Am J Clin Exp Urol 2023;11(5):395-400
www.ajceu.us /ISSN:2330-1910/AJCEU0151448

Original Article

27-year trends in incidence rates for testis cancer across a large statewide registry

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Received May 26, 2023; Accepted August 15, 2023; Epub October 15, 2023; Published October 30, 2023

Abstract: Purpose: To review 27-years of testicular cancer (TC) incidence data (1990-2017) within the state of Pennsylvania to better define incidence, geographic distribution, and trends over time. Methods: The Pennsylvania Cancer Registry was reviewed for statewide and component county age-adjusted TC incidence rates and stage distribution. We reported annual percent changes (APCs) in age-adjusted rates. Maps plotting county-level incidence rates across the state in five-year time intervals were created. Results: In Pennsylvania, 9,933 TC cases were recorded between 1990-2017. Over two-thirds of patients were < 40 years of age and 95% were White. Approximately 89% presented as local and regional disease. Age-adjusted annual rates of total TC increased from 4.80 to 7.20 patients per 100,000 with an APC of 0.94 (95% Confidence Interval (CI) = (0.59, 1.29), P < 0.01) over the study interval. Annual rates of local disease increased from 3.20 to 5.00 patients per 100,000 with an APC of 1.07 (95% CI = (0.67, 1.46), P < 0.01). Annual rates of distant disease were stable and ranged from 0.50 to 0.80 patients per 100,000 with an APC of 0.69 (95% CI = (-0.02, 1.40), P = 0.06). Geospatial investigation noted increased incidence in urban centers. Conclusions: Although TC is rare, incidence is rising. Rates of TC in Pennsylvania almost doubled over the past two decades. Fortunately, this rising trend is primarily attributed to increases in local and regional disease. Counties with higher incidence rates cluster in urban centers which may reflect exposure risk, access to care, or reporting bias.

Keywords: Testicular cancer, epidemiology, statewide trends, diagnosis

Introduction

Testicular cancer (TC) is an uncommon malignancy most commonly seen in younger men with a peak incidence between 25 and 29 years of age. The disease remains highly curable with 5-year survival for all stages being 95%, although survival rates drop to 73% for distant disease, thereby highlighting the importance of early detection [1]. There are disparate TC incidence rates worldwide with rates in the United States (U.S.) being 5.9 patients per 100,000 compared to 7.2-8.7 patients per 100,000 in Europe (with significant variance between countries and within countries) [2].

Although the lifetime risk for men in the U.S. is 1 in 250 persons, the incidence is rising [1]. Specifically, over the past three decades, the TC incidence rates of White men increased from 4.0 men per 100,000 in the 1970s to 6.4 men per 100,000 in the early to mid-2000s. Fortunately, the death rate from TC has remained stable, currently at 0.3 deaths per 100,000 [1].

Cryptorchidism, tetrahydrocannabinol (THC), family history, and fetal estrogen exposure are known risk factors for TC [3]. In addition, studies report associations between TC and race and socioeconomic status, with disease more common among White men and men of higher socioeconomic status [4]. Although risk factors are known and can be mitigated in some cases, the worldwide incidence of TC has continued to increase [5]. Analyzing granular data from

Table 1. Characteristics of patients diagnosed with testis cancer in the Pennsylvania cancer registry from 1990 to 2017

Variables	Number of Cases (%)
Total cases	9933
Age	
0-40	6725 (67.7%)
40+	3208 (32.3%)
0-50	8687 (87.5%)
50+	1246 (12.5%)
Race	
White	9445 (95.1%)
Black	266 (2.7%)
Other/Unknown	222 (2.2%)
SEER stage	
Local	6756 (68.1%)
Regional	1900 (19.1%)
Distant	1097 (11.0%)

smaller geographic regions may help identify hotspots of disease with associated risk factors. More importantly, it may provide targetable locations for intervention.

Herein, we review 27 years of TC data within Pennsylvania to better understand incidence, trends, and staging of these cancers, and identify geographic "hot spots" with higher rates of disease.

Patients and methods

Study cohort

Through the Enterprised Data Dissemination Informatics Exchange (EDDIE), incidence rates of TC between 1990 and 2017 were extracted from the Pennsylvania Cancer Registry; https://www.health.pa.gov/topics/HealthStatistics/EDDIE/Pages/EDDIE.aspx. This study was IRB exempt as the de-identified data were obtained through the EDDIE database. No informed consent was obtained as the EDDIE database is publicly available.

The SEER Summary Staging system (*in situ*, local, regional, and distant) as recorded by the Pennsylvania Cancer Registry was used to report stage distribution across the cohort. In this staging system, *in situ* was defined as cancer that has not spread beyond the basement membrane of epithelial tissue involved, local as cancer confined to the organ of origin, regional as cancer extending beyond the original organ to nearby lymph nodes, organs, or tissues, and distant as cancer spread to distant organs or lymph nodes [6]. Classification of stage was based in stage of cancer at diagnosis. TNM system of classifying testicular cancer was not used in this study [7].

Statistical analysis

JoinPoint Trend Analysis software version 4.7.0.0 was used to compute Annual Percent Change (APC) values based on data downloaded from EDDIE [8]. Briefly, JoinPoint uses a Monte Carlo approach to identify the most parsimonious piecewise linear model for the data. In addition to the age-adjusted incidence rate, which was the dependent variable, the JoinPoint input included standard errors for the age-adjusted incidence rates; year was the dependent variable. Tumor stage was chosen as the "by" variable in order to fit separate piecewise linear models based on incidence rates for tumors classified as invasive, local, regional, and distant. For each tumor stage, the software identified the model with 0 joinpoints as being optimal. The log transformation option was selected in order to obtain 95% confidence intervals for the stage-specific APC values. R 4.0.5 software was used to produce cloropleth maps of county-level age-adjusted incidence rates in five-year intervals from 1993-1997 to 2013-2017 [9]. In particular, the tigris, sf, maps, and ggplot2 R packages were employed [10-13].

Results

Incidence of testicular cancer

A total of 9,933 cases of testicular cancer was recorded in the state of Pennsylvania from 1990-2017. The stage distribution as per SEER definition was as follows: local 68.1%, regional 19.1%, distant 11.0%, and unknown 1.8%. Of these cases, approximately two-thirds were under the age of 40 while 95% were White males. Further demographic and pathologic data for the cohort can be found in **Table 1**.

Trends of testicular cancer

Over the study interval, age-adjusted annual rates of total TC increased from 4.80 to 7.20

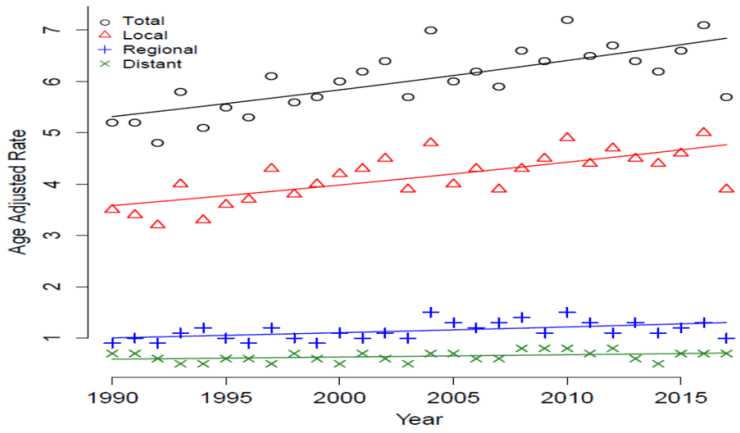

Figure 1. Stage-stratified age-adjusted rates of testicular cancer per 100,000 population, 1990-2017.

patients per 100,000 with an APC of 0.94 (95% Confidence Interval (CI) = (0.59, 1.29), P < 0.01). This increase was mainly driven by increases in age-adjusted rates for patients with local, regional, and distant disease. As seen in **Figure 1**, annual rates of local disease increased from 3.20 to 5.00 patients per 100,000 with an APC of 1.07% (95% CI = (0.67, 1.46), P < 0.01), while annual rates of regional staged disease increased from 0.90 to 1.50 patients per 100,000 with an APC of 0.97% (95% CI = (0.31, 1.63), P = 0.01). The annual rates of distant staged disease over this time period remained stable, ranging from 0.50 to 0.80 patients per 100,000 with an APC of 0.69% (95% CI = (-0.02, 1.40), P = 0.06).

County distribution of testicular cancer

Geospatial investigation of total age-adjusted TC incidence rates across Pennsylvania by county is shown in **Figure 2**. These choropleth maps show growing hot spots of testicular cancer incidence in the Northwestern, Southwestern, and Southeastern regions of Pennsylvania from five-year time increments starting in 1993-1997 to 2013-2017.

Discussion

Testicular cancer is a rare disease in Pennsylvania and the U.S. The incidence of TC in Pennsylvania is 7.8 men per 100,000, which is considerably higher than other states like New Mexico and Oklahoma, which have an incidence rate of 6.3 and 4.9 men per 100,000, respectively [14, 15]. Additionally, the testis cancer rate in Pennsylvania is significantly higher when compared to the national rate of 5.6 men per 100,000 [1]. Despite these slight variations, the survival rates remain favorable at greater than 90% [1, 2, 14].

Although TC is regarded as an uncommon malignancy, its incidence rate is increasing. Rates of TC in the state of Pennsylvania have increased over the past two decades from 4.2 per 100,000 men in 1990 to 7.8 per 100,000 men in 2017. This increase has also been observed nationally across the United States. From 1973 to 1977, the incidence rate of TC in White men was 4.0 per 100,000 population, which increased to 6.4 between 2003-2007 [3]. This increase was not only observed in White men, but also with African American men as well from 0.8 men per 100,000 between 1973-1977 to 1.1 between 2003-2007 [3]. The underlying cause for this rise in incidence remains unknown, although several environmental factors may be implicated as causative influences.

Tetrahydrocannabinol (THC) is a substance that has been most clearly associated with the development of TC. Daling *et al*. demonstrated a 70% increased risk of testicular germ cell tumors with current marijuana use, with an even greater risk for those with at least weekly use or those that began < 18 years of age [16]. Additionally, they noted that this association was found to be independent of other known risk factors, such as cryptorchism [16]. Other studies also demonstrated similar associations, particularly in those that begin marijuana at an early age (< 18-year-old) or those with more consistent usage (at least weekly usage) [17, 18]. Both Leydig and germ cells in the testicles possess cannabinoid receptors, but the extent to which these cells are involved in the pathogenesis of the TC has yet to be determined [19].

TC is primarily a disease that affects young males and is noted as the leading cause of cancer in this population of men. Our study revealed that more than two-thirds (67.7%) of TC patients were below the age of 40. Li *et al.* conducted a

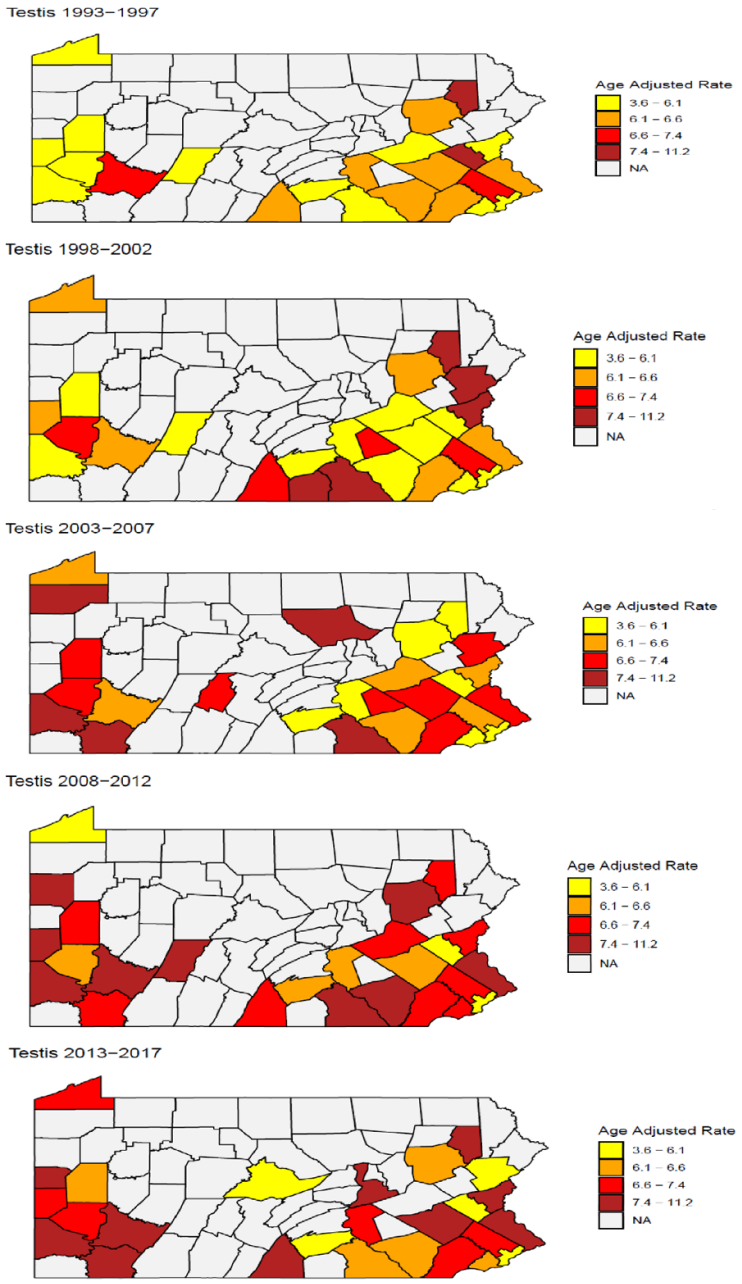

Figure 2. Age-adjusted testicular cancer incidence rates by county in 5-year intervals, 1993-2017.

study looking at the U.S. national incidence rates from 1973 to 2015, which showed that a similar rate of 68.4% were young men [4]. A study by Smith *et al*. concluded that the incidence of TC peaks between the ages of 25 and 29, with approximately 14.3 diagnosed cases per 100,000 men per year [3]. This data also coincides with an Oklahoma study, which showed that the 25-29 age group experienced the highest SEER and Oklahoma incidence rates of 11.4 and 13.5 men, respectively, per 100,000 when compared to any other age group [14].

White race has long been associated with TC [1-3, 20]. Our study continues to support this association with 95% of the TC patients in Pennsylvania identifying as White. When comparing incidence rates between 2014-2018, the U.S. national incidence rate of TC in White men was 7.0 per 100,000 population, which was significantly higher than the observed rates in Black and Hispanic populations (1.6 and 5.2 per 100,000 population, respectively) [21]. Li *et al*. also conducted a study looking at the racial differences in TC and demonstrated similar incidence rates [4]. Currently, the exact mechanism for this difference is largely unknown, though some studies have described an association between a single nucleotide polymorphism (SNP) and the development of TC [22]. This SNP affects the p53 binding site on the KITLG gene and is predominantly observed in people of European Caucasian descent [22]. It has been demonstrated to provide protection in light-skinned people from UV radiation, which could explain why this SNP is not commonly found in people of Black descent.

While we observed about two-thirds of cases with local disease, our study revealed that nearly one-third of all cases in Pennsylvania were regional (19.1%) or distant (11.0%). These results are similar to what was observed in Oklahoma, which demonstrated that 65.3% of cases were local while 17.2% and 11.7% of cases were classified as regional or distant, respectively [14]. Both states exhibit similar numbers when compared to the national data [1]. While the

percentage of local disease has increased, the rise in regional disease is of particular concern due to disease progression at diagnosis. Despite the rise in incidence of more advanced disease, the prognosis of TC remains excellent, likely secondary to advancement of multimodal treatment options.

In our study, wide variation was seen within the state. TC cases were more concentrated in the more urbanized Western and Eastern portions of the state, reaching up to an incidence of 11 men per 100,000 in some areas, compared most of the Central rural portion of Pennsylvania where some areas had less than an incidence of 3 men per 100,000. Our study used the patient's home address zip code to generate the distribution maps, instead of the treatment center zip code. Given this information, we believe that the lower incidence rates of TC in Central Pennsylvania are likely due to the rural nature of the area. Exposure to risk factors may vary, and access to healthcare and disease reported may be more limited compared to the urbanized Eastern and Western parts of the state.

As with any study, we understand that ours has limitations. Given our use of state- and nationwide registries, there is always the possibility of misclassification in stage reporting, as well as selection bias within the data collection. Additionally, there is no standardized pathologic review of these cases, so a unified diagnostic assessment of stage and diagnosis is not possible currently. Despite these limitations, this study provides important information regarding incidence and distribution of testis cancer. Additionally, it highlights the importance of future work regarding the underlying etiologies and mechanisms regarding the pathogenesis of TC.

Conclusion

TC incidence in the state of Pennsylvania has nearly doubled over the past two decades. While most of the disease remains localized, the number of regional cases has continued to increase. Geographic "hot spots" in more urbanized Eastern and Western portions of the state are likely related to greater access to healthcare in these areas compared to rural areas in Central Pennsylvania. Further studies related to etiologies and mechanism for this rise in incidence are still needed.

Disclosure of conflicts of interest

None.

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