Epidemiology of and risk factors for testicular germ cell tumors

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INTRODUCTION

Germ cell tumors (GCTs) account for 95 percent of testicular cancers; they are divided evenly between seminomas and nonseminomatous GCTs. Testicular GCTs are rare prior to puberty [1].

Other testicular malignancies include sex cord-stromal tumors, including Leydig cell and Sertoli cell tumors, gonadoblastoma, and tumors of other cell types presenting in the testes such as lymphoma, carcinoid tumors, and metastatic carcinoma (table 1). (See "Anatomy and pathology of testicular tumors".)

Testicular tumors usually present as a nodule or painless swelling of one testicle, which may be noted incidentally by the patient or by his partner. Approximately 30 to 40 percent of patients complain of a dull ache or heavy sensation in the lower abdomen, perianal area, or scrotum, while acute pain is the presenting symptom in 10 percent. In another 10 percent, the presenting manifestations of testicular cancer are attributable to metastatic disease; symptoms vary with the site of metastasis. Approximately 5 percent have gynecomastia. (See "Clinical manifestations, diagnosis, and staging of testicular germ cell tumors" and "Clinical features, diagnosis, and evaluation of gynecomastia in adults".)

The presentation is different in Leydig cell tumors, which account for 2 percent of testicular tumors. Only 10 percent are malignant, and the clinical presentation is dominated by symptoms of excess estrogen and reduced testosterone [2-4]. There is a bimodal distribution of these tumors; they are found in 6- to 10-year-old boys who present with precocious puberty, and in

26- to 35-year-old men who present with a testicular mass, gynecomastia, impotence, and loss of libido. Sertoli cell tumors are even less common and also present with symptoms of excess estrogen.

EPIDEMIOLOGY

Approximately 10,000 men are diagnosed with testicular cancer each year in the United States, but less than 500 men will die of their disease [5]. Worldwide, there are approximately 75,000 cases and over 9,000 deaths per year due to testicular cancer [6].

Epidemiologic evidence suggests that the incidence of testicular cancer has been increasing worldwide since the early 1900s [7-10]. As examples:

- In data from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute, the overall incidence of testicular germ cell tumors (GCTs) among American men rose 44 percent from 3.35 per 100,000 men in the period from 1973 to 1978 to 4.84 per 100,000 men in the period from 1994 to 1998 [8]. The incidence of seminoma rose 62 percent, while the incidence of nonseminomatous GCTs rose 24 percent.

- A review based upon data from 12 European countries found that the incidence of GCTs was increasing by 1 to 6 percent per year in the various countries [7]. By contrast, mortality rates decreased or were stable in most regions, reflecting improvements in treatment.

The factors responsible for the increased incidence of testicular cancer are unclear. A variety of hypotheses have been proposed, including in utero exposure to diethylstilbestrol (DES), earlier exposure to viruses or other environmental agents, and testicular trauma [11,12]. However, these factors fail to completely account for increase in testicular cancer.

The observed increase has been restricted to White males. Testicular cancer is less common in African Americans, with the incidence in African Americans estimated to be one-fourth that of White Americans [13]. The worldwide incidence is lowest in Africa and Asia, and highest in the Scandinavian countries, Germany, Switzerland, and New Zealand [14].

RISK FACTORS

There are a number of known risk factors for testicular neoplasia, including cryptorchidism, a personal or family history of testicular cancer, infertility or subfertility [15-17], and HIV infection.

All of these risk factors predispose to the development of carcinoma in situ (CIS) and invasive testicular cancer.

Germ cell neoplasia in situ (GCNIS) — In adults, both seminomas and nonseminomatous germ cell tumors (GCTs) are preceded by a premalignant condition germ cell neoplasia in situ (GCNIS). This was formerly called testicular intratubular germ cell neoplasia of the unclassified type (IGCNU) [18]. This abnormality has been found in 0.4 to 1.1 percent of men undergoing testicular biopsy because of infertility, but appears to be less common in the general population. (See "Testicular germ cell neoplasia in situ".)

GCNIS is found in testicular tissue adjacent to GCTs (except spermatocytic seminoma) in approximately 90 percent of adult cases [19]. It also is observed in all patient groups at risk for testicular cancer, including men with cryptorchid testicles (up to 5 percent) [19-21], prior or contralateral testicular GCTs (5 percent) [22-24], and androgen insensitivity [19,25]. These observations suggest the possibility of a field defect, in which genetic or developmental events that produce gonadal dysfunction confer predisposition to malignancy over a wide area [26]. (See 'Contralateral testicular cancer' below and "Pathogenesis and clinical features of disorders of androgen action".)

If GCNIS is left untreated, the risk of progression to invasive malignancy is approximately 50 percent in five years [22]. Whether all cases of GCNIS eventually progress to invasive malignancy is unclear. (See "Testicular germ cell neoplasia in situ".)

Cryptorchidism — Men with cryptorchidism (or testicular malposition) have an increased risk of testicular cancer. Therefore, prophylactic orchiectomy is generally recommended, especially if the testicle is located in the abdomen [27]. Inguinal cryptorchidism is less likely to result in malignancy compared with abdominal cryptorchidism; for these men, deferral of surgery with careful surveillance is a reasonable alternative [21]. Of note, while 10 percent of testicular tumors occur in this setting, approximately 20 percent of cases involve the normally descended testicle. This suggests that testicular malpositioning alone does not explain the increased risk of testicular cancer. A further discussion on cryptorchidism and testicular cancer risk is discussed separately. (See "Undescended testes (cryptorchidism) in children: Management", section on 'Testicular cancer'.)

Hypospadias — The incidence of testicular GCTs appears to be increased in men with a history of hypospadias. In a health registry study from Denmark that included 5441 men with testicular GCTs, the incidence of cancer was significantly increased (relative risk 2.13, 95% CI 1.26-3.61) [28].

Contralateral testicular cancer — A small percentage of men with testicular cancer will have a second testicular cancer, either at presentation or with a subsequent metachronous cancer [29,30]. The largest study analyzed 29,515 cases of testicular cancer in men under the age of 55 reported to the United States National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) program between 1973 and 2001 [29]. At presentation, 175 had a synchronous contralateral cancer (0.6 percent). The 15-year cumulative risk of a contralateral (metachronous) testicular cancer was 1.9 percent, which is similar to that reported in other studies with long-term follow-up [31,32]. Observational data also suggest a decreased risk of metachronous contralateral testicular cancer among men whose primary testicular cancer was treated with platinum-based chemotherapy [32,33].

The incidence of second cancers is similar to the incidence of GCNIS seen in patients with unilateral testicular cancer who undergo biopsy of the contralateral testicle at the time of orchiectomy. Men with contralateral GCNIS appear to be the group at primary risk for the development of contralateral testis cancer [22,24]. This was illustrated in a series of 500 patients with testicular GCTs in whom the contralateral testicle was biopsied at the time of orchiectomy [22]. Seven of 27 men with GCNIS developed later contralateral invasive cancer compared with none of the 473 without GCNIS. (See "Testicular germ cell neoplasia in situ".)

Extragonadal germ cell tumor — Men with extragonadal GCTs are at risk of developing both testicular GCNIS and invasive GCTs. The risk is most pronounced in those with retroperitoneal rather than mediastinal disease, and nonseminomatous histology. (See "Testicular germ cell neoplasia in situ", section on 'Extragonadal germ cell tumor' and "Extragonadal germ cell tumors involving the mediastinum and retroperitoneum".)

Family history and inherited susceptibility — Approximately 1 to 3 percent of men with a testicular GCT have a family member with the disease. This is higher than would be expected by chance alone, suggesting a potential hereditary predisposition [34-36]. The clinical and pathologic manifestations of testicular GCTs in these kindreds appear to be similar to those seen in nonfamilial cases [37].

The overall contribution of familial and inherited factors in testicular cancer has been difficult to quantitate. However, the following factors suggest a strong hereditary component:

- In the largest case-control study examining risk factors for testicular GCT, the greatest risk factor was in fact heredity [38,39].
- The relative risk of testis cancer is increased 6- to 10-fold in the brothers or sons of a man with testicular cancer [38,40-43].

- Family and twin studies have suggested that the estimated heritability of testicular GCTs is as high as 49 percent, making these tumors potentially more heritable than breast, ovarian, or colorectal cancer [44].

Despite these findings, no highly penetrant Mendelian testicular cancer predisposition genes have been identified [45]. Nevertheless, a number of rare defined inherited disorders have been linked to an elevated risk of testicular cancer [46], and candidate chromosomal regions have been suggested [47-49]. As an example, among families with testicular GCTs compatible with X-linked inheritance, a locus has been suggested on chromosome Xq27; this locus may also predispose to undescended testes [48].

Isochromosome 12p is present in most patients with testicular GCTs [50,51]. In a series of 179 analyzed cases of testicular GCT, abnormal karyotypes were present in 101 (59 percent), and 79 of these had the isochromosome 12p abnormality [51]. However, the role of this abnormality in familial GCTs is undefined. (See "Anatomy and pathology of testicular tumors", section on 'Molecular markers'.)

Moderate-risk and low-risk single nucleotide polymorphisms, identified through genome-wide association studies, are thought to explain approximately one-third of father-to-son familial risk for testicular GCT [44,52-54], leaving most of the cases of potential testicular GCT heritability yet to be elucidated.

An intriguing study showed that testicular GCTs were exceptionally enriched for reciprocal loss of heterozygosity; this DNA double-strand break-enriched genomic signature suggested the possibility that increased DNA damage with deficient repair might be central to the development and progression of testicular GCTs. A subsequent study of inherited DNA repair gene alterations in 205 unselected men with a testicular GCT identified 22 pathogenic germline DNA repair gene variants in 20 men, one-third of which were in the checkpoint kinase 2 (*CHEK2*) gene [55,56]. Unselected men were four times more likely to carry germline loss-of-function *CHEK2* variants as compared with cancer-free, ancestry-matched controls. Furthermore, individuals with the loss-of-function *CHEK2* variants developed a testicular GCT six years earlier than did those with *CHEK2* wild-type alleles.

HIV infection — A modest increased incidence of testicular GCTs, particularly seminomas, has been described in HIV-infected men compared with HIV-negative men. In a combined analysis of seven studies with over 440,000 men with AIDS or HIV infection, there was a modest increase in the incidence of testicular cancer, with a standardized incidence ratio of 0.7 to 1.8 compared with the general population [57]. The increase appears to be limited to seminoma and does not

appear to affect the incidence of nonseminomatous GCTs [58-60]. (See "HIV infection and malignancy: Management considerations", section on 'Testicular neoplasms'.)

Testicular microlithiasis — The relationship between testicular microlithiasis and testicular malignancy is controversial, in part because microlithiasis is most frequently identified in men who are being assessed because of testicular symptoms. Microlithiasis is usually found by scrotal ultrasonography, as diffuse echogenic foci within the seminiferous tubules [61].

The possible relationship between testicular microlithiasis and testicular malignancy was analyzed in the literature review and meta-analysis that included data from 33 reports in which men had been referred for testicular ultrasound [62]. Overall, the incidence of testicular GCT or GCNIS was significantly increased in the 1347 men with testicular microlithiasis compared with those in whom testicular microlithiasis was absent (risk ratio 8.5, 95% CI 4.5-16.1).

However, the utility of this observation is limited, since the relatively high frequency of microlithiasis in healthy young men precludes using this finding as a screening tool for testicular cancer. Two population-based screening studies found an incidence of microlithiasis of 5.6 and 2.4 percent, respectively, which exceeds the incidence of testicular cancer in healthy young men by approximately 1000-fold [63,64].

Furthermore, the incidence of microlithiasis appears to be higher when more sensitive equipment is used to perform the examinations. In a series using high-frequency linear transducers, microlithiasis was identified in 195 of 1079 patients (18 percent) [65]. Testicular tumors were identified in only 12 of these 195 men (6 percent).

Androgen insensitivity syndromes and mixed gonadal dysgenesis — Intersex individuals with androgen insensitivity syndrome or mixed gonadal dysgenesis are at high risk of GCNIS, and germinal and nongerminal neoplasms in cryptorchid gonads [66-68]. (See "Pathogenesis and clinical features of disorders of androgen action" and "Diagnosis and treatment of disorders of the androgen receptor" and "Testicular germ cell neoplasia in situ".)

Genetic disorders

Klinefelter syndrome and Down syndrome — Klinefelter syndrome is associated with mediastinal extragonadal GCTs, and Down syndrome has been associated with testicular cancer [69-72]. (See "Extragonadal germ cell tumors involving the mediastinum and retroperitoneum" and "Causes of primary hypogonadism in males", section on 'Klinefelter syndrome' and "Down syndrome: Clinical features and diagnosis", section on 'Urologic abnormalities'.)

Peutz-Jeghers syndrome — Males with Peutz-Jeghers syndrome have an increased incidence of Sertoli cell testicular tumors that are often hormonally active [73]. Some present with gynecomastia, rapid growth, and advanced bone age with markedly elevated levels of estradiol [74]. Rarely, testicular metastases occur from a gastric cancer [75]. (See "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management" and "Epidemiology, pathophysiology, and causes of gynecomastia".)

Carney complex — Sertoli cell testicular tumors also occur with increased frequency in patients with Carney complex [76]. This is an autosomal dominant disorder characterized by two major types of findings: pigmented lentigines and blue nevi on the face, neck, and trunk; and multiple tumors, both endocrine (testicular Sertoli cells and occasionally adrenal, pituitary, or thyroid) and nonendocrine (cutaneous, mammary, and atrial myxomas, and psammomatous melanotic schwannomas). (See "Carney complex" and "Testicular sex cord stromal tumors", section on 'Sertoli cell tumors' and "Cushing's syndrome due to primary bilateral macronodular adrenal hyperplasia".)

In utero estrogenic effects — Some case-control studies suggest that higher exposure to estrogenic compounds in utero increases the risk of testicular GCT. In one report, exposure to exogenous estrogens in utero was associated with a 4.9-fold increase in the risk of testicular GCT [77]. However, a similar association was not observed for malignant GCTs arising in children younger than 15 years [78].

The role of diethylstilbestrol (DES) in the development of testicular cancer has been the subject of controversy. Cryptorchidism has been reported in the sons of women exposed to DES or oral estrogens during pregnancy, and anecdotal reports have linked DES exposure to testicular cancer. More rigorous studies have failed to prove, but have not definitely excluded an epidemiological link between DES and testicular cancer [79,80].

Additional, indirect evidence supporting a role for hormonal influences comes from a case-control study that found increased blood levels of organochlorine pesticides in men with testicular GCTs compared with matched controls [81]. These persistent pesticides are known to bind to estrogen receptors, and exposure in utero or early in life may contribute to the risk of testicular GCTs.

Lack of risk with vasectomy — There has been concern that the risk of testicular cancer may be increased in men after vasectomy. However, data do not support an association between vasectomy and testicular cancer [82,83].

Ethnicity — Testicular cancer is less common in African Americans, with the incidence in African Americans estimated to be one-fourth that of White Americans [13]. However, this racial

disparity may be changing. In a review of data on testicular cancer incidence from nine registries of the NCI SEER database, the incidence of testicular cancer among Black men started to increase in 1988, and doubled between 1988 and 1992 and from 1998 to 2001 [84]. The incidence of seminoma rose by twice as much as nonseminoma (124 versus 64 percent increase). The reasons for this increase are unknown.

There appears to be a higher risk of death among African Americans, Native Americans, Filipinos, Hawaiians, and Hispanic Americans [85]. Of 16,086 cases of primary testicular cancer diagnosed during 1973 to 1999 in the SEER database, diagnosis occurred at a later stage of disease among these minority groups. Even after adjustment for stage, histology, and period of diagnosis, the relative risk of dying from testicular cancer ranged from 1.4 to 3.6 when compared with non-Hispanic White Americans.

Dietary issues and cholesterol — Case-control studies have suggested a mild association between risk of testicular cancer and high intake of total as well as saturated fat, dietary cholesterol, and dairy products [86-88].

A relationship between high serum cholesterol and testicular cancer risk was also suggested in a cohort study of 44,864 Swedish men who were enrolled in a mass screening health trial between 1963 and 1965, and followed for 25 years [89]. Men who developed testicular cancer during the first two years of the follow-up period were excluded. There was a significant positive correlation between serum cholesterol and testicular cancer incidence. The hazard ratio [HR] for the highest cholesterol category (≥7 mmol/L [270 mg/dL]) compared with the lowest (<5.7 mmol/L [220 mg/dL]) was 4.5 (95% CI 1.3 to 16.2).

Despite these data, the relationship between serum cholesterol and testicular cancer risk remains uncertain. A potential confounding factor is the possibility that both testicular cancer and high serum cholesterol are independently associated with low birth weight [90-92]. In addition, serum cholesterol concentrations have declined in recent decades in Sweden [93], at a time when the incidence of testicular cancer has risen.

Marijuana — Multiple studies have looked at the relative risk of testicular GCTs in men based upon the relatively frequent use of marijuana in this demographic group. Two meta-analyses found an approximately twofold increase in the risk of nonseminoma GCTs among those using marijuana on a regular basis, either frequently (ie, at least weekly) or chronically (ie, for more than 10 years) [94,95]. Another study in Swedish military conscription recruits found a similar increase among "heavy" users [96].

SUMMARY

Although testicular cancer accounts for only 1 percent of all cancers in men, it is the most common solid malignancy affecting males between the ages of 15 and 35. Approximately 95 percent of testicular cancers are germ cell tumors (GCTs), and these are divided evenly between seminomas and nonseminomatous GCTs. (See 'Epidemiology' above.)

A number of factors have been associated with the subsequent development of testicular GCTs:

- The incidence of testicular cancer is significantly increased in males with cryptorchidism, and approximately 10 percent of testicular tumors occur in this setting. Orchiopexy reduces the likelihood of malignancy, although the optimal age for surgery is uncertain. (See 'Cryptorchidism' above and "Undescended testes (cryptorchidism) in children: Management", section on 'Testicular cancer'.)

- In adults, both seminomas and nonseminomatous GCTs can be preceded by a premalignant condition termed germ cell neoplasia in situ (GCNIS), formerly called intratubular germ cell neoplasia of unclassified type (IGCNU). If GCNIS is left untreated, the risk of progression to invasive malignancy is approximately 50 percent in five years. Whether all cases of GCNIS eventually progress to invasive malignancy is unclear. (See 'Germ cell neoplasia in situ (GCNIS)' above.)

- There are a number of other hormonal or genetic factors that appear to be associated with increased risk of testicular GCTs, but these factors appear to have only a limited impact on the total incidence of testicular cancer.

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GRAPHICS

Classification of testicular tumors

Noninvasive germ cell tumors
Germ cell neoplasia in situ (GCNIS)
Intratubular seminoma
Intratubular embryonal carcinoma
Invasive germ cell tumors
Seminoma
Nonseminomatous germ cell tumors
Embryonal carcinoma
Choriocarcinoma
Yolk sac tumor (endodermal sinus tumor)
Teratoma
Teratoma with malignant/somatic transformation
Mixed germ cell tumor
Spermatocytic tumor
Sex cord-stromal tumors
Sertoli cell tumor
Leydig cell tumor
Granulosa cell tumor
Mixed types (eg, Sertoli-Leydig cell tumor)
Unclassified
Mixed germ cell and stromal tumors
Gonadoblastoma
Adnexal and paratesticular tumors
Adenocarcinoma of rete testis
Adenocarcinoma of the epididymis
Mesothelial neoplasms
Malignant mesothelioma
Adenomatoid tumor

Miscellaneous tumors
Carcinoid
Lymphoma
Metastatic tumors (prostate carcinoma is the most common)

Data from: Tumours of the Urinary System and Male Genital Organs. Moch H, Humphrey PA, Ulbright TM, et al (Eds), In: World Health Organization Classification of Tumours. Lyon 2016.

Graphic 81626 Version 8.0

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