by 3.96% (95% confidence interval, 3.88%-4.03%), resulting in the highest rate of increase of any racial/ethnic group. By 2026, the highest TGCT rates in the US will be among Hispanics because of increases in both seminomas and nonseminomas. Rates among NHWs will slightly increase, whereas rates among other groups will slightly decrease. **CONCLUSIONS:** By 2026, Hispanics will have the highest rate of TGCT of any racial/ethnic group in the US because of the rising incidence among recent birth cohorts. Reasons for the increase in younger Hispanics merit further exploration. **Cancer 2017;000:000-000.** Published 2017. This article is a U.S. Government work and is in the public domain in the USA.

KEYWORDS: Incidence, ethnic groups, North American Association of Central Cancer Registries (NAACCR), testicular cancer, testicular germ cell tumor (TGCT), trends.

INTRODUCTION

Testicular germ cell tumors (TGCTs) are rare tumors in the general population, but are the most common malignancy among men between ages 15 and 44 years in the United States (US).¹ TGCTs are histologically classified into 3 groups: seminomas, nonseminomas, and spermatocytic tumors. Seminomas and nonseminomas comprise 98% to 99% of all TGCTs and have a peak incidence at approximately ages 35 and 25 years, respectively. Spermatocytic tumors (before 2016 known as spermatocytic seminomas)² are very rare at all ages, accounting for only 1% or 2% of TGCTs, and have a peak incidence at age 55 years.

The incidence of TGCT has been rising in the US and in many other countries since at least the mid-20th century.^{1,3} Although non-Hispanic white (NHW) men have the highest incidence of TGCT, the rate of increase over time has slowed, whereas the incidence among Hispanics has increased.^{1,4,5} A previous study by our group examining data from the Surveillance, Epidemiology, and End Results (SEER) program and the National Program of Cancer Registries (NPCR) demonstrated that, between 1998 and 2011, the largest increase in TGCT incidence was experienced by Hispanics, followed by only a slight increase in rates among NHWs.⁵ Incidence rates also increased among Asian/Pacific Islander (A/PI) men, but the increase was not significant. Rates remained relatively stable among both non-Hispanic black (NHB) and American Indian/Alaska Native (AI/AN) men. Reasons for the increases in rates are not clear, because there are few well identified risk factors.⁶ However, previous studies have indicated that there is a significant birth-cohort effect on TGCT rates in many countries, such that rates are higher at all ages in each successive birth cohort.⁷⁻¹³ These effects are present for both seminomas and nonseminomas.

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In the 2010 US Census, Hispanics (16.3%) surpassed blacks (12.6%) as the largest minority group in the US.¹⁴ This shift in the US population, along with the significant increase in TGCTs among Hispanic men, suggests that the future profile of TGCTs might differ from the current profile. Thus, the objective of the current study was to forecast trends in TGCT incidence, taking into account heterogeneous birth-cohort effects, to determine whether incidence rates among Hispanics and men of other racial/ethnic backgrounds could approach the rates among NHWs in the US.

MATERIALS AND METHODS

Incident TGCT Data

Data for the current study were drawn from the Cancer Incidence in North America (CiNA) analytic file provided by the North American Association of Central Cancer Registries (NAACCR). Population-based cancer incidence data were obtained from NAACCR member registries, which are funded by the National Cancer Institute's SEER program and/or the Centers for Disease Control and Prevention's NPCR.¹⁵ Participating registries met NAACCR's data-quality criteria for the December 2014 submission cycle. Data for the years 1999 through 2012 from 39 registries were included. These registries cover approximately 84% of the US population. The CiNA analytic file dates back to 1995; however, because of missing data from many of the registries, we included data from 1999 through the most recent available year: 2012. Two data files were provided: 1) the CiNA analytic file for expanded races, and 2) the CiNA analytic file for the NAACCR Hispanic Origin Identification Algorithm (version 2).⁶ The first data file was used to obtain data on A/PI populations, and the second was used to obtain data on NHW, Hispanic (all races), and NHB populations. The NAACCR Hispanic/Latino Identification Algorithm (NHIA), version 2.2.1, uses a combination of NAACCR variables to directly or indirectly classify individuals as Hispanic/Latino for analytic purposes. The algorithm uses the following NAACCR standard variables: Spanish/Hispanic origin (item 190), name-last (item 2230), name-maiden (item 2390), birthplace (item 250), race 1 (item 160), sex (item 220), and Indian Health Service link (item 192).¹⁶

TGCT was defined using the International Classification of Diseases for Oncology (third edition) topography codes (C62) and morphology codes (seminoma: 9060/3-9062/3, 9064/3; nonseminoma: 9065/3-9102/3; spermatocytic tumors: 9063/3).¹⁷ Data on race, Hispanic

ethnicity, histology, year of diagnosis, and age at diagnosis were available for patients with TGCT. Incidence rates per 100,000 man-years, which were age-adjusted to the US 2000 standard population, and their 95% confidence intervals were calculated. Age-adjusted TGCT incidence rates were calculated for NHW, Hispanic (all races), NHB, and A/PI men. Small numbers of TGCTs among AI/AN men prevented their inclusion in the analysis. Similarly, spermatocytic tumors could not be analyzed because of small case counts.

Birth Cohort Analysis

To examine TGCT incidence by birth cohort, we used data from the SEER 9 registries for the years 1975 through 2012. The SEER program of the National Cancer Institute collects and publishes statistics from population-based cancer registries in the US.¹⁸ The SEER 9 registries cover approximately 9.5% of the US population and include cancer registries in Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah.

Population Data

National population projections were used to estimate future TGCT case counts and calculate the future TGCT burden (percent change in the numbers of cases). In December 2012, the US Census Bureau released the 2012 national population projections, which provide projected population estimates from July 1, 2012 to July 1, 2060, stratified by age (single years), sex, race, and Hispanic ethnicity. The population projections are based on the July 1, 2011 population estimates and include assumptions about future births, deaths, and net migration.¹⁹

Statistical Analysis

We evaluated temporal trends in TGCT incidence using age-period-cohort (APC) models. A detailed description of our forecasting model was previously described.²⁰⁻²² In brief, the expected rate is a product of the age incidence, in a reference cohort, times the cohort relative risk, where the relative risk of future cohorts is obtained by extrapolating the last segment of the joinpoint analysis of the observed cohort relative risk.^{20,23} Specifically, given data for men ages 15 to 59 years in calendar years 1999 through 2012, the observed cohorts are the cohorts born between 1940 and 1997; and the future cohorts, whose experience must be projected in forecasts, are the cohorts born between 1998 and 2011. APC models are complicated by the nonidentifiability issue. Age, period, and cohort metrics are interconnected such that 2 of the 3 factors coexist

TABLE 1. Age-Standardized Testicular Germ Cell Tumor Incidence Rates per 100,000 Man-Years and Burden Through 2026 by Histologic Subtype and Race/Ethnicity

	1999 Rate ^a	2012 Rate ^a	2013		2020		2026		2013-2026 Burden, % Change ^b	Estimated Annual Percent Change	
			Count	Rate	Count	Rate	Count	Rate		1999-2012	2013-2026
All TGCTs											
All men	7.97	8.37	8053	8.60	8936	9.21	9976	9.98	23.88	0.38	1.17
Non-Hispanic whites	9.84	10.51	6037	10.66	6018	10.83	5950	10.86	-1.44	0.45	0.15
Hispanics (all races)	5.30	6.76	1337	7.47	1992	9.68	2862	12.41	114.06	2.10	3.96
Non-Hispanic blacks	1.97	2.25	269	2.14	271	2.00	267	1.83	-0.74	0.20	-1.12
Asian/Pacific Islanders	2.98	3.04	212	3.25	231	3.10	242	3.00	14.15	0.48	-0.46
Seminoma											
All men	4.87	4.75	4385	4.80	4553	4.81	4816	4.90	9.83	-0.20	0.18
Non-Hispanic whites	5.96	5.97	3387	6.03	3152	5.76	2862	5.28	-15.50	-0.01	-1.00
Hispanics (all races)	3.16	3.68	637	3.78	876	4.46	1167	5.27	83.20	1.15	2.58
Non-Hispanic blacks	1.35	1.49	176	1.44	161	1.25	143	1.03	-18.75	0.12	-2.39
Asian/Pacific Islanders	1.82	1.98	123	1.92	136	1.88	148	1.85	20.33	-0.21	-0.27
Nonseminoma											
All men	3.08	3.60	3621	3.75	4160	4.18	4728	4.66	30.57	1.25	1.69
Non-Hispanic whites	3.85	4.53	2617	4.57	2645	4.69	2594	4.70	-0.88	1.17	0.22
Hispanics (all races)	2.35	3.25	709	3.77	1068	5.02	1532	6.47	116.08	2.98	4.21
Non-Hispanic blacks	0.69	0.96	120	0.90	126	0.88	129	0.84	7.50	0.47	-0.45
Asian/Pacific Islanders	1.69	1.37	110	1.66	130	1.74	159	1.94	44.55	0.31	1.49

Abbreviation: TGCTs, testicular germ cell tumors.

^aThe numbers of patients with TGCTs for 1999 and 2012 are not provided, because they were based on Surveillance, Epidemiology, and End Results/National Program of Cancer Registries data and were not extrapolated to the entire US population.

^bBurden is defined as the percent change in the number of cases between 2013 and 2026 and is calculated using the formula ((2026 count - 2013 count) / (2013 count)) * 100).

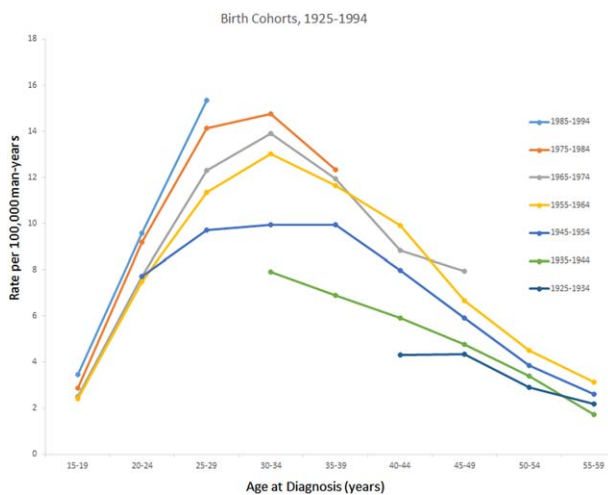


Figure 1. Age-standardized testicular germ cell tumor incidence rates are illustrated by decade of birth cohort and age at diagnosis (Surveillance, Epidemiology, and End Results 9 Registries, 1975-2013).

on the same time scale. The statistical strategy of restricted APC models does not overcome the nonidentifiability issue, but rather offers the ability to formally test for differences in 2 sets of incidence rates and derive estimable functions when age, period, and cohort are orthogonally derived into their linear and nonlinear components.

For each APC model, goodness of fit was evaluated based on the magnitude of the over-dispersion statistic, normality of residuals, and similarity between observed and fitted rates. Incidence rates were age-standardized per 100,000 man-years using the 2000 US standard population. To compute the burden, or the projected absolute number of new TGCT cases, we multiplied the projected incidence rates by age from the APC model by the projected population size from the US Census Bureau.²⁰ We also calculated estimated annual percentage changes (EAPC) for the observed rates from 1999 through 2012, the forecast rates from 2013 through 2026 rates, and the percent change in burden between 2013 and 2026. All analyses were conducted using MATLAB (version 14).

RESULTS

In this study, data were observed for 1999 through 2012 and were forecast for 2013 through 2026. In the observed period, TGCT incidence rates were highest among NHW men, followed in order by Hispanic, A/PI, and NHB men (Table 1). Rates for both seminomas and nonseminomas followed the same ranking. Among all men, temporal analyses revealed that the incidence of TGCT modestly increased during the observed period (EAPC₁₉₉₉₋₂₀₁₂ = 0.38%), and the increase is forecast to

continue during the next decade (EAPC₂₀₁₃₋₂₀₂₆ = 1.17%). The overall increase is being determined largely by nonseminoma, because rates of nonseminoma increased between 1999 and 2012 (EAPC₁₉₉₉₋₂₀₁₂ = 1.25%) and are forecast to continue to increase throughout the next decade (EAPC₂₀₁₃₋₂₀₂₆ = 1.69%). In contrast, rates of seminoma between 1999 and 2012 changed little (EAPC₁₉₉₉₋₂₀₁₂ = -0.20%) and are forecast to remain fairly stable (EAPC₂₀₁₃₋₂₀₂₆ = 0.18%). Similar to previous studies using APC models, we observed a birth cohort effect in TGCT incidence trends. Figure 1 illustrates incidence rates of TGCT by birth cohort. Incidence rates increased at all ages for each 10-year birth cohort between the 1925 to 1934 cohort and the 1985 to 1994 cohort (Fig. 1).

Table 1 also lists the observed and projected age-standardized incidence rates (per 100,000 man-years) by race/ethnicity. Although TGCT rates were highest among NHW men, the greatest increase in rates between 1999 and 2012 was experienced by Hispanic men (EAPC₁₉₉₉₋₂₀₁₂ = 2.10%) (Table 1, Fig. 2A). Rates increased slightly among A/PI men (EAPC₁₉₉₉₋₂₀₁₂ = 0.48%) and NHW men (EAPC₁₉₉₉₋₂₀₁₂ = 0.45%) and remained relatively stable among NHB men (EAPC₁₉₉₉₋₂₀₁₂ = 0.20%). Throughout the next decade, the largest increase in rates are forecast among Hispanic men (EAPC₂₀₁₃₋₂₀₂₆ = 3.96%), whose rates will surpass those among NHW men by 2026 (age-standardized rate [ASR]_{Hispanic, 2026} = 12.41 vs ASR_{non-Hispanic white, 2026} = 10.86). TGCT rates are forecast to remain relatively stable among NHW men (EAPC₂₀₁₃₋₂₀₂₆ = 0.15%) and to decrease modestly among NHB men (EAPC₂₀₁₃₋₂₀₂₆ = -1.12%) and A/PI men (EAPC₂₀₁₃₋₂₀₂₆ = -0.46%).

Among nonseminomas, the greatest increase in incidence is forecast among Hispanic men (EAPC₂₀₁₃₋₂₀₂₆ = 4.21%), whose rates will surpass the rates among NHW men by 2026 (ASR_{Hispanic, 2026} = 6.47 vs ASR_{non-Hispanic white, 2026} = 4.70) (Table 1, Fig. 2B). Nonseminoma rates are also forecast to increase among A/PI men (EAPC₂₀₁₃₋₂₀₂₆ = 1.49%), to remain relatively stable among NHW men (EAPC₂₀₁₃₋₂₀₂₆ = 0.22%), and to decrease among NHB men (EAPC₂₀₁₃₋₂₀₂₆ = -0.45%). Over the next decade, seminoma rates are forecast to increase only among Hispanic men (EAPC₂₀₁₃₋₂₀₂₆ = 2.58%), whose rates will equal those of NHW men by 2026 (ASR_{Hispanic, 2026} = 5.27 vs ASR_{non-Hispanic white, 2026} = 5.28) (Table 1, Fig. 2C). Seminoma rates are forecast to decrease among NHB men (EAPC₂₀₁₃₋₂₀₂₆ = -2.39%), NHW men (EAPC₂₀₁₃₋₂₀₂₆ = -1.00%), and A/PI men

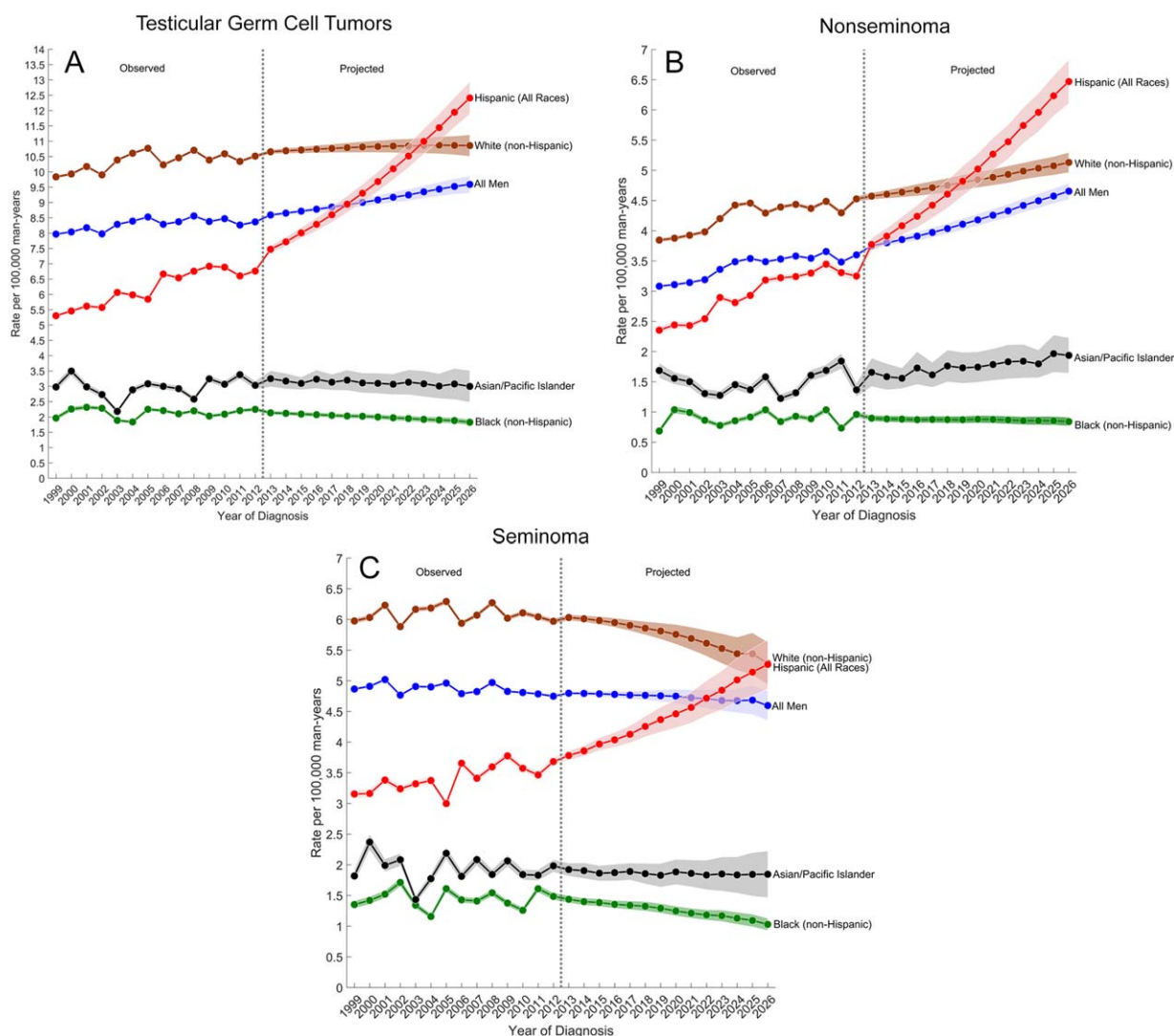


Figure 2. Observed (1999-2012) and projected (2013-2026), age-standardized incidence rates of (A) testicular germ cell tumors, (B) nonseminomas, and (C) seminomas are illustrated among non-Hispanic white men, Hispanic men (all races), non-Hispanic black man, Asian/Pacific Islander men, and all men (Surveillance, Epidemiology, and End Results/National Program of Cancer Registries data). Shaded bands indicate 95% confidence intervals.

($EAPC_{2013-2026} = -0.27\%$). The APC-based cohort rate ratios (Supporting Fig. 1; see online supporting information) depict an increasing cohort effect on both seminoma and nonseminoma rates among young Hispanic men born since 1975, reinforcing the increase in TGCT incidence rates among Hispanic men in our forecast models.

Although NHW men are forecast to have only the second highest rate of TGCT in the US by 2026, they will remain the largest racial/ethnic group in the country and thus will continue to have the greatest number of TGCTs. The largest percent increase in the number of TGCT cases from 2013 to 2026, however, will be among Hispanics (114.06%) (Table 1).

Figure 3 illustrates the observed and projected age-standardized incidence rates by age group for each TGCT histologic subtype. Overall, men ages 25 to 34 years have the highest incidence of TGCT and are forecast to have the greatest increase in rates throughout the next decade (Fig. 3A). Rates are second highest among men ages 35 to 44 years but are forecast to gradually decline over the next decade, whereas rates among men ages 15 to 24 years (third highest) are forecast to increase and reach the rates among those ages 35 to 44 years around 2026. The lowest rates are among men ages 45 to 59 years, and these rates are forecast to remain unchanged.

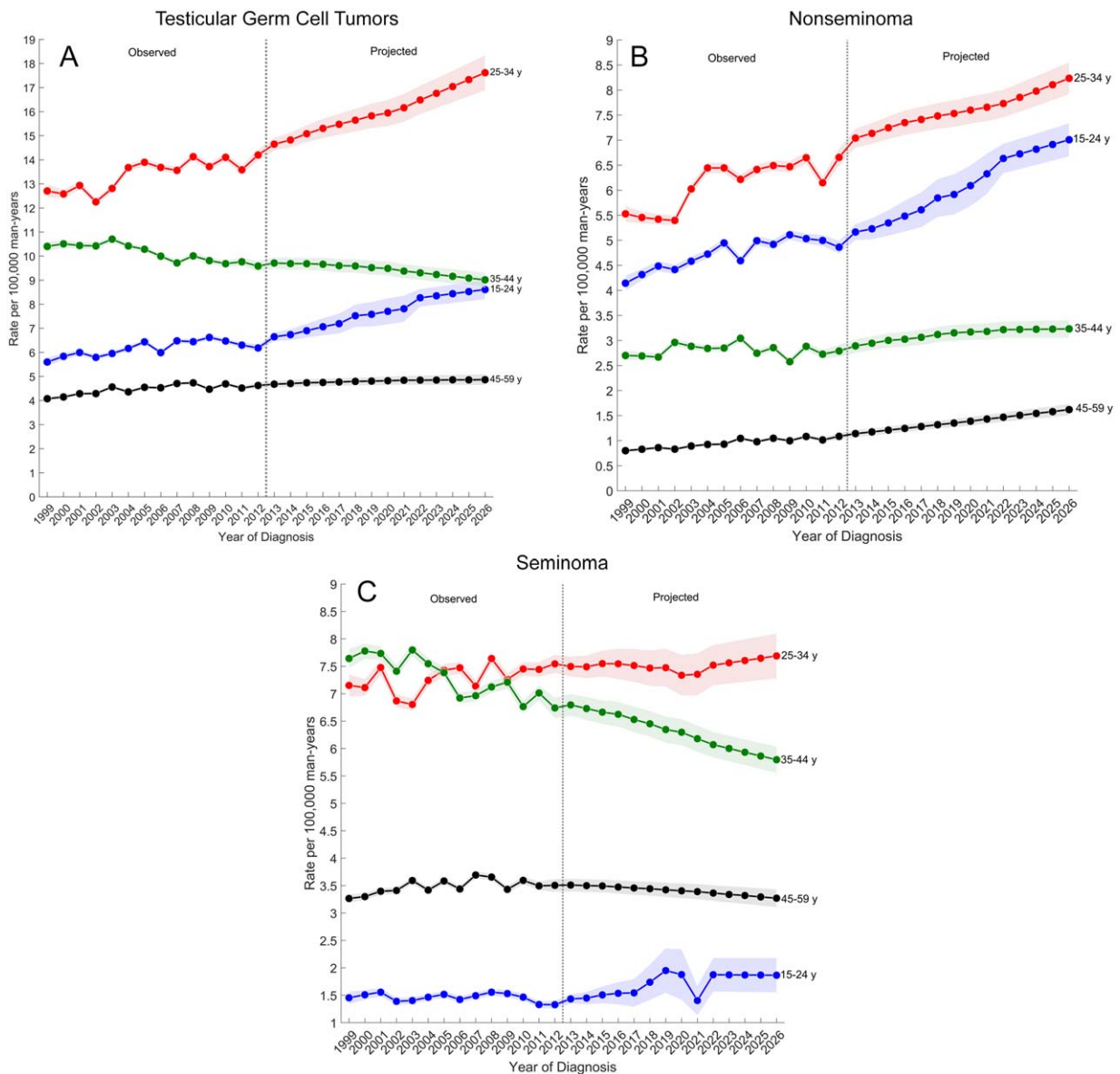


Figure 3. Observed (1999–2012) and projected (2013–2026), age-standardized incidence rates of (A) testicular germ cell tumors, (B) nonseminomas, and (C) seminomas are illustrated by age group (Surveillance, Epidemiology, and End Results/National Program of Cancer Registries data). Shaded bands indicate 95% confidence intervals.

Among nonseminomas (Fig. 3B), incidence rates were highest among men ages 25 to 34 years followed by men ages 15 to 24 years. Incidence rates for both age groups are forecast to increase over the next decade. Rates were lower among men ages 35 to 44 and 45 to 59 years and are forecast to increase modestly over the next decade. Among seminomas (Fig. 3C), incidence rates are highest for men ages 25 to 34 years, followed by those ages 35 to 44 years, and those ages 45 to 59 years, and rates were lowest among men ages 15 to 24 years. During the observed period, rates remained relatively unchanged among all

men except for men ages 35 to 44 years, whose rates decreased. Similarly, in the projected period, rates are forecast to decrease among men ages 35 to 44 years and are forecast to remain unchanged among all other men.

DISCUSSION

The current study indicated that, although NHW men had the highest incidence of TGCT between 1999 and 2012, the greatest increase in incidence was experienced by Hispanic men, who were the only racial/ethnic group to experience increases in both histologic subtypes. Over

the next decade, incidence rates among Hispanic men are forecast to continue to increase and surpass the rates among NHW men by 2026.

Overall, the increase in TGCT incidence was largely because of the increase in nonseminoma rates. Why there are differences in the rate patterns of nonseminomas and seminomas is unclear, because large differences in risk factors have not been identified.⁶ The only risk factor that has been consistently associated with one histologic subtype (nonseminoma) is marijuana use.²⁴⁻²⁷ The prevalence of marijuana use in the US has increased in the general population and among Hispanics.²⁸ Although it is possible that the positive association between marijuana use and nonseminoma could explain some of the increase in TGCT rates, this interpretation should be made with caution, because the existing studies on marijuana use and TGCT are limited in study design (all are case-control studies) and rely on self-reported data.²⁵⁻²⁷

It is unclear why there are differences in the risk of TGCT among different racial/ethnic groups in the US. Environmental risk factors for TGCT have not been well identified; the only well described risk factors for TGCT include a personal and family history of TGCT, cryptorchidism, hypospadias, and impaired spermatogenesis.⁶ The collection of these male reproductive disorders, termed the testicular dysgenesis syndrome (TDS), has been hypothesized to have a common in utero etiology.²⁹ Whether the prevalence of all TDS conditions varies by racial/ethnic group remains unknown. A prior study using data from the Collaborative Perinatal Project (CPP) indicated that white boys had higher rates of cryptorchidism than black boys.³⁰ The difference in cryptorchidism prevalence in the CPP, however, was far lower than the difference in TGCT incidence between white and black men in the US.³⁰

The notable disparity in TGCT risk by racial/ethnic group and the increased risk among first-degree relatives^{16,31-33} have supported the existence of a genetic component to TGCT susceptibility. Linkage studies have failed to identify a major gene effect^{34,35}; however, genome-wide association studies to date have identified 16 loci associated with TGCT susceptibility.³⁶⁻⁴¹ An examination of the allele distribution of the TGCT risk loci indicates that the distribution among Hispanic men is more similar to the distribution among European men than among men of low risk, such as Africans.⁴² In particular, the allele distribution of the major TGCT genome-wide association studies locus at *KITLG* (KIT ligand) is very similar among Hispanics (A allele, 17%; G allele, 83%) and Europeans (A allele, 20%; G allele, 80%) in

contrast to the distribution among Africans (A allele, 75%; G allele, 25%).⁴²

Genetic susceptibility to TGCT may explain some of the difference in rates observed by race/ethnicity; however, it cannot solely explain the steady increases observed in rates since the mid-20th century. These rapid increases in incidence suggest that environmental factors play an important role in etiology.⁴³ One such factor that has been widely hypothesized to be related to risk is maternal exposure to endocrine-disrupting chemicals.⁶ Although evidence suggests that endocrine-disrupting chemicals, such as p,p'-dichlorodiphenyldichloroethylene (DDE) and the chlordane-related compounds cis-nonachlor and trans-nonachlor, may be associated with TGCT risk, there is currently less evidence of their association with other TDS disorders.⁴⁴

Similar to findings from previous studies,^{1,5} the current study indicated that the most pronounced increase in TGCT incidence is among Hispanic men. The 2010 US census reported that the majority of Hispanics in the US are of Mexican ancestry (63.0%), followed by Puerto Rican (9.2%), Cuban (3.5%), Salvadoran (3.3%), Dominican (2.8%), and Guatemalan (2.1%) ancestries.⁴⁵ Estimated TGCT incidence rates in Mexico (2.8 per 100,000 man-years), Puerto Rico (3.1 per 100,000 man-years), Cuba (1.4 per 100,000 man-years), El Salvador (0.4 per 100,000 man-years), Dominican Republic (0.4 per 100,000 man-years), and Guatemala (0.6 per 100,000 man-years)⁴⁶ are variable, but all are lower than the rate among US Hispanics (3.9 per 100,000 man-years). A possible explanation for the higher rates observed among US Hispanics is that rates among Hispanics rise with migration to the US. Previous studies of migrants from countries with lower to higher rates have reported that changes in TGCT incidence do not occur among the first generation of migrants but rather among subsequent generations.^{47,48} Thus, it is possible that the increase in TGCT rates among the US Hispanic populations could be related to exposures that are present in the US but not in the home countries of individual persons who immigrate; however, information on migration status was not available from the SEER/NPCR registries.

As reported in previous studies,⁷⁻¹³ a significant birth cohort effect on TGCT incidence trends was evident in the current study. Originally identified by Moller¹³ when examining TGCT rates in Danish men, TGCT incidence was more strongly dependent on birth cohort than on calendar period. Although birth cohort effects in TGCT incidence trends have been widely documented, calendar period effects have also been reported.^{11,12,49-54}

A previous APC analysis of SEER data restricted to whites during 1973 through 2008 revealed that calendar period deviations were highly statistically significant for TGCT overall and for seminoma.¹² What is determining either birth cohort or calendar period effects, however, remains unclear.

Strengths of the current study were the use of population-based cancer registry data from 39 registries, which captured a large sample of the US population, and the use of novel APC models for forecasting incidence rates. Limitations include the inability to examine rates of spermatocytic tumors and to include AI/AN populations because of small case counts. In addition, the current study lacked information on place of birth and country-specific ancestry, which may be useful in examining hypotheses concerning environmental and genetic risk factors of TGCT. An additional limitation was the use of the NHIA algorithm for the identification of Hispanic ethnicity, because this could result in potential misclassification; however males are arguably less likely to be incorrectly classified.

The current study indicates that TGCT incidence is increasing most rapidly among US Hispanic men and is forecast to increase over the next decade. Reasons for the increase in rates and trends are unclear but could be related to various as yet unidentified exposures, place of birth, country of ancestry, and/or length of residence in the US. The increasing rates among Hispanic men suggest an area where future public health efforts should be targeted.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Armen A. Ghazarian: Conceptualization, methodology, software, formal analysis, investigation, data curation, writing—original draft, writing—review and editing, and visualization. **Scott P. Kelly:** Software, formal analysis, data curation, and writing—review and editing. **Sean F. Altekruze:** Software, validation, formal analysis, data curation, and writing—review and editing, supervision. **Philip S. Rosenberg:** Conceptualization, methodology, software, validation, formal analysis, data curation, writing—review and editing, and supervision. **Katherine A. McGlynn:** Conceptualization, methodology, validation, formal analysis, writing—review and editing, and supervision.

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