



# Global Burden of Testicular Cancer and Its Risk Factors

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## Abstract

Testicular cancer (TC) is a rare cancer accounting for 5% of total urologic tumors. It occurs in distinct age groups of adolescents and young adults unlike other cancers peaking in the older age groups. About 95% of TC arises from germ cells. The histological classification of TC consists mainly of seminomas and nonseminomas. Based on GLOBOCAN 2022, the continent with the highest incidence rate was Europe (Age-adjusted rate-6.4), while Africa (0.59) had the lowest incidence. The highest mortality rates were estimated for Latin America and the Caribbean (0.58) followed by Europe (0.35) while the lowest was for the Asian continent (0.14). The highest prevalence of TC was in Europe followed by Oceania and Northern America, while Africa had the least prevalence of TC cases among all. A myriad of risk factors is associated with TC; Cryptorchidism is the strongest associated risk factor of TC increasing the risk by fivefold. Other risk factors identified include family history increasing the risk by four- to eightfold, increased adult height, infertility (1.6- to 2.8-fold), pesticide exposure (threefold), and gr/gr deletion (threefold). Clinically, TC generally presents as a painless scrotal swelling often mistaken as a hydrocele and the bulk of disease growing in the retroperitoneum can be asymptomatic even after growing to a huge size. This article aims to present the global burden of TC and also discusses its etiological risk factors.

## Keywords

- ▶ testicular cancer
- ▶ epidemiology
- ▶ GLOBOCAN
- ▶ etiology
- ▶ cryptorchidism

## Introduction

The burden of testicular cancer (TC) has doubled in the past 40 years. Coded as C62 as per the International Classification of Disease-Oncology-3rd Edition, it accounts for 5% of urologic tumors, globally.<sup>1-3</sup> Despite being rare, it is an important public health issue due to its impact on the quality of life in men.<sup>4</sup> Due to data scarcity, the epidemiology of TC is not explored to its full potential, unlike other cancer sites.<sup>5</sup> However, increased attention is required due to its grim

consequences affecting the quality of life in men due to treatment of TC such as cytotoxicity and cardiometabolic issues affecting the most productive years of adolescents and young adults.<sup>6</sup>

Depending on the cell type from which the cancer has originated, TC is divided into two types; those from the germ cells and the other arising from the nongerml cells of the testis.<sup>7</sup> Around 95% of TC arises from germ cells, while the remaining 5% arises from sex cord or stromal cells and miscellaneous nonspecific stromal cells.<sup>8</sup> Of these, 95% of

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testicular germ cell tumors (TGCTs) are further divided based on the histologic features into seminomas, nonseminomas, and spermatocyte seminomas.<sup>4</sup>

The burden of TC is observed to peak in the age group 15 to 40, thus it is predominantly regarded as the cancer of adolescents and young adults.<sup>5,6,9</sup> There is a lack of clear appearance of signs and symptoms of TC with the exception of a unilateral lump or painless swelling; detecting TC cases in the early stage is a challenge. This calls for a clear understanding of the etiology as well as the current epidemiology of TC. This article aims to add to the literature on TC emphasizing its epidemiology and etiology.

## Burden of Testicular Cancer

The current epidemiology of TC across continents is described in terms of incidence, mortality, prevalence, and survival. ►**Table 1** presents the burden of TC in different continents as per GLOBOCAN 2022.<sup>10</sup>

### Incidence and Mortality

Literature indicates an increasing incidence of TC worldwide.<sup>2</sup> There exists a geographical difference in the incidence of TC.<sup>11</sup> Based on GLOBOCAN 2022, a total of 72,040 incidence cases of cancer were recorded with a global incidence age-adjusted rate (AAR) for TC of 1.7 per 100,000 population. The continent of Europe has the highest incidence rate of TC with 6.4 per 100,000, followed by Northern America (5.5) and Oceania (5.5), Latin America, and the Caribbean (3.8), while the lowest incidence rates were estimated for Africa (0.59) and Asia (0.76).

Similarly, for mortality, a total of 9,068 deaths due to TC were estimated, with a global mortality AAR of 0.21. Though the overall death rate due to TC is low, of all the continents highest mortality of TC was noted for Latin America and the Caribbean (0.58), followed by Europe (0.35), Northern America (0.26), and Africa (0.23), while continents of Oceania (0.20) and Asia (0.14) recorded the lowest mortality rates for TC. The 5-year prevalence proportion for TC shows that there are 297,454 prevalent cases of TC with a global estimate of 7.5 cases per 100,000 proportions. The highest prevalence is in Europe (30.2), followed by Northern America (26.7),

Oceania (25.7), and Latin America (16.3), while the lowest were in Asia (3.0) and Africa (1.3).<sup>10</sup>

Based on the Human Development Index (HDI), which is defined as a summary measure of average achievement in key dimensions of human development of the country,<sup>12</sup> the highest burden is recorded in European and Nordic countries such as Norway, the Netherlands, Denmark, and Slovenia where the burden has doubled in past two decades, while the comparatively lower burden of TC is observed in the African and Asian countries belonging to comparatively lower and medium HDI, respectively.<sup>2,6</sup>

The incidence and mortality of TC across all continents is presented in ►**Figs. 1** and **2**.<sup>10</sup>

### Survival

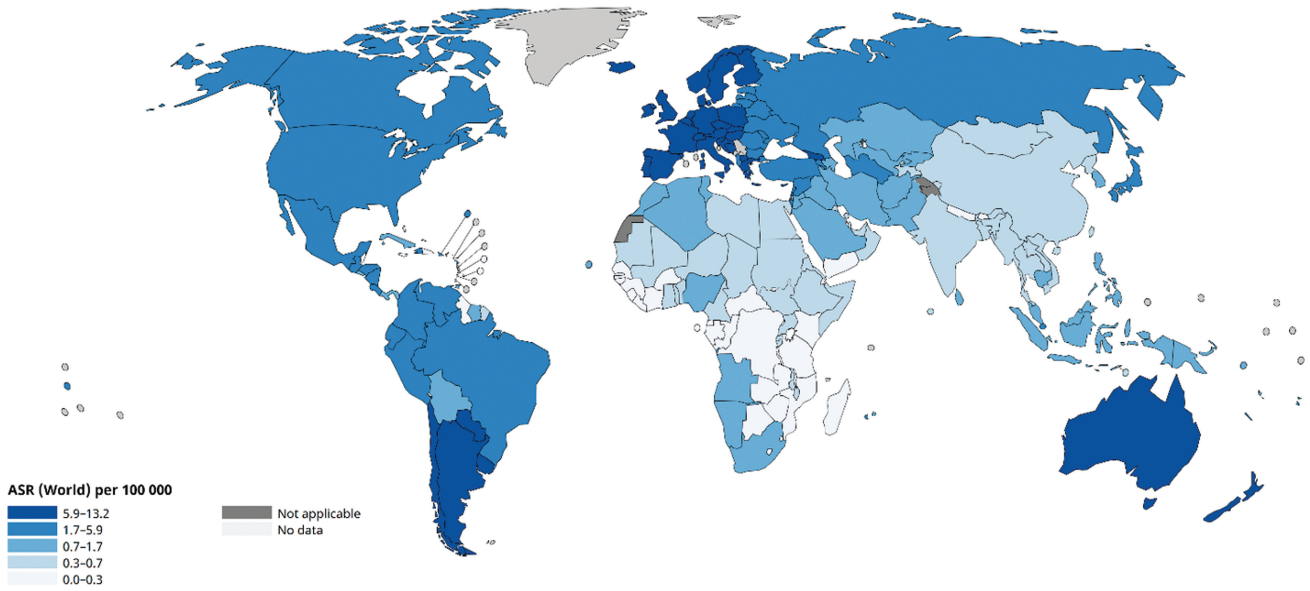
The data on the survival of TC is scarce. According to the Surveillance, Epidemiology and End Results organization, a very high 5-year overall survival rate of 95% was observed for all-stage TC and 99.2% for localized TC in the United States.<sup>2</sup> The increase in survival was attributed to the introduction of platinum-based chemotherapy regimens and guidelines to help standardize tumor management, thus increasing the 5-year survival rates from 63% to more than 90% during the last three decades.<sup>10,13</sup> Improved survival can also be attributed to increased awareness, wider use of ultrasonography at the primary level, and centralization of care and guidelines.<sup>14</sup>

### In the Context of Cancer Registries Represented in CI5 XII

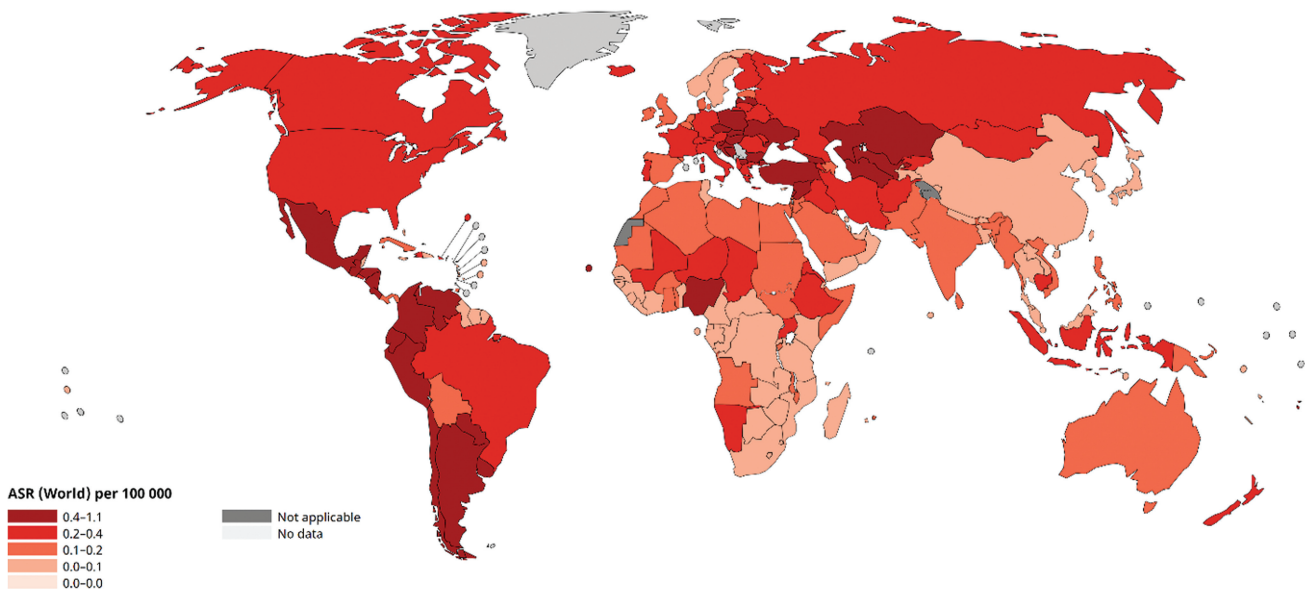
Based on the data from Cancer Incidence in Five Continents Volume XII, the range of incidence rates for TC in cancer registries from different continents is presented in ►**Table 2**. Of the total 589 cancer registries represented in CI5 XII, the cancer registry with the highest AAR for TC was the Chile, Valdivia Cancer Registry with AAR of 15.5 per 100,000 population. This registry belongs to the South, Central America and the Caribbean continent. The lowest incidence rate for TC was recorded in the Eldoret, Kenya registry in the African continent and the Nebraska Cancer Registry in the North American continent.<sup>15</sup>

**Table 1** Burden of testicular cancer in different continents as per GLOBOCAN 2022

Continents	Incidence		Mortality		Prevalence	
	Cases	AAR per 100,000	Deaths	AAR per 100,000	Previous cases	Proportion per 100,000
Africa	3,139	0.59	1,080	0.23	9,026	1.3
Latin America and Caribbean	13,650	3.8	2,103	0.58	53,322	16.3
North America	10,546	5.5	565	0.26	49,417	26.7
Asia	19,388	6.4	3,660	0.35	70,947	30.2
Europe	24,070	5.5	1,611	0.20	109,109	25.7
Oceania	1,247	0.76	49	0.14	5,633	3.0
Total	72,040	1.7	9,068	0.21	297,454	7.5



**Fig. 1** Age-standardized rate (world) per 100,000, incidence of testicular cancer as per GLOBOCAN 2022.



**Fig. 2** Age-standardized rate (World) per 100,000, mortality of testicular cancer as per GLOBOCAN 2022.

As per GLOBOCAN 2020, Chile reported the highest mortality for TC. A retrospective study based on a 41-year follow-up at a Chilean cancer institute noted that approximately 40% of the patients who were registered with TC as the cause of death had unspecific information in their death certificates, thus owing to the high burden of TC in Chile to the erroneous labeling of TC as the cause of death.<sup>16</sup>

**In Context of Indian Cancer Registries**

Of the 72,040 new incident cancer cases of TC (Age-standardized incidence rate [ASIR] 1.7 and Cum.risk: 0.13) recorded worldwide, India recorded 4,456 new cancer cases (ASIR: 0.57). By the year 2050, India is estimated to observe a 24.4% increase

in the proportion of TC cases, which is slightly higher than the estimated global increase of TC cases by 22.7%.<sup>10</sup>

Published data from the Indian cancer registries were used for the year 2013 to 2019 to understand the difference in the incidence rate of TC. The incidence rate was higher than the national rates in Wardha, Maharashtra (0.8), Trivandrum, Kerala (0.8), Dibrugarh, Assam (0.8), Bhopal, Madhya Pradesh (0.8), and New Delhi (0.7).

As per CI5 XII, the rates for seminomas germ cell tumors among Indian cancer registries ranged from 0.5 to < 0.1 per 100,000 with the highest recorded in Wardha (0.5), Trivandrum (0.4), Kamrup urban district (0.4), Barshi, Paranda, and Bhum (0.4), and lowest in Mizoram (< 0.1) cancer registry.

**Table 2** Testicular cancer incidence rates as per cancer registries represented in CI5 Volume XII

Continent	Number of registries represented in CI5	Range of testicular cancer incidence rate			
		High		Low	
		Name of registry	AAR	Name of registry	AAR
Africa	14	France, La Réunion	2.8	Kenya, Eldoret	0
America, Central and South, and Caribbean	27	Chile, Valdivia	15.5	Brazil, Recife	0.7
America, North	175	Canada, Yukon	13.2	USA, Nebraska: Black	0.3
Asia	230	Türkiye, Trabzon	6.3	China, Yiyuan County China, Yongkang City China, Yunmeng County	0.1
Europe	123	Switzerland, Graubünden Glarus	14.4	Russian Federation, Arkhangelsk	1.7
Oceania	20	Australia, Tasmania	9.9	USA, Hawaii: Filipino	1.9

Similarly, for nonseminomas, the rates ranged from 0.4 to < 0.1 per 100,000 with the highest recorded in Chandigarh (0.4), Bhopal (0.3), New Delhi (0.3), and Kollam (0.3), while lowest in Mizoram (< 0.1) cancer registry.<sup>15</sup>

Worldwide, 9,068 deaths (Age-standardized mortality rate [ASMR]: 0.21 per 100,000) have occurred due to TC. Of these, 1,050 deaths (ASMR: 0.14) were recorded in India. By the year 2050, India will observe a 45.5% increase in mortality, which is slightly higher than the 40% increased proportion estimated globally.<sup>10</sup> This increasing burden of mortality indicates focused attention towards early diagnosis, treatment, and survival of TC cases in the forthcoming decades.

For India, as per GLOBOCAN 2022, the prevalence of TC estimated for 5-year period is 2.0 proportion per 100,000 population.<sup>10</sup>

Globally, a wide variation is observed in the epidemiology of TC. The attribution of these variations can be to the differences in the environmental and genetic factors, health infrastructure such as diagnostics and treatment availability, as well as reporting infrastructure.<sup>14</sup>

The high burden in high HDI countries is a result of lifestyle factors as well as the robust diagnostic infrastructure availability, while declining mortality rates are attributed to improved treatment modalities. The global variation of TC is also associated with the HDI, gross domestic product, alcohol drinking, overweight, sedentary lifestyle, obesity, and hypercholesterolemia. Understanding the risk factors is of prime importance while understanding the overall epidemiology of TC.<sup>14</sup>

## Risk Factors of Testicular Cancer

There is a myriad of factors that contribute to the etiology of TC. These risk factors can be broadly divided into biological, lifestyle, genetic, and environmental factors.

### Biologic Factors

#### Cryptorchidism

Cryptorchidism, synonymous with un/maldescended testis is the most common congenital malignancy in males and is

diagnosed in approximately 1% of boys who reach 1 year of age. In this condition, the testis lies above the external inguinal ring either within the inguinal canal or within the abdomen.<sup>17-19</sup> The testes failing to descend normally in the scrotum elevates the local temperature, which is posited to be procarcinogenic. This in addition to the hormonal conditions predisposes to both cryptorchidism and TC. Among all the other risk factors, it is the most established and strongest risk factor associated with TC.<sup>20</sup> History of cryptorchidism is associated with an almost fourfold increased risk of developing TC (odds ratio [OR]: 3.99, 95% confidence interval [CI]: 2.80-5.71).<sup>21</sup> While men whose cryptorchidism was resolved before the age of 15 had reduced risk by twofold.<sup>22</sup> Other conditions being explored for their role in TC development include Down syndrome and Klinefelter syndrome.<sup>6</sup>

#### Age

The natural history of TC is seen to have a distinct age group peak for the disease, unlike other cancers presenting at older age. The risk disposition of TC is within the reproductive age group<sup>9</sup> of 20 to 35 years, while the older age peaks between 50 and 55 years.<sup>2,4,6</sup> A peak in the reproductive age group could be attributed to sex hormones (androgen levels) as well as high estrogen levels in utero.<sup>4,9</sup>

#### Family History

Familial risks for TC are among the highest of all cancers. However, data are limited for histological types of TC and possible familial associations of TC with other cancers.<sup>23</sup> Individuals whose fathers had TC were four to six times more likely to develop TC, this risk, however, almost doubled to 8 to 10 times if the brother had TC.<sup>6,24</sup>

#### Perinatal and Physical Factors

Studies have emphasized early exposure could be a potential risk factor. Though the majority of the studies present inconclusive results, the likely factors that contribute include low birth weight, maternal exposure to estrogen, maternal smoking, gestational weight gain, inguinal hernia, birth defects, and serum cholesterol levels.<sup>4,6,25</sup>

An increase in height was associated with an increased risk of TC in several studies.<sup>25–28</sup> A 5-cm increase in adult height was associated with a 3% increased risk of TC.<sup>26</sup> Controversial results about body mass index (BMI) exist<sup>4</sup>; however, majority of studies conclude that increased BMI increases the risk of TC.<sup>7,19</sup>

### Hormonal and Reproductive-Related Factors

A meta-analysis including eight studies from Western countries concluded that there was no significant association between vasectomy and the risk of TC (OR: 1.10, 95% CI: 0.95–1.30).<sup>29</sup> However, infertility in men increases the risk of TC by 1.6 to 2.8 times.<sup>24</sup>

A study found a nonsignificant inverse association between an increasing number of children fathered 5 years before diagnosis and risk of TC (OR per additional child 0.78, 95% CI: 0.58–1.04).<sup>30</sup>

### Lifestyle-Related Factors

#### Diet

Increased caloric intake was associated with a higher risk of TC, all types, especially nonseminoma cancer.<sup>19</sup> This particularly explains the high burden of TC in Scandinavian countries that have a higher intake of dairy products. Dairy in addition to fish and meat was also postulated to be the source of intake of organochlorines responsible for increased risk of TC.<sup>31</sup> Fruit and vegetable consumption is regarded to be protective against cancer in general, and hormone-related cancers in particular, by reducing the enterohepatic recirculation of estrogens.<sup>32</sup> Various studies in animals reported that cocoa and theobromine, the main stimulant of cocoa, exert toxic effects on the testis, inducing testicular atrophy and impaired sperm quality.<sup>33</sup>

#### Physical Activity

A recent meta-analysis of studies presents controversial and inconclusive results for physical activity (PA) and its effect on the risk of TC.<sup>14</sup> However, older studies have found moderate effects of PA on TC. The conflicting results on the relationship between PA and TC risk should not be taken as a lack of relation; further research using strict methodology is needed to get definitive findings.<sup>4</sup>

#### Occupational Factors

Literature comprised several studies on occupational exposures, potential carcinogens and their impact on TC risk. Exposures reported in most studies were of pesticides, textile dust, aliphatic, alicyclic hydrocarbons, organic solvents, endocrine disrupting factors such as polychlorinated biphenyls, organochlorines, nonionizing radiation, radiofrequency emitters, electrical machines, and high voltage lines. Exposure to organochlorine pesticides like cis-nonachlor, trans-nonachlor, and p,p'-dichlorodiphenyldichloroethylene was observed to cause an increasing risk of TGCTs with increasing concentration in blood. Relative risks were higher for seminoma than nonseminoma.<sup>4,27,34–37</sup>

Occupations assessed in the literature included agriculture work, gardening, chemical manufacturers, metal trimming, welding, industrial production of glue, railway traffic supervisors, firefighters, electrical engineers, and programmers. For police officers, a positive association was found with TC (OR = 1.31), which was mostly attributed to hand-held radar<sup>38</sup>; however, a similar study among military personnel had inconclusive results.<sup>4</sup> Similarly, regarding the use of cellular and cordless telephones, no increased risk of TC was reported<sup>39</sup> Among farmers, the risk of TC due to pesticides increased by threefold, with organochlorines responsible for the catapulted risk.<sup>33</sup> Understanding the exposures is important due to their potential to influence the risk of TC by interfering with the hormonal pathways of the body.

#### Social and Behavioral Factors

Recent literature have shared findings of increased risk of TC among individuals belonging to low-income group. For diagnosis, lower levels of education and SES are risk factors for later stage TC diagnosis and hence higher TC mortality.<sup>25</sup> The behavioral factor for TC risk encircles the consumption of alcohol and substance use. A meta-analysis stated 62% increased odds of developing TC due to cannabis use. These studies are mainly conducted in developed countries.<sup>40,41</sup>

#### Genetic and Environmental Factors

The presence of the “gr/gr” deletion in the Y chromosome was associated with a twofold increased risk of TGCT (OR: 2.1, 95% CI: 1.3–3.6,  $p = 0.005$ ), and a threefold increased risk among patients with a family history of TC (OR: 3.2, 95% CI: 1.5–6.7,  $p = 0.0027$ ). The gr/gr deletion was more strongly associated with seminoma (OR: 3.0, 95% CI: 1.6–5.4,  $p = 0.0004$ ) than with nonseminoma.<sup>42</sup> The rarity of the condition of TC is attributed to the lack of reliable studies with large samples to confirm the genetic background and its role in TC. Though the role of genetics is undeniable, large-scale studies providing clear evidence are required to comprehend the role of genetics in the development of TC.<sup>4</sup>

Environmental exposures to toxins through industrialization contribute majorly to the increased risk of TC. The testicles' anatomical placement in the scrotum may be crucial in the development of cancer since they are mostly exposed to environmental pollutants such as intense heat,  $\gamma$ -radiation, and electromagnetic fields.<sup>43,44</sup> The environmental genotoxins majorly consist of endocrine disruption with estrogenic, antiandrogenic, and mixed estrogenic antiandrogenic properties,<sup>45</sup> organochlorines, and polychlorinated biphenyls, these derivatives are similar to those found in pesticides.

Testicular dysgenesis syndrome (TDS) comprises hypospadias, undescended testis, spermatogenesis, and TGCT. It has a common fetal origin attributed to the fetal androgen production deficiency in addition to the failure in normal differentiation of the fetal cells, similar to that of TC, thus TDS have been associated with TC.<sup>46,47</sup> However, there is a lack of detailed studies on the effect of TDS or one of its components



on the oncological outcomes of TC. The etiology of TDS and TC is linked to environmental exposures and genetic susceptibility.<sup>48</sup> Fetal exposures to “di-n-butyl phthalate” are the most likely to be responsible for TDS and TC.<sup>49,50</sup>

The majority of the environmental exposure evidence-based studies are conducted in small cohorts gauging mainly occupational exposure. Thus, large sample size-based studies are requisite to understand the environmental exposures and their impact on the risk of TC.

Anatomically, the testis is present outside the body and is prone to environmental temperature. Occupational exposure to extreme conditions has been demonstrated to significantly increase the risk of TGCT.<sup>51</sup> Temperature exposure at workplaces is hypothesized as a potential association with the increased risk of TC.<sup>52</sup>

The summarization of risk factors identified from the study is mentioned in ►Table 3.

**Table 3** Summary of identified risk factors

Risk factors identified	References
Cryptorchidism <sup>a</sup>	17–22
Age	2,4,6
Family history • TC in father and brother	6,23,24
Perinatal or maternal factors • Low birth weight, maternal exposure to estrogen, maternal smoking, gestational weight gain, inguinal hernia, birth defects, serum cholesterol levels	4,6,25
Physical features • Increased height, increased BMI	6,19,26–28
Hormonal or reproductive factors • Infertility, vasectomy (-), increasing sibship size (-)	4,9,24,29,30
Diet • Dairy products, cheese, cocoa, fruits, and vegetable (-)	19,32,33
Physical activity	14
Occupational factors • Pesticides, textile dust, aliphatic, alicyclic hydrocarbons, organic solvents, endocrine disrupting factors such as polychlorinated biphenyls, organochlorines, nonionizing radiation, radiofrequency emitters, electrical machines, and high voltage lines	4,27,33–39,52
Socioeconomic factors • Lower levels of education and socioeconomic position	25
Genetic factors	42
Environmental exposure • Extreme heat exposure, γ-radiation and electromagnetic fields, organochlorines, and polychlorinated biphenyls • Testicular dysgenesis	37,44–52

Abbreviations: BMI, body mass index; TC, Testicular cancer.

Note: (-) indicates an inverse risk of TC.

<sup>a</sup>Factors supported by strong evidence.

## Discussion

Considering the rarity of the condition and the distinct age group in which it occurs, that is, the reproductive age group consisting of adolescents and young adults affects productivity and incurs a financial burden on the country. The highest incidence has been observed in Central Europe (Denmark, Norway, and Germany) and generally in Caucasian populations of developed countries.<sup>53</sup> In addition to this, in low- and middle-income countries (LMICs) there is an increase in the proportion of cancer burden projected in the coming years, thus addressing the issue of TC is crucial.<sup>40</sup> Understanding the epidemiology of TC will help in resource allocation and developing health policies and diagnostic guidelines.

The first imaging modality that is recommended for examining the TC is scrotal ultrasonography. Orchiectomy serves as both a diagnostic and a therapeutic measure if a tumor is found. Platinum-based chemotherapy has revolutionized the treatment of TC and is considered a significant success in the area of oncology due to its high cure rate.<sup>24,40</sup> However, some studies emphasize the toxicity induced due to the treatment of TC and the compromised long-term quality of life.<sup>6,24</sup> Radiation and chemotherapy increases the risk of secondary malignancies and cytotoxicity. Survivors of TC have a fivefold increased risk of cardiovascular disease, metabolic syndrome, pulmonary toxicity, nephrotoxicity, and ototoxicity.<sup>54</sup> Thus, though the survival of TC has improved owing to the newer treatment regimens, the quality of life remains questionable.

### Indian Context of Testicular Cancer

Compared with those in Western nations, patients in India who have TGCTs typically present at an advanced stage and with a greater International Germ Cell Cancer Collaborative Group risk. Compared with the West, patients with TC had worse results in LMICs like India. The late-stage presentations with significant nodal disease load, numerous therapy discontinuations, dosage compromise, and scrotal orchiectomy are held responsible for this.<sup>40</sup> There is a need for improvement in the care provided for TC by implementing evidence-based management and prevention strategies, especially in LMICs; however, there exists a severe paucity of data with limited to no data available on demographic features, management, and outcomes.<sup>40</sup> Cancer registries are excellent tools to gauge and record the burden of cancer in any given geographical region.<sup>55,56</sup> India has a total of 52 population-based cancer registries and more than 250 hospital-based cancer registries.<sup>57,58</sup> These registries can be employed to understand the population-level pattern of TC and to study the clinical management of TC, thus improving the disease prognosis and quality of life of the patients.

The beneficial effects of centralization of care on the outcome of TC has been established. With the existing health policies in India, centralization of cancer care is difficult and that could be another reason for an inferior outcome seen here.<sup>59</sup>

## Conclusion

The current epidemiology of TC shows lower rates of TC in low HDI countries as compared with other high HDI countries. Developed countries are shielded with their robust health care system and newer and improved treatment regimens. Unfortunately, this is not the scenario in the health care systems of resource-constrained settings; therefore, reliance on preventive and early detection is the effective strategy to tackle the issue of TC. Since TC is a rare condition and data are scarce, efforts should be taken to maintain a proper database of cases that deals with the treatment and management of TC. This database can be employed to conduct several studies to understand the etiology and management of TC.

This study found that there are several risk factors related to studies of TC. However, the majority of the studies have been conducted on selected samples or small cohorts, thus yielding inconclusive results. An extensive approach that considers both biological and epidemiologic risk factors is required to precisely determine each person's risk of TC and, consequently, to tailor appropriate prevention and management strategies.<sup>4</sup> Therefore, understanding the epidemiology is essential to plan cancer management strategies. To accurately study the changes in incidence and outcomes of TC and all tumor types, the availability of high-quality cancer registry data is required.<sup>9</sup>

### Patient Consent

This a review article based on published literature, therefore patient consent was not required.

### Authors' Contributions

S.M.: Writing original draft, data curation, and visualization.

S.B.: Writing - review and editing, data curation, and visualization.

S.S.: Writing - review and editing, data curation, and visualization.

P.K.: Writing - review and editing.

G.P.: Writing - review and editing.

A.B.: Conceptualization, writing - review and editing, and supervision.

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### Conflict of Interest

None declared.

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