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Etiologic factors in testicular germ cell tumors

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Abstract

Globally, testicular cancer incidence is highest among men of northern European ancestry and lowest among men of Asian and African descent. Incidence rates have been increasing around the world for at least 50 years, but mortality rates, at least in developed countries, have been declining. While reasons for the decreases in mortality are related to improvements in therapeutic regimes introduced in the late 1970s, reasons for the increase in incidence are less well understood. An accumulating body of evidence suggests, however, that testicular cancer arises in fetal life. Perinatal factors, including exposure to endocrine disrupting chemicals, have been suggested to be related to risk.

Keywords

testicular germ cell tumor; seminoma; nonseminoma; perinatal etiology

Although a rare cancer in the general population, testicular cancer is the most common malignancy among young men in many countries. Approximately 98% of testicular cancers are germ cell tumors (TGCT). The remaining 2% include stromal tumors such as Leydig cell (~0.2%) and Sertoli cell tumors (~0.1%), as well as other more rare or poorly defined histologic types. Among TGCTs, approximately 55% are classic seminomas, 44% are nonseminomas (embryonal carcinomas, teratomas, yolk sac tumors, choriocarcinomas) and 1% are spermatocytic seminomas.

Ontogenesis of Testicular Germ Cell Tumors

Notable advances in the understanding of TGCT ontogenesis have occurred in recent years. It is now generally appreciated that testicular carcinoma *in situ* (CIS) gives rise to all seminomas and nonseminomas of adolescents and young adults [1], but not to infantile nonseminomas or spermatocytic seminomas [2]. The discovery that CIS cells expressed many markers (e.g., OCT 3/4, NANOG) in common with embryonic stem cells and gonocytes (fetal germ cells), suggested that CIS arose at a very early stage in development of germ cells that failed to differentiate properly [3,4]. Recently, demonstration that CIS cells have expression patterns more similar to those of gonocytes than of embryonic stem cells, has suggested that CIS either arises from a gonocyte, or is, itself, an arrested gonocyte [5]. As gonocytes, in general, do not persist after birth, the ability of the arrested gonocyte/CIS cell to thrive until it progresses to TGCT is not currently understood.

In contrast to the tumors of adolescents and young adults, infantile nonseminomas appear to arise from either embryonic stem cells or early primordial germ cells [6]. Spermatocytic seminomas, in comparison, arise from pre-meiotic germ cells [7,8]. Both infantile nonseminomas and spermatocytic seminomas are thought to be etiologically distinct from the more common TGCTs that occur in young men and adolescents. In contrast to the TGCTs of young men, neither infantile nonseminomas nor spermatocytic seminomas have increased in incidence in the past several decades.

Incidence

The incidence of TGCT peaks in young adulthood. Eighty-four percent of TGCT occurs among men between the ages of 15 and 44 years, 15% occurs in men aged 45 years and older, while only 1% occurs in boys less than 15 years of age (Figure 1). The incidence of nonseminoma peaks at approximately age 25 years, while the incidence of seminoma peaks ten years later, at age 35 years. Among very young boys (0 to 4 years), nonseminomas are the sole histologic type of TGCT. In the U.S. SEER registries between 1973 and 2004, 67% of the nonseminomas in this young age group were yolk sac tumors, 17% were embryonal carcinomas and 13% were teratomas. The median age at diagnosis of the rarest type of TGCT, spermatocytic seminoma, is approximately 54 years [9].

In 2002, the global age-standardized incidence rate of testicular cancer was 1.5 per 100,000 men [10]. The highest incidence rates in the world occur in populations of northern European ancestry, regardless of where they reside (Figure 2). Scandinavian men, in particular Norwegian and Danish men, have rates five to ten times higher than men of African and Asian descent [11]. In countries with multi-ethnic populations, the incidence of TGCT among white men is, in general, notably higher than the incidence among men of other backgrounds. For example, in the United States, the incidence of TGCT between 1973 and 2004 among white men was 5.46 per 100,000, while the incidence among black men was 0.95 per 100,000 [12].

In addition to having the highest absolute rates, men of European ancestry have experienced the greatest increase in incidence over the last half-century. In the United States, testicular cancer incidence increased in white American men by 52% between 1973 and 1998. Similar increases in incidence among men of European heritage were seen in Ontario [13], Norway [14], Denmark, Sweden, the former East Germany, Poland [15] and Australia [16].

In almost all populations studied, the increase in incidence has been found to be more consistent with a birth-cohort effect than with a calendar-period effect [15,17,18]. The increase began among cohorts born after 1920, although a notable decrease in risk occurred among men born in Scandinavia during the years surrounding World War II (1939-1945). The cohort-specific dip in risk has suggested that war-related deprivations might be responsible [19]. In contrast, the cohort of men born in Poland, the former East Germany and Finland experienced a continued increase in risk during the war years [17]. The overall pattern of increasing incidence only among specific ethnic and/or racial groups argues that there has either been an ethnic-specific change in a risk factor or that there has been a global change in a risk factor that only affects genetically susceptible men.

Associated medical conditions

A number of pre-existing medical conditions have been associated with the development of TGCT. These conditions include prior diagnosis of TGCT in the contralateral testicle [20,21], cryptorchidism [22], impaired spermatogenesis, inguinal hernia [23,24], hydrocele [24,25], disorders of sex development, prior testicular biopsy [26,27], atopy [28], and testicular atrophy [25,29,30]. In 2001, Skakkebaek and colleagues proposed the existence of a Testicular Dysgenesis Syndrome (TDS) composed of TGCT, impaired spermatogenesis, cryptorchidism and hypospadias [31] as the four conditions appear to share some common risk factors, may originate during fetal life and may have increased in incidence during the past several decades. More recently, it has been hypothesized that the TDS conditions may originate due to low testosterone levels which result from somatic cells malfunctioning in the developing testes [32]. The possible role of endocrine disrupting chemicals as risk factors has also been postulated [33].

Cryptorchidism

Cryptorchidism, or undescended testis, is the antecedent medical condition most closely associated with TGCT [25-28]. A meta-analysis has estimated the relative risk of TGCT among men with prior cryptorchidism to be 4.8 (95%CI=4.0-5.7) [22]. Nevertheless, only 10% of TGCTs develop in men with prior cryptorchidism. Whether cryptorchidism predisposes to cancer or whether the two outcomes share common risk factors is unclear. Evidence in support of a common etiology is that 10-25% of men with unilateral cryptorchidism develop TGCT in the contralateral gonad [34]. In addition, both conditions have been associated with common risk factors such as low birth weight, premature birth and the presence of other gonadal anomalies [35]. Several reports have noted no ethnic discrepancy in the incidence of cryptorchidism, despite the pronounced discrepancy in incidence of TGCT [36,37]. In addition, Kallmann Syndrome, a condition of congenital hypogonadotropic hypogonadism, is characterized by cryptorchidism, but not by TGCT [38]. Arguing, however, that cryptorchidism itself increases risk of TGCT is the observation in some studies that delayed orchiopexy substantially increases the risk of TGCT [39-42]. However the two outcomes are related, it is clear that cryptorchidism itself cannot explain the increase in TGCT. Although the prevalence of cryptorchidism has been reported by some studies to have increased between the 1950s and the 1980s, the proportion of testicular cancer patients with cryptorchidism appears to have remained constant at approximately 10% [43].

Impaired fertility

Prospective studies have found that subfertile men are at increased risk of TGCT [44-47]. Whether temporal trends in fertility are correlated with trends in TGCT, however, has been a matter of controversy. The results of a 1992 meta-analysis supported a global decline in semen quality over the prior 50 years [48], however, the study's conclusions and methodology have been widely debated [49-54]. Subsequent research on trends in male fertility has proven inconclusive [55].

Disorders of Sex Development

Disorders of sex development (DSD), as defined by the LWPES/ESPE Consensus Group, are congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical [56]. The risk of germ cell tumors, as noted by the Consensus Group, is somewhat difficult to estimate, but appears to be highest (on the order of 15-35%) in testis-specific protein Y encoded positive gonadal dysgenesis and in partial androgen insensitivity syndrome (PAIS) with intra-abdominal gonads. Conversely, risk of TGCT among men with complete androgen insensitivity syndrome (CAIS) is reported to be lower, at between 0.8 and 2%, although data are limited [56,57].

Perinatal Risk Factors

The hypothesis that TGCT is initiated in very early life has spurred a great deal of interest in perinatal factors such as birth weight, gestational age, maternal age, maternal smoking, maternal parity, birth order and sibship size. Low birth weight has been reported to be associated with TGCT risk by a number of studies [58-62]. A recent meta-analysis, however, found only modest support for the relationship, estimating the overall odds ratio to be 1.28 (95%CI=0.99-1.65) [63]. While high birth weight has also been associated with TGCT in at least one study [64], the majority of studies have not supported a relationship [63]. A factor closely related to low birth weight, decreased gestational age, has also been linked to TGCT risk [23,64,65]. Disentangling the effects of birth weight and gestational

age, however, has proven to be challenging, particularly as gestational age is often imprecisely recorded [66].

Maternal age has been both inversely [23,67-69] and directly [62,70-72] associated with TGCT risk. In addition, several studies have reported no association [73-75]. The combined results may indicate there is a U-shaped relationship between maternal age and TGCT risk, such that risk is increased in association with both younger (<20) and older (≥ 30) maternal age.

Low maternal parity and low birth order have been linked to TGCT risk in some [69,70,76-79], but not all [23,64,67,68] studies. Supportive studies have estimated a risk of two-thirds for sons born third or later, compared to first-born sons. The causal link between low maternal parity and TGCT risk has been speculated to be due to higher maternal estrogen levels in primiparous mothers [80] but other explanations, such as late exposure to a common infectious agent or a different psychosocial environment, are also possible.

Sibship size has also been considered in relation to TGCT risk and is likely to be a proxy for other exposures distinct from those related to parity. A large Swedish study found a risk ratio of 0.71 (95% CI: 0.62-0.82) for testicular cancer for five or more siblings versus none [81]. Some previous studies have found similar associations [69,76,79,82] while others have not [35,67,77]. The high correlation between sibship size and birth order makes the independent effect of each difficult to distinguish, but a large stratified analysis indicated that the variables are independent risk factors [79]. The estrogen hypothesis does not fully explain the association of TGCT risk with sibship size, and does not account for parental subfertility, which has been proposed to be the causal factor of this relationship [76]. Lastly, a decline over time in the association of sibship size and TGCT risk may be due to decreasing sensitivity of sibship size as a proxy for fertility [79].

An examination of parallel trends in rates of testicular cancer and female lung and bladder cancers led Clemmesen [83] to hypothesize that maternal cigarette smoking was a risk factor for TGCT. Using a similar ecologic design, Pettersson and colleagues [84] found a correlation between the prevalence of smoking among young women and testicular cancer incidence in Sweden, Norway and Denmark, though not in Finland. In contrast to the ecologic studies, the maternal smoking hypothesis has not been supported by retrospective studies [23,60,74,76,85-88], a recent meta-analysis [89], or by an examination of serum cotinine levels in mothers and TGCT in sons [89].

A number of other perinatal factors have occasionally been associated with risk for TGCT. The factors for which there is some evidence of association include hormone use during pregnancy [61,74], bleeding during pregnancy [60,74], maternal body weight [61,90], maternal socioeconomic status [35], breech presentation [23,69], twin birth [67,91] and trisomy 21 (Down syndrome) [68,92]. The evidence for hyperemesis gravidarum [23,68], Cesarean section [62] and having been breastfed [23] is equivocal. At present, there is little evidence that paternal age [69,71,79], birth length [68,69,71], preeclampsia [64,69], circumcision [28], varicocele [24,25] and neonatal jaundice [64,69] are associated with TGCT.

Indirect evidence suggests that the intrauterine hormonal milieu may affect the risk of TGCT. For example, excessive nausea early in pregnancy, reported by some studies to increase the risk of TGCT [75,93] is believed to be due to increased estrogen levels. Similarly, the increased risk reported among first born sons and dizygotic twins may be related to higher maternal estrogen levels [94]. Maternal obesity, a condition consistent with decreased sex hormone binding globulin (SHBG) levels and increased serum free estradiol levels, has also been associated with TGCT risk [95]. Because of these associations, the

‘estrogen hypothesis’ of TGCT was formally introduced in 1993 [96]. A complementary hypothesis has suggested that high maternal estrogen levels may not be as culpable as low maternal testosterone levels [97]. This hypothesis was based on the observation that African-American women had higher testosterone levels in pregnancy than white American women [97]. The direct evidence to support the maternal hormone hypotheses, however, has not been great. Several studies have examined maternal hormone levels in relationship to cryptorchidism but these studies, in general, have not supported either the maternal estrogen or the maternal androgen hypothesis [98-101].

The effect of exogenous, as well as endogenous, hormone exposure has also been examined. Diethylstilbestrol (DES), a nonsteroidal estrogen first synthesized in 1938, is several times more potent than the endogenous estrogen, 17 β -estradiol. Prescribed to prevent miscarriage between the late 1940s and mid 1970s, DES was removed from the market after being associated with clear cell adenocarcinoma of the vagina and cervix among daughters of exposed women. Several case reports have noted the occurrence of testicular cancer in sons of DES-exposed mothers [102], and a multi-center study reported a non-significant three-fold risk of TGCT based on seven cases in the exposed group and two cases in the non-exposed group [103]. Other researchers have reported conflicting results [61,65,104] and reviews of the literature have concluded, in general, that the supporting data are equivocal [105]

Like DES, endocrine disrupting chemical (EDC) exposure could potentially alter the hormonal milieu [106]. EDCs have been defined as exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes [107]. As DES was hundreds to thousands of times more potent than any known EDC, it has been argued that it would be unlikely to see outcomes associated with the EDCs that were not associated with DES [106]. However, it is conceivable that the net combined estrogenic effects of EDCs may exceed those of DES. EDCs include compounds that are estrogenic (e.g., isoflavones, phthalates, o,p’-DDT, o,p’-DDE, bisphenol A, alkylphenols, some PCBs), anti-estrogenic (e.g., dibenzo-p-dioxin, tributyltin, some PCBs), anti-androgenic (e.g., vinclozolin, p,p’-DDE, methoxychlor, dibenzo-p-dioxin, flutamide, linuron, natural pyrethrin, tris(4-chlorophenyl)-methanol) and anti-gestagenic (e.g., carbamate) [108]. Of these chemicals, groups that have received particular attention in regard to male reproductive disorders are the persistent organochlorine pesticides (POPs) (e.g., aldrin, dieldrin, endrin, dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE)) and the polychlorinated biphenyls (PCBs).

Several epidemiologic studies of EDCs and TGCT have now been reported. A Swedish study of 58 TGCT cases and 61 controls found that the cases had significantly higher levels of *cis*-nonachlor than did controls [109]. The *cis*-nonachlor finding was supported by a larger U.S. study [110], which also reported that cases had significantly higher levels of a related compound, *trans*-nonachlor, as well as higher levels of p,p’-DDE. The same study reported, however, that the TGCT cases had significantly lower levels of PCBs than the controls [111]. Another U.S. study, however, did not find any associations between TGCT and organochlorine pesticides [112]. Differences in the dates of sample collection may explain some of the discrepancy in results.

Postnatal risk factors

A number of studies have examined associations between body size and TGCT. While two studies found an inverse relationship with body mass index [93,113] and two studies found a direct relationship [114,115], most studies have reported no association [24,39,116-124].

Height, in contrast, has been positively associated with risk in most studies [24,39,113,117-119,123-126], though four studies reported no association [93,116,121,122]. Overall, the bulk of the evidence suggests that taller men are at increased risk. Childhood nutrition [24], individual variation in the insulin-like growth factor I system [127] and/or age at puberty [113] could explain the relationship. Although younger age at puberty has been reported by some studies to increase risk [39,104], other studies have found that risk is not increased by younger age at puberty, but is decreased by older age at puberty [21,24,35,39,126,128]. As later age at puberty tends to result in greater height, the associations of puberty and height with TGCT risk are not likely to be mediated by a common pathway.

A nutritional etiology of TGCT has not been examined extensively, however associations have been reported for diets high in fat and total calories [129,130]. An association with dairy food, particularly milk and cheese [114,131-134], has suggested that naturally occurring or synthetic hormones may be culpable [133]. No relationship has been found for dietary phytoestrogen intake and TGCT [135]. It is also possible that an association between dairy food consumption and TGCT might appear to exist because populations with the highest risks of TGCT, northern Europeans, are the populations least likely to suffer from lactose intolerance.

The suggestion that exogenous endocrine modulators may affect risk of TGCT raises the question of whether endogenous hormones might also affect risk. This has been a difficult question to address because of the retrospective nature of most TGCT studies. Several studies, however, have compared endogenous hormone levels of men prior to orchiectomy with levels in control men [46]. In general, these studies have found that men with TGCT have higher follicle stimulating hormone (FSH) levels and somewhat lower testosterone levels than do control men. Studies in cryptorchid men have reported a similar hormonal milieu [136]. The associations of reduced body muscle mass and reduced frequency of baldness among men with TGCT have also suggested that testosterone levels in TGCT patients may be in the lower end of the spectrum [93,135]. Similarly, evidence that severe acne during adolescence may be inversely related to TGCT, has suggested that higher testosterone levels are protective [61,135]. The observations of high FSH and low testosterone have suggested that TGCT arises in a state of 'gonadotropin overdrive' in which the testes have lost the ability to respond to gonadotropins [30]. Arguing the importance of hypersecretion of gonadotropins in TGCT is the observation that men with low levels of gonadotropins (e.g., men with hypogonadotropic hypogonadism) rarely develop TGCT despite their high rate of cryptorchidism.

A protective effect of childhood physical activity has been reported by several studies [24,137,138], but not by others [121,139,140]. Two of the null studies had fewer than 50 cases [121,140], however, and the third study based physical activity solely on adult occupational history [139]. In addition, one study found a direct association between physical activity and TGCT risk [120]. Overall, however, the evidence suggests that increased childhood physical activity and TGCT risk may inversely associated.

Occupational studies of TGCT have not unanimously endorsed any single profession as a risk factor. Some studies have found an increased risk of TGCT among firefighters [141,142] metal workers [143,144], leather workers [145], aircraft technicians [146,147], agricultural workers [148,149], unionized carpenters [150], paper mill maintenance employees [151] and writers [152]. In general, white collar workers have been found to be at higher risk of TGCT than blue collar workers, thus observed occupational associations could be confounded by socioeconomic status [153]. Early studies indicated that higher socioeconomic status was associated with an increased risk [61,154,155] while more current

studies have found little association [23,35]. Decreasing variation between socioeconomic strata may have limited the further use of socioeconomic status as a discriminatory variable [156].

An infectious etiology of testicular cancer was first suggested based on epidemiologic similarities with Hodgkin disease [157]. More recent support for a viral etiology has been the reports of increased risk of TGCT among men infected with human immunodeficiency virus (HIV) [158-162]. While a number of studies have directly examined viral antibody titres in TGCT, few have had adequate power to test the hypotheses. Two member of the herpes virus family, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) have been implicated in the etiology of TGCT [163-166]. Both viruses are known to cause p53 over-expression, a common finding in TGCT [167] and both viruses have been demonstrated to have oncogenic potential [168]. Conversely, inverse associations between TGCT and mononucleosis, a manifestation of EBV infection, [104] and CMV infection [166] have also been reported.

TGCT risk has been reported by several studies to be associated with testicular trauma [21,29,169]. Some early evidence that increased scrotal temperatures, perhaps due to tight outer- or underwear, might be related to risk [29], has not received wide support by most studies [39,169,170]. It remains unclear whether testicular torsion [25,171] or having had a history of at least one sexually transmitted disease [137,172,173] are risk factors for TGCT.

Histologic Differences in Risk Factors

A number of studies have examined whether there are differences in risk factors between seminomas and nonseminomas. As noted by Moller and colleagues [174], it is unlikely that huge differences in risk factors exist between tumors of various histologies because of the similarity in incidence trends. In addition, mixed tumors composed of both seminomatous and nonseminomatous elements are not uncommon. The majority of risk factor analyses stratified by histologic group also appear to support a shared etiopathogenesis [61,62,70,74,⁷⁷,104,148,175,176]. Nevertheless, there is some evidence that certain factors may be more strongly associated with one histologic type or the other. Several studies have reported that cryptorchidism [16,21,176,177], low birth weight [71,72] and low birth order [70,79] are factors predominantly associated with an increased risk of seminoma. Moreover, participation in specific sporting activities [21] and long gestational duration [64] may be more protective against seminoma [21]. Risk factors primarily associated with an increased risk of nonseminoma include testicular trauma [16,21], history of at least one sexually transmitted disease [21], younger age at shaving initiation [124] and short gestational duration [64]. In addition, later puberty may have a stronger protective effect against nonseminoma than seminoma [21,35,104]. The literature as a whole, however, is not congruent for any one of these histologic dissimilarities.

Family and Twin Studies

In comparison with the general population, the risk of testicular cancer has been reported to be eight-fold higher in brothers and four-fold higher in sons of affected men [178-180]. In order for an environmental exposure to fully account for such an observation, the exposure would have to be perfectly shared amongst siblings and to increase risk by more than ten-fold [181]. The higher familial risk amongst brothers of cases, compared to fathers, is consistent with that a recessive mode of inheritance or a susceptibility locus on the X gene. Evidence supporting a recessive model was reported from a segregation analysis of 978 Scandinavian testicular cancer patients and their families, although a dominant model could not be conclusively ruled out [182]. A similar inference was derived from an analysis of bilateral disease [183]. Both studies estimated a risk of disease among homozygotes at 45%.

Less evidence for a dominant mode of inheritance, however, may simply reflect that paternal transmission may have been significantly hampered in earlier generations. Prior to the introduction of cisplatin as a chemotherapeutic agent in the late 1970's [184] the poor prognosis for metastatic disease made it likely that affected individuals would not live long enough to reproduce. In addition, reduced fertility is associated both with the cancer itself and with its treatment [39].

Regardless of whether a greater risk is associated with an affected brother or father, a relative risk of 6 to 10 is consistent with the involvement of predisposing genes [185]. Candidate locus studies have provided evidence of risk associated with the gr/gr deletion on the Y chromosome [186] and with variation in the phosphodiesterase 11A (*PDE11A*) gene [187]. In addition, two genome-wide association studies have implicated risk-associated loci on chromosomes 5, 6 and 12 [188,189]. The strongest of these associations, that of genetic variants in the region of the *KITLG* locus on the short arm of chromosome 12, may be particularly important as the *KITLG* gene is a key factor in primordial germ cell migration and proliferation [190].

The risk of testicular cancer risk has been reported to be higher among twins than non-twins [67,91] and higher among dizygous than monozygous twins [191-193]. The higher risk among dizygous twins may provide support for the 'hormone hypothesis' as maternal estrogen levels may be higher in dizygous births due to the existence of two placentae [80]. Alternatively, it has been suggested that hypersecretion of FSH could be linked to TGCT in sons as mothers of dizygotic twins have a genetic tendency to hypersecrete which may be a heritable trait [194]. In support of this postulate, it has been reported that men with TCGT have higher FSH levels at diagnosis, than do unaffected men [195]. In addition, men with Down syndrome [195], a condition associated with testicular cancer [92], have higher FSH levels, as do their mothers [196].

Despite the evidence that testicular cancer has a genetic component, it is likely that the risk is largely mediated by environmental exposures. Firstly, familial occurrence of testicular cancer is very rare with the number of diagnoses made in first-degree relatives of index cases constituting just 1 to 2.8% of the total [179,180,197-199]. Secondly, testicular cancer risks are higher in brothers whose ages differ by fewer than five years [179]. Thirdly, testicular cancer has been reported to have the highest proportion of childhood environmental effects in a familial study of all main cancers [200]. These studies emphasize the environmental component of testicular cancer pathogenesis and underscore the need to identify such factors.

Conclusions

Despite the increasing rates of testicular germ cell tumors seen during much of the twentieth century, TGCT etiology remains poorly understood. Large geographic and ethnic discrepancies in rates argue that both environmental and genetic factors may contribute to causing TGCT. The association with perinatal risk factors and congenital anomalies, as well as young age of onset, suggest that the tumor may originate in utero. The challenge in testicular cancer epidemiology will be to obtain accurate information about events surrounding the perinatal period of adults. A second challenge will be determining, if the tumor is initiated in utero, whether life style choices, such as diet and physical activity, can decrease the risk of developing the tumor.

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Figure 1.
Incidence of testicular germ cell tumors, seminomas and nonseminomas by age, U.S. SEER-9 registries, 1973-2006.

Figure 2.

Age-standardized global incidence of testicular cancer. From: J. Ferlay, F. Bray, P. Pisani and D.M. Parkin. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. IARC CancerBase No.5, version 2.0, IARC Press, Lyon, 2004.