# Risk Factors for Testicular Cancer

Subjects: Primary Health Care

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A large piece of knowledge suggests that most testicular cancers originate from a potential noxa during fetal life. Nevertheless, the environment, familial history, ethnicity as well as diet and occupational exposures are other important actors involved in testis carcinogenesis.

testicular cancer risk factor genetics environment andrology urology

## 1. Introduction

Testicular cancer is the most common type of neoplasm among young men aged 15 to 40 years, representing 1% of adult neoplasms and 5% of urological tumors, reaching an incidence of 3–11 cases per 100,000 males per year in the Western world [1]. Although it is relatively rare, testicular cancer is an important public health concern due to its impact on the quality of life and reproductive function of affected men [2]. Early detection and treatment of testicular cancer are crucial to improve outcomes and death risk reduction [3]. In particular, testicular cancer represents a sort of unicity among cancers due to the possibility to be effectively treated with surgery and/or radiation therapy and presenting an overall excellent prognosis, with a >90% cure rate and >95% five-year survival rate, especially for early detected patients [4]. However, considering the lack of clear symptoms and signs in the early stages, with the exception of a unilateral lump or painless swelling, the early detection of the disease could be challenging [5]. This is the reason why understanding the risk factors associated with testicular cancer is crucial for early detection and treatment. The exact causes of testicular cancer are not well understood, but several risk factors have been identified, including age, cryptorchidism, abnormal testicle development, personal and familiar history of testicular cancer, ethnicity, and a weakened immune system [6]. Additionally, certain medical conditions, such as Klinefelter syndrome and Down syndrome, may also increase the risk of developing testicular cancer [7][8][9]. Considering the rarity of the condition, the relative ease of diagnosis due to the accessibility of the testis to imaging and clinical exploration, and the potential impairment to fertility related to the treatment, the role and the identification of risk factors in the development of testicular cancer still represent a topic of high clinical interest.

## 2. Etiology and Histopathology

Testicular cancer could derive from any cell type found in the testicles. Nevertheless, more than 95% of testicular cancers arise from germ cells, which are further divided, according to the histologic features, into seminomas, non-seminomas, and spermatocytic seminomas. The remaining 5% is represented by sex cord or stromal cell tumors as well as miscellaneous non-specific stromal cell tumors [10]. Interestingly, the incidence of testicular cancer does

not increase with age but instead presents a peak at 25–29 years for non-seminomas and 35–39 for seminomas [11][12]. Despite several environmental and hormonal factors that have been hypothesized to be related to testis carcinogenesis, nevertheless, the only factors clearly associated with testicular cancer are prior unilateral testicular cancer, family history of testicular cancer, and congenital anomalies such as cryptorchidism [13][14][15]. Germ cell tumors develop secondary to a tumorigenic event in utero, successively leading to an intratubular germ cell neoplasia, which is derived from gonocytes that failed to differentiate into spermatogonia. With the hormonal changes happening during puberty, these cells develop their invasive potential. Seminomas consist instead of transformed germ cells with a blocked differentiation. Finally, embryonal carcinoma cells are more similar to undifferentiated stem cells with a gene expression similar to those cells and intratubular germ cell malignancies. Stromal cell tumors, as well as sex cord and non-specific stromal tumors, have instead an extraembryonic/somatic differentiation [11][16].

Testicular cancer definitions are based on cell type derivation. According to the WHO, the histopathological classification comprises [17]:

- Germ cell tumors.
- Derived from Germ Cell neoplasia in situ (GCNIS): seminoma, embryonal carcinoma, yolk sac tumor (post-pubertal), trophoblastic tumors, teratoma, mixed germ cell tumors.
- Germ cell tumors unrelated to GCNIS: spermatocytic tumor, yolk sac tumor (pre-pubertal), mixed germ cell tumor (pre-pubertal).
- Sex cord/stromal: Leydig cell tumor, Sertoli cell tumor, granulosa cell tumor, thecoma, unclassified, gonadoblastoma.
- Miscellaneous non-specific tumors: ovarian epithelial tumors, tumors of the collecting ducts and rete testis, adenoma, carcinoma, adenomatoid tumor, mesothelioma, epididymal tumor, cystadenoma of the epididymis, papillary cystadenoma, mesenchymal tumor of the spermatic cord.

# 3. Epidemiological Risk Factors

## 3.1. Cryptorchidism

Cryptorchidism is the most common birth defect involving male genitalia and is characterized by the absence of at least one testicle from the scrotum, most commonly the right. Up to 80% of cryptorchid testes descend within the third month of life [18]. Nevertheless, about 10% of all cases of germ cell tumors occur in men with a history of cryptorchidism with the most accredited hypothesis related to the elevated temperature of the undescended testis, thus inhibiting the differentiation of spermatogonia and resulting in an arrest of spermatogenesis, germ cell depletion, and fibrosis. In addition, the altered position of the testis could alter the function of the somatic cells

forming the niche for spermatogonial stem cells' self-renewal and differentiation. The overall risk of developing testicular cancer in patients who were or are cryptorchid is 3.7–7.5 times higher than in the normal population [19][20].

## 3.2. Family History

Based on clinical observations and systematic investigations, it has been suggested that a family history of testicular cancer represents a major risk factor for this kind of cancer. In particular, it has been evaluated that there is a 3.1-fold increased relative risk for first-degree relatives of patients with testicular cancer, despite the fact that the age at presentation was not significantly different compared to patients without a familiar history of this cancer [21]. A proper familiar testicular cancer, i.e., two or more affected men in the same bloodline, is quite uncommon, although it has been estimated to occur in about 3% of families. Nevertheless, considering the rarity of the condition at the baseline, a genetic analysis is difficult and even when it has been performed, no cytogenetic abnormalities were found [22][23][24].

## 3.3. Maternal and Perinatal Factors

Considering the natural history of testicular cancer and the relatively young age at the diagnosis, exposure to risk factors during early life could be a part of the initial stages of carcinogenic transformation. Cryptorchidism represents the most obvious example. In particular, a recent meta-analysis suggested how low birth weight, perinatal inguinal hernia, and twinning, in addition to cryptorchidism, are associated with an increased risk of testicular cancer, reporting, respectively, an odds ratio (OR) of 1.34, 1.63, and 1.22 [25]. Another potential risk factor is associated with the age of the mother at conception. In particular, older ages of mothers at conception were associated with a reduced risk of testicular cancer (OR = 0.73), in addition to a relatively lower risk in men who had been breastfed for 6 months or more (OR = 0.63) [26]. These findings support the potential role of higher estrogen exposure in mothers as a potential risk factor for testicular cancer [27].

## 3.4. Age

As previously reported in the epidemiological data, the age distribution of testicular cancer presents a peak at the ages of 25–35 while a smaller peak is reported after 80 years of age. The peculiar age distribution of this cancer is mostly supposedly related to sex hormone activity. Nevertheless, testicular cancer is rare before age 15 [28]. Regarding testicular cancer in older men (>50 years), it has to be reported, however, that the most commonly occurring testicular malignancy is testicular lymphoma, often secondary to non-Hodgkin lymphoma, while the primary testicular lymphoma is rare and could have a different age range [29][30][31].

### 3.5. Ethnicity

Different research posed particular attention to the ethnic differences in testicular cancer, considering that the incidence of this disease largely varies among Caucasians, Hispanics, Asians, and African-Americans. In particular, as reported by Li et al., which analyzed the data of SEER (Surveillance, Epidemiology and End Results),

Caucasians reported the highest incidence rate (2.08:100,000), followed by Hispanics (1.19:100,000), Asians (0.60:100,000), and African-Americans (0.36:100,000) [32].

## 3.6. Hormonal Levels

Apart from the role of hormones during fetal life, little to no evidence is reported regarding the effects of sex hormones on testicular cancer. A 1997 study by Petridou et al., reported how patients with baldness reported a lower risk of testicular cancer, suggesting indirect evidence of the protective role of androgens regarding testicular cancer [33]. In particular, to support this hypothesis, a previous study by Depue et al. showed how a story of severe acne at puberty was inversely correlated with testicular cancer. Despite the likely relation of androgens to pubertal acne, it has not been conclusively established [34][35].

## 3.7. Age at Puberty

Several studies have reported a potential link between early puberty and increased risk of testicular cancer, although data are controversial [36]. It is known that patients with precocious puberty are at increased risk of Leydig cell tumors, a rare testicular tumor that could provoke a pseudo precocious puberty [37].

## 3.8. Body Mass Index

The association between body mass index (BMI) and testicular cancer is also controversial. Although height has been somewhat associated with an increased risk of germ cell testicular cancer in a 2002 study, no significant associations were found regarding BMI and weight. As stated by the authors, this data could be a proxy for energy intake during early life and therefore could be biased [38]. Conversely, a 2006 study by Bjørge et al. reported, on 1357 testicular cancers, a protective role of increased BMI, with overweight and obese men showing an OR of 0.89 and 0.83, respectively. Interestingly, the risk of testicular cancer was not associated with adolescent BMI [39].

## 3.9. Infections

The relation between infections and testicular cancer relies mostly on the response to chronic inflammation which is involved in several different steps leading to carcinogenesis. Inflammation cells such as macrophages and leukocytes produce, indeed, reactive oxygen and nitrogen species that could affect DNA integrity [40][41]. One of the first infections identified as a possible risk factor for testicular cancer is represented by HPV, as reported by Garolla et al. In particular, analyzing 155 testicular cancer patients, the prevalence of HPV infection in the semen was 9.5% compared to 2.4% in healthy controls [42].

## 3.10. Testicular Trauma

Testicular trauma has been included in the past as a potential risk factor for testicular cancer but its current role in testes carcinogenesis has been diminished [43]. Despite an initial elevated risk for testicular cancer in relation to the testis or groin trauma having been found, data were inconsistent and the hypothesis of an aetiologic role of testis

trauma in testicular cancer has not been supported [44]. It seems more plausible that a prior testis trauma could lead the patients to seek proper medical attention and, therefore, lead to the diagnosis of testicular cancer [45][46].

## 3.11. Smoking

Testicular cancer appears to have the least amount of data related to its relationship to cigarette and tobacco smoking. According to a study by Srivastava and Kreiger, a significant association was found between testicular cancer and smoking, in particular for those who smoked 12 to 24 pack-years, reporting an OR of 1.96 which could increase up to 2.31 [47].

## 3.12. Drugs

Differently from the exposure to tobacco smoke, the use of recreational drugs and, in particular cannabis, seems to be associated with an increased risk of testicular tumor. Compared to a never-user, the consumption of cannabis yields a twofold increase in developing testicular cancer, with an OR of 1.94 while the use of cocaine was negatively associated with this tumor (OR = 0.54) [48].

## 3.13. Physical Activity

The role of physical activity in testicular cancer represents another controversial factor. As reported by an old study, strenuous physical activity was associated with a moderate effect on the risk of testicular cancer, reporting an OR = 2.36 which increased to 2.58 for strenuous physical activity greater than five times a week [49]. Nevertheless, more recent evidence reported no association with testicular cancer, with a lack of internal consistency of the findings of prior studies [50][51]. As for other risk factors, a meta-analysis including thirteen studies permitted to clear the contrasting findings, reporting, indeed, no evidence of an association between physical activity and subsequent risk of testicular cancer. However, it has to be stated that the observational studies included in the meta-analysis had several limitations which could have affected the results and the heterogeneity of the findings.

## 3.14. Diet

Diet has been associated with testicular cancer in several older studies, with particular attention to the consumption of milk and dairy products. In a study crossing the data of the International Agency for Research on Cancer (IARC) and the Food and Agriculture Organization (FAO) on 42 countries, cheese was most correlated with the incidence of testicular cancer between 20 and 39 years, followed by animal fats and milk, reporting a correlation coefficient (r) of 0.804 when consumed at prepubertal ages and 0.654 when consumed after puberty [52]. In an effort to evaluate this correlation between dairy products and animal fats and testicular cancer, Walcott et al. conducted a hospital-based case-control study involving 159 patients and 136 matched controls, in order to explore, considering the potential influence of estrogens in testicular cancer, the relationship between dietary phytoestrogens and testicular cancer. Although a U-shaped pattern was observed for coumestrol (a natural organic compound acting as a phytoestrogen) and lignans (a large group of polyphenols found in plants), no consistent data was observed [53].

## 3.15. Heat

The role of testicular temperature and heat in testicular function is well known since the 1960s [54][55]. Starting from this evidence, researchers have investigated the possible association between increased testicular temperature and testicular carcinogenesis. To date, no relationship between these conditions has been found despite a potential role of extreme temperatures in the workplace leading to the hypothesis of a potential association with testicular cancer [56]. Similarly, no association was found between varicocele and testicular cancer [57].

### 3.16. Electromagnetic Fields

The effects of electromagnetic fields on testicular cancer, similar to other minor risk factors, are controversial. If 1990s studies reported a potential increased risk of testicular cancer for subjects professionally exposed to a magnetic field, more recent studies did not report an increased risk of testicular cancer even in subjects working near radar units, radiofrequency emitters, electrical machines, and high-voltage lines [58][59][60][61].

### 3.17. Occupational Risk Factors

Several occupational studies have investigated potential occupations with increased risk of testicular cancer, highlighting how some occupational exposure could also involve higher exposure to environmental factors for occupational purposes [62]. Plastic-related industries were initially associated with an increased risk for testicular cancer, particularly for those involving the production and manufacturing of polyvinyl chloride (PVC). Nevertheless, although a potential link with PVC was suggested due to the exposure to xenoestrogens–phthalates used in PVC which have estrogenic properties, no association was found [63][64]. Similarly, no association was found for other plastic components such as styrene and urethane [65]. Workers in metalworking industries, notwithstanding a heterogeneous range of occupations which makes it difficult to compare cohorts, reported an increased risk for testicular cancer among furnace workers (standardized incidence ratio [SIR] = 2.30), metal temperers (SIR = 5.85), watchmakers (SIR = 7.52), and precision toolmakers (SIR = 2.15) [66][67]. Similarly, paper workers reported an increased risk for testicular cancer (SIR = 7.4) [68]. Nevertheless, it could be possible that considering the high heterogeneity of workers, the retrospective nature of the studies and the presence of potential confounding factors (such as socio-economic status), the data obtained would be highly biased, albeit the effects of heavy metals and extreme temperatures are well known to alter the functionality of testis [69][70][71].

## 4. Genetic Risk Factors

Despite the lack of clear evidence supporting the genetic background of testicular cancer and the importance of environmental factors in contributing to the development of testicular cancer, the important and crucial role of genetics in the development and risk of testicular cancer is undeniable. Unfortunately, the lack of reliable studies, mostly limited by the rarity of the condition and, therefore, the difficulty in reaching a large sample size, represent one of the major challenges in unveiling the role of genetics in this disease. Starting from linkage studies, such as that of Crockford et al. which involved 237 pedigreed families with a history of testicular cancer, or that of Nathanson et al. which identified the chromosome Y AZFc region (with a gr/gr deletion) as a testicular cancer risk locus, yielding an OR of 3.2 and 2.1 in familial and sporadic testicular cancers respectively, six regions of interest

on chromosomes 2p23, 3p12, 3q26, 12p13-q21, 18q21-q23, and Xq27 were identified as susceptibility loci [23][72]. Other gene mutations associated with testicular cancer are those related to *KRAS* and *KIT*. The first encodes a GTPase that activates, among its downstream target, the MAPK and PI3K-AKT pathways. The hyperactivations of these pathways are however associated with the initiation of tumorigenesis in many cancers [73][74]. The second encodes a tyrosine kinase transmembrane receptor and its mutations are observed in up to 25% of seminoma cases [75]. Differently from other malignancies, testicular cancer is, however, a genetically complex and polygenic disease and multiple risk loci contribute to the testis carcinogenesis [76][77].

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