
The Epidemiology of Testicular Cancer

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Abstract: Testicular cancer is the most common neoplasm among young men aged 15–40 years. Overall, it is a rare malignancy and represents about 1% of the adult neoplasms and 5% of urological tumors. In 2020, the International Agency for Research of Cancer (IARC) recorded 74,458 new cases worldwide. Incidences vary greatly across the globe, ranging from 3 to 12 new cases per 100,000 males/per year in Western societies. In contrast, figures are very low in Asian and African countries. European White men seems to be more affected overall, independently of the country of residence and migration compared to other ethnicities. Incidence is increasing worldwide, and some countries, such as Slovenia and the Netherlands, registered a doubling of testicular cancer cases in the last two decades. Reasons are still unclear. Cryptorchidism (undescended testis), which increases the chances of developing testicular cancer by 3.7–7.5 times compared to the general male population, is the only risk factor unanimously recognized. Despite the increase in incidence, testicular cancer remains a relatively indolent disease with mortality figures substantially unchanged for over three decades.

Keywords: age-standardized rates of testicular cancer; cryptorchidism and testicular cancer; epidemiology of testicular cancer; incidence of testicular cancer; mortality from testicular cancer

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INTRODUCTION

Testicular cancer is classified into two main histopathological groups: germ cell and non-germ cell tumors. Germ cell tumor represents the vast majority with 90–95% of the total cases (1). For this reason, we often find that testicular germ cell tumor and testicular cancer are used as synonyms. Germ cell tumors can be grouped histologically into seminomas, nonseminomas, and spermatocytic seminomas and mixed (2). The peak ages of occurrence of nonseminomas are 25–29 years, and 35–39 years for seminomas (3). In contrast to other type germ cell malignancies, spermatocytic seminomas are generally less aggressive and do not appear to share common risk factors with seminomas and nonseminomas. They also have an older peak age of occurrence (50–54 years). Spermatocytic seminomas are extremely rare, comprising only 0.6% of all germ cell tumors, while seminomas comprise 56% and nonseminomas, 43% (1). The small percentage (2%) of testicular cancers that are not germ cell tumors include stromal tumors, such as Leydig cell and Sertoli cell tumors, as well other rare or poorly defined histologic sub-types.

Over the last five decades the incidence of testicular cancer has been increasing in the developed world, while mortality rates since 1970 have declined owing to major improvements in chemotherapeutic regimes (4). The latest data from SEER (Surveillance, Epidemiology, and End Results) Program recorded an overall survival of 95%. Survival figures range from 99% for localized disease to 73% for those affected by distant metastasis. In case of local involvement of nearby structures or lymph nodes, the survival rate is 96% (5).

RISK FACTORS

At present the prevailing hypothesis about testicular cancer is that the risk is mostly or solely determined prenatally or in utero. The only unanimously recognized risk factor is a congenital anomaly, Cryptorchidism (undescended testis), which increases the chances of developing testicular cancer by 3.7–7.5 times compared to the general male population (6). The other factors associated with increased risk are prior unilateral testicular cancer, family history of testicular cancer, and increased adult height. Of these, the highest relative risk is conferred by having a brother with testicular cancer, which increases an individual's risk by approximately 10-fold (7).

Multiple genomic studies have been performed with the aim of identifying genetic loci likely related to testicular cancer. These studies have identified six loci on four chromosomes that seem to be correlated to testicular cancer: 9q24 (*DMRT1*), 5q31 (*SPRY4*), 12p13 (*ATF7IP*), 6p21 (*BAK1*), 5p15 (*TERT*, *CLPTM1L*) and 12q21 (*KITLG*). The strongest association has been identified in a single-nucleotide polymorphisms in the 12q21 locus, which confer an increase in risk of cancer of approximately three-fold per affected allele. However, even among first-degree relatives of men with testicular cancer, these risk loci are estimated to account for a very minor 11% of the risk of developing testicular cancer in brothers and 16% of the risk in sons (8).

It is still unclear the cause or combination of factors causing the progressive increase in testicular cancer among mainly white men of European origins.

Few studies have in fact determined that this ethnicity is more likely to develop testicular cancer than black or Asian men living in the same geographic region (9). Moreover, white men have experienced the greatest increases in incidence throughout the late twentieth century than any other ethnic group. In a number of countries, analyses of testicular cancer incidence trends have found them to be more consistent with a birth-cohort effect than with a calendar-period effect (3). No environmental factors or diet habits have been identified as risk factor at present.

TESTICULAR CANCER AROUND THE GLOBE

Testicular cancer is the most common type of neoplasm among young men (aged 15–40 years) in many parts of the world (10). Overall, it represents 1% of adult neoplasms and 5% of urological tumors, with incidence ranging from 3 to 11 new cases per 100,000 males/per year in Western societies (1). In 2020, the highest incidence rates were recorded in the European Area with Norway, Slovenia, and Denmark occupying the first three positions (11). In contrast, incidence rates are very low in Asian and African countries. Testicular cancer is a rare disease. In 2020, the International Agency for Research of Cancer (IARC), recorded 74,458 new cases worldwide. Age standardized rates (ASR) vary significantly across the globe with the highest figures recorded in industrialized countries such as, Europe, North America, and Australia which collectively account for 49.6% (36852 cases) of the total cases (Figure 1). Numbers are particularly high in Europe, and it is worth noting that the Top 10 countries with highest cancer incidence are all European.

Even though it is the most common cancer diagnosed in men aged 15 to 35 years, the ASR peaks in men aged between 25 and 29, and 30 to 43 years (14.5 and 13.7 per 100,000 men from 2008 to 2012, respectively), with lower rates in older and younger age groups. However, testicular cancer can be still diagnosed at any age. Its incidence varies by ethnic group, with white men having higher age-adjusted incidence rates when compared with Afro-Americans and Hispanic population, 6.7 vs 1.5 vs 4.9 per 100,000 men respectively (5). Incidence has been increasing over the past decades in the United States and other Western countries for reasons that are still unknown. Turning our attention to cancer specific mortality, the SEER Program data show a very high 5-year overall survival rates of 95.0% for all stage cancers and 99.2% for localized to testis cancers (5).

North America

Testicular cancer is the most common cancer diagnosed in men between 15 and 35 years in the USA. In 2020, 10617 new cases of testicular cancer were recorded, which represented 14.3% of the total cases diagnosed worldwide (11). Its incidence seems to constantly increase. In 2015, ASR was reported to be 5.6 cases for 100,000 (11) while by 2019, it increased to 5.9 (5). A review from Khem et al (12) published in 2019 showed that between 1975 and 2015, there has been an annual percent change (APC) of +1.69 for localized cancers in men aged between 25 and 39 years. Previous studies using the USA SEER database have reported that the incidence of testicular germ cell tumors increased by 51% between 1973 and 1995 (13, 14). Those figures correlate with the IARC database which recorded

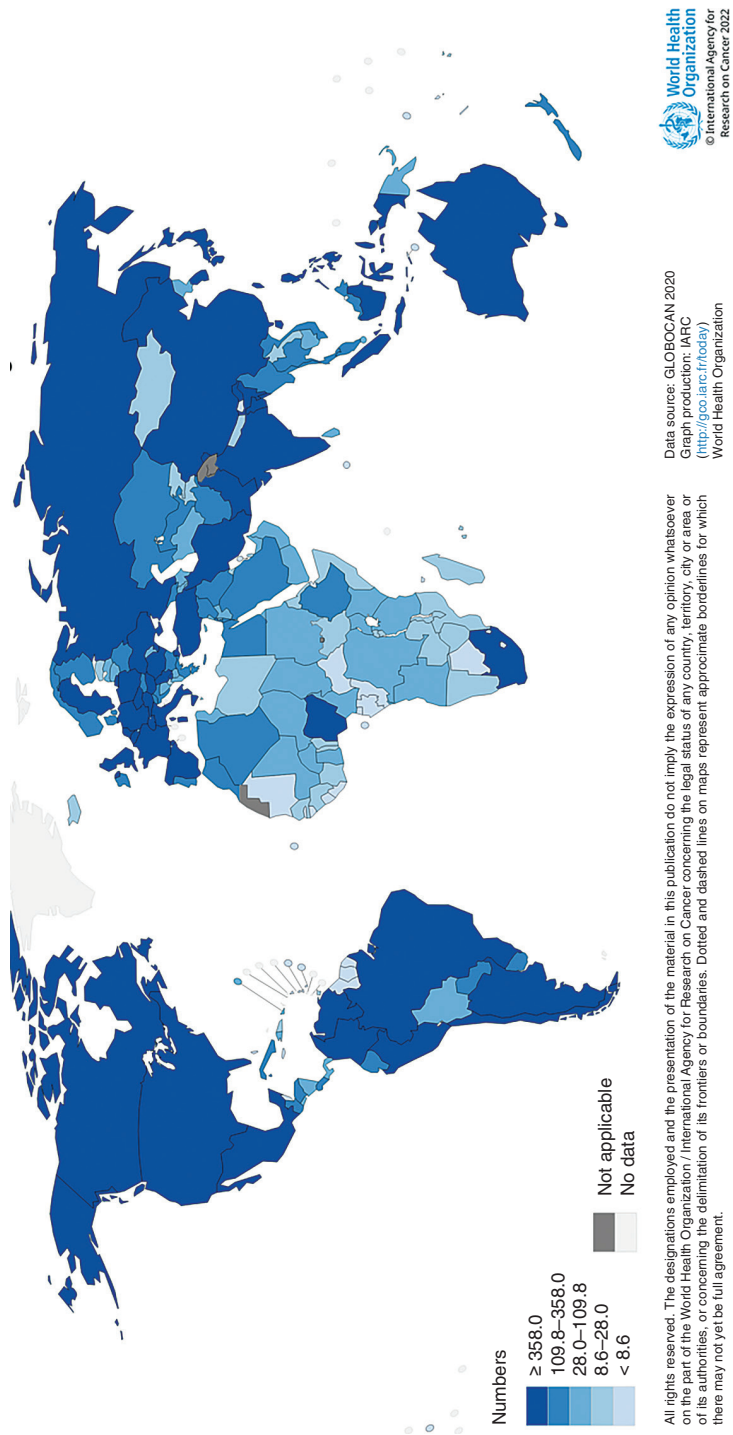
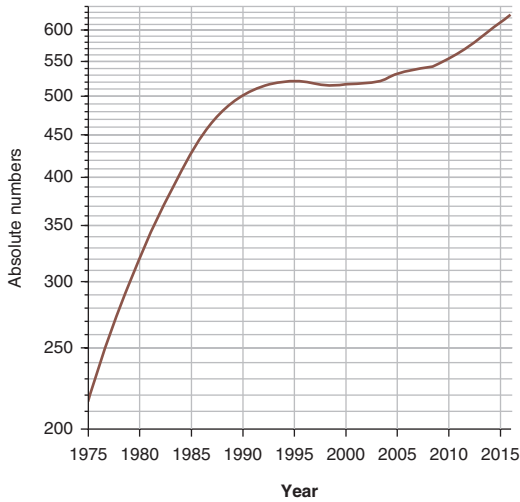


Figure 1. World map of estimated number of new testicular cancer cases in 2020 (11).



Rates are shown on a semi-log scale

Line are smoothed by the LOESS regression algorithm (bandwidth: 0.25)



Source: GLOBOCAN 2020. <https://gco.iarc.fr/today>

Figure 2. New cases diagnosed in the USA over the period 1975–2015.

220 cases in 1975, which increased to 414 in 1985, 497 in 1995, 533 in 2005 and 618 by 2016 (11) (Figure 2).

A study from Nigam et al. showed that over the period 1992–2009, 18,037 men were diagnosed with testicular cancer, of those, 10,661 (59%) were seminomas and 7376 (41%) were non-seminomas. Overall, ASR was the highest among White men (8.3 cases per 100,000 men), followed by Hispanic men (4.6 cases per 100,000 men), Asia/Pacific Islander men (API) (2.3 cases per 100,000 men), and Black men (1.5 cases per 100,000 men).

If we stratify the data in seminomas vs non-seminomas, we notice that for seminomas, the ASR for White men (5.0 cases per 100,000 men) was twice the Hispanic men (2.5 cases per 100,000 men), followed by Black men (1.0 cases per 100,000 men). In non-seminomas, the ASR for White men (3.3 cases per 100,000 men) was just slightly higher than in Hispanics (2.1 cases per 100,000 men) but almost 7 times higher than in Black men (0.5 cases per 100,000 men). Turning to mortality figures, according to SEER, by the end of 2022, 460 deaths are to be expected due to testicular cancer, which will represent the 0.1% of all cancer deaths. Trend in mortality has remained unchanged over the period 1992–2019 with a value of 0.3 death per 100,000. Over the period 2012–2018, the 5-year related survival was 95% for all cancer, and 99.2% for localized disease (5).

South America and the Caribbeans

Unfortunately, there is no comprehensive epidemiological literature on testicular cancer covering the South American countries. According to the IARC, Latin America and the Caribbeans recorded 13653 cases in 2020, which represented 18.3% of the total cases recorded worldwide. Brazil, Mexico, Argentina, and Colombia are the top four countries per incidence with 3388 (24.8%), 3337

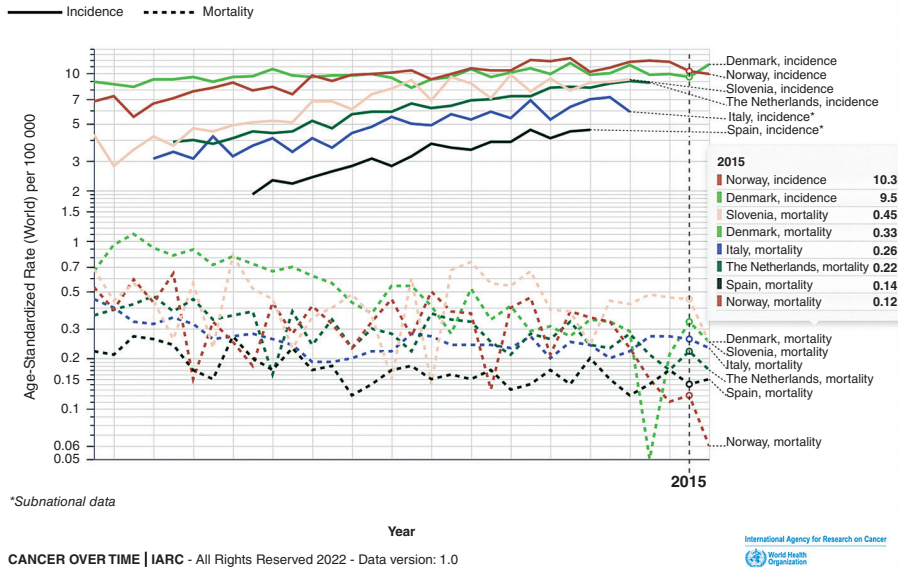
(24.4%), 2047 (15%), and 1369 (10%) cases, respectively. Looking at the ASR, Argentina occupies the top of the list with 8.7 cases per 100,000 men followed by Uruguay and Chile with an ASR of 8,1 and 7,6 cases per 100,000 men respectively. Those figures are among the highest worldwide. From the few publications available, the figures seem to be increasing over the last few decades. As shown by Shanmugalingam et al., the annual testicular cancer ASR in Colombia varied significantly during the period studied (1983–2002) with fluctuations in incidence observed from 1 to 3 per 100,000 men. This was mirrored in the changes in annual percent change +29.1% [1989–1992] and +10.8% [1995–2002]) although these were not significant. Overall, an annual increase in incidence rates of +2.3% was observed (1983–2002) (15).

Europe

With 25,058 new cancers in 2020, which represents the 33.7% of cases registered worldwide (11), Europe accounts for the highest testicular cancer figures recorded worldwide. Western Europe, with an ASR of 8.7 per 100,000 men, leads, followed by Northern Europe (7.2), Southern and Central, and Eastern Europe (5.9 and 3.2 cases per 100,000 men respectively). Looking at specific countries, Norway, Slovenia, and Denmark occupy the top three position in Europe (and worldwide) for incidence rates with 11.8, 10.8, and 10.4 cases per 100,000 men respectively. In Table 1 are shown the 10 countries with the highest incidence in Europe. A study published in 2014, that tried to predict what would be the ASR in Europe by 2025, reported almost 23,000 new cases of testicular cancer in Europe per year, a rise of almost 24% from the estimated 18,400 cases in 2005. As can be seen at the beginning of the paragraph these

TABLE 1		The top 10 countries with highest testicular cancer incidence	
IARC 2020	Top 10 Countries per testicular cancer incidence, worldwide		
Country	Cases*	ASR (Cases per 100.000 men)	Mortality Cases per 100.000 men)
Norway	343	11.8	0.15
Slovenia	114	10.8	0.22
Denmark	300	10.4	0.22
Germany	4503	10.0	0.27
The Netherlands	830	9.9	0.19
Croatia	192	9.6	0.58
Slovakia	263	9.5	0.71
Hungary	476	9.5	0.68
Switzerland	429	9.4	0.26
France	2752	9.0	0.34

GLOBOCAN 2020 (11). *Data are referred to 2020.



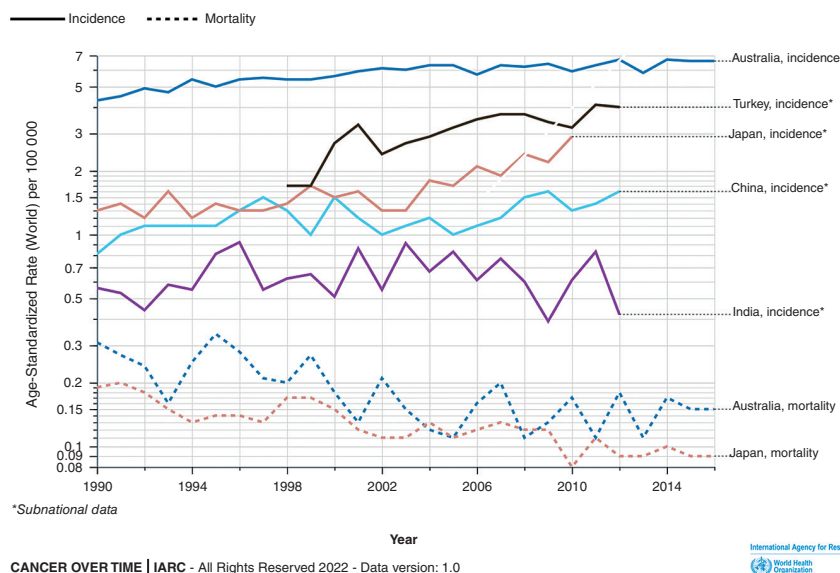
Source: GLOBOCAN 2020. <https://gco.iarc.fr/today>

Figure 3. Age-standardized rates and mortality for some of the European countries with highest testicular cancer incidence. Some trends are incomplete due to lack of data available. Period analyzed 2018-2016.

figures were significantly underestimated, considering that by 2020, we surpassed 25,000 confirmed cases. Figure 3 shows trends in ASR and mortality in some of the European Countries with the highest testicular cancer rates over a period of 18 years. As can be seen, nations such as Slovenia and the Netherlands have more than doubled their cancer incidence. The IARC Website does not allow comprehensive analysis of data that are more recent than 2016 (depending on country) but as we can see from Figure 3, by 2020, these figures increased further, reaching rates of almost 12 cases per 100,000 men in Denmark and almost 11 in Slovenia. In contrast, mortality, overall, seems either stable or decreasing as noted by Park et al. in 2018 (1).

Africa

The incidence of testicular cancer in Africa is among the lowest worldwide; however, it is highly likely to be underreported. It ranges between 0.3 and 0.6 cases per 100,000 (16). According to IARC, the African continent accounted for 3302 cases which represented the 4.4% of the total in 2020. Data from GLOBOCAN 2008 show relatively high mortality rates in Sub-Saharan countries like Mali, Ethiopia, Niger, and Malawi. Mortality rate has shown a reverse trend to its incidence with higher rates in low- and middle-income countries (0.5 per 100 000) than in high-income countries. However, in the absence of a national cancer registry, it is difficult to achieve the true incidence at a national level (16).



Source: GLOBOCAN 2020. <https://gco.iarc.fr/today>

Figure 4 Age standardized rates and mortality for some of the middle east, Asian countries, and Australia. Some trends are incomplete due to lack of data available. Period analyzed: 1990–2016.

Middle East and Asia

We have scanty data from Eastern countries. In 2020, 20651 cases of testicular cancer were reported in the whole of Asia and Middle East. The five countries with the highest figures are India, China, Japan, Turkey, and Indonesia with respectively 4638 (22.7%), 4502 (21.8%), 2458 (11.9%), 1605 (7.8%) and 1497 (7.2%) cases (11). ASR is generally low; Turkey leads with a reported ASR of 4 cases per 100,000 men followed by Japan and China with respectively 2.9 and 1.6 cases per 100,000 men recorded last in 2012 and 2010. China IARC figures seems to be higher than those reported by Pang et al. (17). Data were obtained from NCCR of China 2015 annual report. The overall incidence of testicular cancer was 0.46 cases per 100,000 men. Testicular cancer incidence were 0.53 cases per 100,000 men in urban and 0.39 cases per 100,000 men in rural areas (17). Trends seem to be following the rest of the globe with a progressive and steady increase of the cases year after year, with just few exceptions. Since 1990, countries such as Turkey, Japan, and China witnessed their cases doubling. In contrast, India has figures substantially unchanged (11) (Figure 4).

CONCLUSION

Testicular cancer is a rare malignancy representing only the 5% of all urological cancers. However, its incidence increases dramatically in specific age groups. It is the commonest cancer in young men between the ages of 15 and 40 years.

European white men seem to be the most affected and the overall incidence has been steadily increasing over the last 2–3 decades. Some countries such as Slovenia and the Netherlands witnessed their cases doubling over the same period of time. Unfortunately, the causes are still unclear. Very few risk factors have been identified at present. The only unanimously recognized risk factor is Cryptorchidism (undescended testis), which can increase the chances of developing testicular cancer by 3.7–7.5 times compared to the average population. Fortunately, despite the increase in incidence, testicular cancer remains a relatively indolent disease with mortality figures substantially unchanged for over three decades.

Conflict of Interest: The author declares no potential conflicts of interest with respect to research, authorship and/or publication of this article.

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