

Chapter 2

The Epidemiology of Testicular Cancer

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2.1 Introduction

Testicular cancer is a rare tumor among the general population, but is the most common type of cancer among young men in many countries. The vast majority of testicular cancers are germ cell tumors. As a result, the terms “testicular cancer” and “testicular germ cell tumors” (TGCT) are often used interchangeably. Globally, the incidence of TGCT is highest among men of northern European ancestry and lowest among men of Asian and African descent. Incidence rates of TGCT 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 TGCT arises in fetal life. As the great majority of TGCTs arise among men between the ages of 15 and 44 years, this chapter will focus on the etiology of the tumors in this age group.

2.2 Histology and Precursor Lesions

Approximately 98% of all primary testicular cancers arise from germ cells. 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 testicular germ cell tumors (TGCTs), approximately 55% are classic seminomas, 44% are nonseminomas (embryonal carcinoma, teratoma, yolk sac tumor, choriocarcinoma), and 1% are spermatocytic seminomas.

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In 1972, Skakkebaek first proposed that testicular carcinoma in situ (CIS) was the precursor lesion for TGCT (Skakkebaek 1972). It is now generally accepted that CIS (also known as intratubular germ cell neoplasia, unclassified type or IGCNU) gives rise to all seminomas and nonseminomas of adolescents and young adults, but not to infantile nonseminomas or spermatocytic seminomas (Oosterhuis and Looijenga 2005). CIS cells have many features in common with primordial germ cells and early gonocytes, suggesting that CIS arises at a very early stage of development in cells that failed to differentiate properly (Rajpert-De Meyts et al. 1998). In contrast to the tumors of adolescents and young adults, infantile nonseminomas appear to arise directly from primordial germ cells or gonocytes (Almstrup et al. 2006). Spermatocytic seminomas, which largely occur in older men, appear to arise from premeiotic germ cells (Stoop et al. 2001). Both infantile nonseminomas and the spermatocytic seminomas of older men are thought to be etiologically distinct from the TGCTs that occur in young men and adolescents. For a detailed discussion of the pathology of testes cancer, see the chapter by Wojno and Bégin in this volume.

2.3 Incidence and Mortality

2.3.1 Incidence: Age Patterns

Unlike most types of cancer, 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 (Fig. 2.1). The incidence of nonseminoma peaks at approximately age 25 years, while the incidence of seminoma peaks 10 years later, at age 35 years. Among very young boys (0–4 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 (surveillance Epidemiology and End Results 2006).

2.3.2 Incidence: Racial and Geographic Patterns

In 2002, the global age-standardized incidence rate of testicular cancer was 1.5 per 100,000 men (Ferlay et al. 2004). In comparison, the age-standardized incidence rate of lung cancer, the most common tumor among men, was 35.5 per 100,000. In general, the incidence of testicular cancer is better correlated with ethnic/racial group than with geographic location. For example, the highest rates of testicular cancer in the world are seen in populations of northern European ancestry, regardless of where they reside (Fig. 2.2). Scandinavian men, in particular Danish and Norwegian men, have rates five

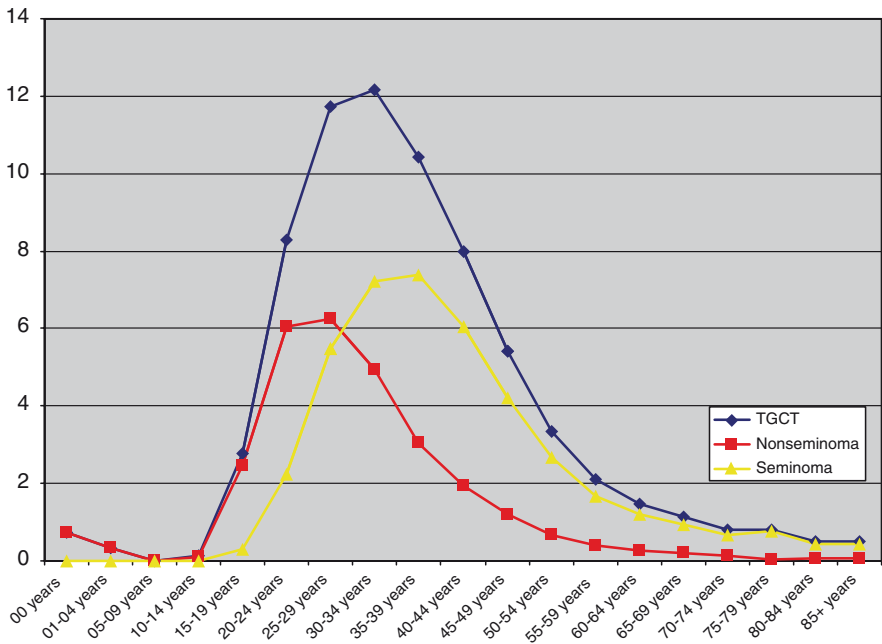


Fig. 2.1 Incidence of testicular germ cell tumors (TGCT), seminoma, and nonseminoma by age. SEER-9 registries, 1973–2005

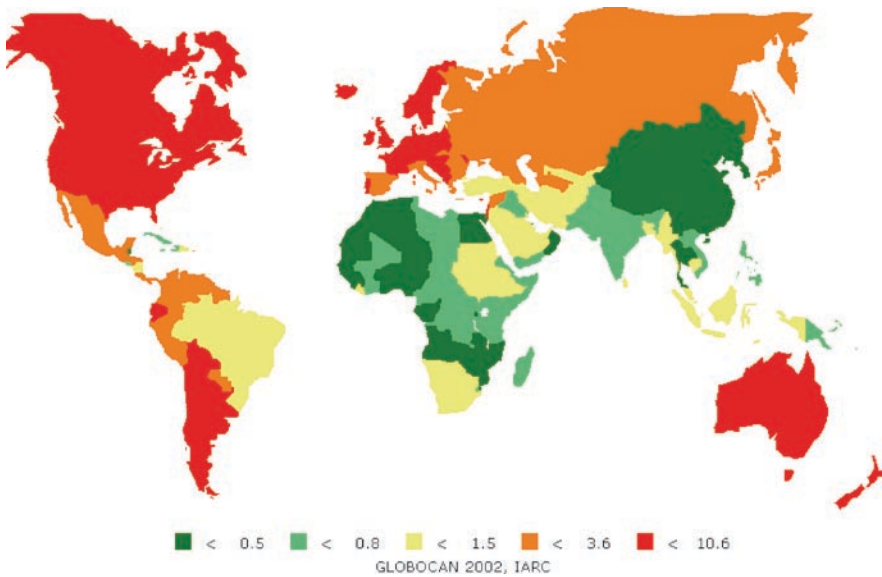


Fig. 2.2 Testis age-standardized incidence rate per 100,000

to ten times higher than men of African and Asian descent. In the great majority of countries with multiethnic populations, the incidence of TGCT among white men is appreciably higher than the incidence among men of other races and ethnicities. For example, in the United States, the incidence of TGCT between 1973 and 2004 among white men was 5.46 per 100,000. In contrast, the incidence among black men was 0.95 per 100,000, while the incidence among men of Native American or Asian ancestry was 2.05 per 100,000 (Shah et al. 2007). Similarly, in a comparison of incidence rates among South Africans, men of European ancestry had significantly higher rates than men of African ancestry (Coovadia 1978). One notable exception to this general pattern, however, is found in New Zealand where the incidence among Maori men (10.6 per 100,000 in 2002) is three times higher than the incidence among non-Maori men (3.5 per 100,000) (New Zealand Health Information Service 2006).

In addition to experiencing high absolute rates, men of European ancestry have seen the greatest increase in incidence over the last 50–70 years. An example occurs in the United States where testicular cancer incidence increased in white American men by 52% between 1973 and 1998. Similar increases in incidence among men of European heritage have been seen in Ontario (Weir et al. 1999), Norway (Wanderas et al. 1995), Denmark, Sweden, the former East Germany, Poland (Bergstrom et al. 1996), and Australia (Stone et al. 1991). Northern European rates began to increase among men born after 1920 (Bergstrom et al. 1996). Data from the Connecticut Tumor Registry mirror this observation among white American men, whose rates began to increase by the mid-1950s (Zheng et al. 1996). Recent reports suggest that incidence of TGCT, particularly of nonseminoma, may have begun to stabilize in some high-risk populations (McGlynn et al. 2003). In contrast, rates among African-American men, a low-risk population, appear to have begun increasing in the 1990s (McGlynn et al. 2005a).

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 (Bergstrom et al. 1996; Ekbom and Akre 1998; McGlynn et al. 2003). Dating back to at least the 1930s, incidence has generally increased with successive birth cohorts. A notable exception to the increase occurred among the cohort of men born in Denmark, Norway, and Sweden during the years surrounding World War II (1939–1945). The cohort-specific dip in risk has suggested that war-related deprivations were responsible (Moller 1989). In contrast, the cohort of men born in Poland, the former East Germany, and Finland, countries that, arguably, were even more affected by wartime deprivations, saw a continued increase in risk during the war years (Ekbom and Akre 1998). 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 ethnic groups. At this time, however, the factor or factors responsible for the increase in rates remain unidentified.

2.3.3 Mortality

The prognosis of TGCT since the late 1970s in developed countries has been very favorable, with a survival rate between 90 and 95% (Boyle 2004). Prior to that time, the survival rate was approximately 10%. The great improvement in a short period of time was largely due to the introduction of cisplatin-based therapy (Einhorn and Donohue 1977) and the appreciation of the combined management of disease (Peckham et al. 1979). As a result of these developments, mortality from TGCT has declined dramatically in most developed countries; examples being Denmark (Osterlind 1986), England and Wales (Power et al. 2001), Scotland (Boyle et al. 1987), Canada (Bertuccio et al. 2007), and the United States (Bertuccio et al. 2007). In contrast, mortality from TGCT remains elevated in countries where state-of-the-art therapy is unavailable; examples being many countries of Central and South America (Bertuccio et al. 2007), as well as countries of Southern and Eastern Europe (Bray et al. 2006).

2.3.4 Migrant Patterns

The majority of migrant studies of testicular cancer have found that first-generation migrants (i.e., foreign-born men of foreign-born parents) retain the risk of their home country, regardless of whether they migrate from low-risk to high-risk, or high-risk to low-risk, countries (Graham and Gibson 1972; McCredie et al. 1994; Swerdlow et al. 1995; Parkin and Iscovich 1997; Hemminki and Li 2002a; Ekblom et al. 2003). These findings support the hypothesis that TGCT risk is determined in early life, but do not distinguish between genetic and environmental effects. Studies of second-generation migrants (i.e., native-born men of foreign-born parents) have been limited by rather small numbers. In general, however, the studies have reported that second-generation men have risks similar to their parents' home countries (Graham and Gibson 1972; Parkin and Iscovich 1997; Hemminki and Li 2002a). The interpretation of the risks in second-generation men, however, is uncertain as many immigrant families retain customs from the parents' home country.

2.4 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 gonad (Coupland et al. 1999; Fossa et al. 2005), cryptorchism (Dieckmann and Pichlmeier 2004) impaired spermatogenesis, inguinal hernia (Gallagher et al. 1995; Coupland et al. 2004), hydrocele (Gallagher et al. 1995; Moller et al. 1996),

prior testicular biopsy (Swerdlow et al. 1997b; Moller et al. 1998), atopy (Swerdlow et al. 1987b), testicular atrophy (Haughey et al. 1989; Oliver 1990; Moller et al. 1996), and microlithiasis (Ikingier et al. 1982). In 2001, Skakkebaek and colleagues proposed the existence of a Testicular Dysgenesis Syndrome (TDS) that included TGCT, impaired spermatogenesis, cryptorchism, and hypospadias (Skakkebaek et al. 2001). The proposal was based on reports that 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. At the current time, the existence of the syndrome remains largely hypothetical, though it has provided a good theoretical framework for ongoing research.

2.4.1 Cryptorchism

Cryptorchism, or undescended testis, is the antecedent medical condition most closely associated with TGCT (Osterlind et al. 1991; Colls et al. 1996; Wanderas et al. 1997; McMaster et al. 2006). The relative risk of TGCT among men with a prior diagnosis of cryptorchism has been estimated in various populations to be between 2.5 (Schottenfeld et al. 1980) and 17.0 (Coldman et al. 1982). A recent meta-analysis of 20 case-control studies, however, estimated the overall relative risk to be 4.8 (95%CI: 4.0–5.7) (Dieckmann and Pichlmeier 2004). Nevertheless, only 10% of testicular cancers develop in men with cryptorchism (United Kingdom Testicular Cancer Study Group 1994a). Whether cryptorchism itself predisposes to cancer or whether the two outcomes share common risk factors is not well understood. Evidence suggesting that the two conditions may simply share a common etiology is that 10–25% of men with unilateral cryptorchism develop TGCT in the contralateral gonad (Batata et al. 1982). In addition, both conditions have been associated in some studies with common risk factors such as low birth weight, premature birth, and the presence of other gonadal anomalies (Moller and Skakkebaek 1996). Several reports have noted no ethnic discrepancy in the incidence of cryptorchism among newborns, despite that fact that the rate of TGCT is five times as great in European-American men as in African-American men (Berkowitz et al. 1995; McGlynn et al. 2005a). In addition, Kallmann Syndrome, a condition of congenital hypogonadotropic hypogonadism, is characterized by cryptorchism, but not by testicular cancer (Ginsburg 1997). Arguing, however, that the condition of cryptorchism is itself risk-producing is the observation in some studies that orchiopexy (i.e., surgical repair of cryptorchism) prior to 10 years of age substantially reduces the risk of TGCT (United Kingdom Testicular Cancer Study Group 1994a; Pettersson et al. 2007b). In whatever way the two outcomes are related, it is clear that cryptorchism itself cannot explain the increase in TGCT. Although the prevalence of cryptorchism has been reported by some studies to have increased between the 1950s and the 1980s, the proportion of testicular cancer patients with cryptorchism appears to have remained constant at approximately 10% (Chilvers and Pike 1989).

2.4.2 *Subfertility*

Prospective studies have demonstrated that subfertility precedes diagnosis of, and likely transformation to, TGCT (Lass et al. 1998; Petersen et al. 1999; Jacobsen et al. 2000; Raman et al. 2005). Whether temporal trends in subfertility are correlated with trends in TGCT, however, has been a matter of some controversy. A meta-analysis of 61 studies of sperm counts concluded in 1992 that there had been a global decline in semen quality over the previous 50 years (Carlsen et al. 1992). The study's conclusions and methodology were the subject of some debate, however (Olsen et al. 1995; Fisch and Goluboff 1996; Fisch et al. 1996; Lerchl and Nieschlag 1996; Becker and Berhane 1997; Swan et al. 1997). Subsequent research on the topic has proven inconclusive, with some studies reporting significant decreases in sperm count, some studies reporting no decreases, and some reporting increases (Safe 2000). While the accumulated research has been unable to reach consensus on whether sperm counts are declining, it has amply demonstrated that there is great diversity in sperm counts, both geographically and temporally.

2.4.3 *Microlithiasis*

Testicular microlithiasis is characterized by multiple microcalcifications found within the seminiferous tubules. This asymptomatic, nonprogressive disease was first linked to testicular cancer by Ikinger et al. (1982) and has subsequently been found to be present in 2.4–5.6% of asymptomatic men (Peterson et al. 2001; Serter et al. 2006). Interestingly, the prevalence of testicular microlithiasis is higher in African American (14.1%) than white men (4.3%) (Peterson et al. 2001), which is the converse trend of testicular cancer risk in these ethnic groups (McGlynn et al. 2003).

There have been many reports of concomitant presentation of testicular microlithiasis and testicular cancer (Cast et al. 2000; Bach et al. 2001; Lam et al. 2007), while numerous case reports have described patients who have received a diagnosis of testicular cancer subsequent to that of microlithiasis (Pourbagher et al. 2005). Some prospective studies, however, have not found an increased testicular cancer risk in men with microlithiasis (Ganem et al. 1999; Bennett et al. 2001; Lam et al. 2007); others have (Derogee et al. 2001; Otite et al. 2001; von Eckardstein et al. 2001). Testicular CIS, the precursor lesion of TGCT, has also been shown to be associated with microlithiasis (Lenz et al. 1996; von Eckardstein et al. 2001; Holm et al. 2003). However, the extent, location, and laterality of testicular microlithiasis have been shown not to correlate with the presence or absence of testicular cancer (Backus et al. 1994). Testicular microlithiasis likely represents a condition which has a shared etiology with testicular cancer and may be a marker of general testicular dysgenesis, given its reported associations with cryptorchidism (Renshaw 1998), subfertility (von Eckardstein et al. 2001), and other benign conditions (Nistal et al. 2006). For a further discussion of microlithiasis and testes cancer risk, see the chapter by Rapley in this volume.

2.5 Perinatal Risk Factors

In recent years, the theory that TGCT is initiated in very early life has spurred a great deal of interest in perinatal factors. While a number of associations have been examined, factors that have received particular attention include birth weight, gestational age, maternal age, maternal smoking, maternal parity, birth order, and sibship size.

2.5.1 *Birth Weight and Gestational Age*

Low birth weight has been reported to be associated with TGCT risk by a number of studies (Depue et al. 1983; Brown et al. 1986; Akre et al. 1996; Moller and Skakkebaek 1997; Ahlgren et al. 2007). A recent meta-analysis, however, found only modest statistical support for the relationship, estimating the overall odds ratio to be 1.28 (95%CI=0.99–1.65) (Richiardi et al. 2007). High birth weight has also been associated with TGCT in at least one study (Richiardi et al. 2002), although the majority of studies have not supported a relationship (Richiardi et al. 2007). A factor closely related to low birth weight, decreased gestational age, has also been associated with increased TGCT risk (Gershman and Stolley 1988; Richiardi et al. 2002; Coupland et al. 2004). Disentangling the effects of birth weight and gestational age, however, has proven to be challenging, particularly as gestational age is often imprecisely recorded (Klebanoff 2007). A combination of birth weight and gestational age, size-for-gestational-age, may be a better measure of risk than either factor alone (Richiardi et al. 2002).

2.5.2 *Maternal Age*

Maternal age has been reported to be both inversely (Dieckmann et al. 2001; Coupland et al. 2004; Aschim et al. 2006) and directly (Moller and Skakkebaek 1997; Sabroe and Olsen 1998; Wanderas et al. 1998; English et al. 2003) associated with risk. In addition, several studies have reported no association (Swerdlow et al. 1982; Weir et al. 2000). The results, however, are not necessarily contradictory as it is conceivable 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.

2.5.3 *Maternal Parity, Birth Order, Sibship Size*

Low maternal parity and low birth order have been associated with increased TGCT risk in some (Swerdlow et al. 1987a; Prener et al. 1992; Sabroe and Olsen 1998; Westergaard et al. 1998; Richiardi et al. 2004), but not all (Dieckmann et al. 2001;

Richiardi et al. 2002; Coupland et al. 2004; Aschim et al. 2006) studies. Studies that have reported finding a link between TGCT and low birth order estimate 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 (Sharpe 2003) 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 birth order. A large Swedish study, investigating sibship size and risk of all solid tumors, found a risk ratio of 0.71 (95%CI: 0.62–0.82) for testicular cancer for five or more siblings versus none (Altieri and Hemminki 2007). Some previous studies have found similar associations (Morrison 1976b; Swerdlow et al. 1987a; Richiardi et al. 2004) while others have not (Prenen et al. 1992; Moller and Skakkebaek 1996; Dieckmann et al. 2001). 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 both variables are independent risk factors (Richiardi et al. 2004). 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 (Swerdlow et al. 1987a). 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, which may have resulted from increased reproductive control offered by technological advances and increased accessibility to contraception and assisted reproductive techniques (Richiardi et al. 2004).

2.5.4 *Maternal Smoking*

An examination of parallel trends in rates of testicular cancer and female lung and bladder cancers led Clemmesen (1997) to hypothesize that maternal cigarette smoking was a risk factor for TGCT. Clemmesen also suggested that the maternal smoking hypothesis was consistent with the dip in TGCT risk among men born during World War II in Denmark (Moller 1989). Using a similar ecologic design, Pettersson et al. (2004) 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 (Henderson et al. 1979; Brown et al. 1986; Swerdlow et al. 1987a; Moller 1996; Weir et al. 2000; Coupland et al. 2004; McGlynn et al. 2006; Pettersson et al. 2007a). It seems unlikely, therefore, that maternal smoking is a risk factor for TGCT. It remains possible, however, that lung cancer in mothers and testicular cancer in sons cluster in families due to a common genetic mechanism rather than to a common environmental exposure.

2.5.5 Other Perinatal Factors

A number of other perinatal factors have occasionally been associated with risk for testicular cancer. These factors for which there is some evidence of association include hormone use during pregnancy (Depue et al. 1983; Weir et al. 2000), bleeding during pregnancy (Brown et al. 1986; Weir et al. 2000), maternal body weight (Depue et al. 1983; Aschim et al. 2005), maternal socioeconomic status (Moller and Skakkebaek 1996), breech presentation (Coupland et al. 2004), twin birth (Dieckmann et al. 2001; Hemminki and Li 2002b), and trisomy 21 (Down syndrome) (Aschim et al. 2006; Patja et al. 2006). The evidence for hyperemesis gravidarum (Coupland et al. 2004; Aschim et al. 2006), Cesarean section (Moller and Skakkebaek 1997), and having been breastfed (Coupland et al. 2004) is unclear. At present, there is little evidence that paternal age (English et al. 2003; Richiardi et al. 2004), birth length (English et al. 2003; Aschim et al. 2006), pre-eclampsia (Richiardi et al. 2002), circumcision (Swerdlow et al. 1987b), varicocele (Gallagher et al. 1995; Moller et al. 1996), and neonatal jaundice (Richiardi et al. 2002) are associated with TGCT.

2.6 Maternal Endogenous Hormones

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 (Petridou et al. 1997), 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 in these pregnancies (Bernstein et al. 1986). Maternal obesity, a condition consistent with decreased sex-hormone-binding globulin (SHBG) levels and increased free estrogen levels, has also been associated with TGCT risk (Henderson et al. 1988b). Because of these associations, the “estrogen hypothesis” of TGCT was formally introduced in 1993 (Sharpe and Skakkebaek 1993). A complementary hypothesis has suggested that high maternal estrogen levels may not be as culpable as low maternal testosterone levels (Henderson et al. 1988a). This hypothesis was based on the observation that African-American women had higher testosterone levels in pregnancy than white American women (Henderson et al. 1988a). The direct evidence to support the maternal hormone hypotheses, however, has not been great due to the difficulty in examining the relationship between maternal hormone levels and risk of cancer among children 30 years later. Several studies, however, have examined maternal hormone levels in relationship to cryptorchism (Burton et al. 1987; Bernstein et al. 1988; Key et al. 1996; McGlynn et al. 2005b). The results of these studies, in general, have not supported either the maternal estrogen or the maternal androgen hypothesis.

2.7 Maternal Exogenous Hormones

Diethylstilbestrol (DES), a nonsteroidal estrogen first synthesized in 1938, is several times more potent than the endogenous estrogen, 17 β -estradiol. In 1947, the U.S. Food and Drug Administration approved the use of DES in pregnant women to prevent threatened or recurrent abortion. Although it was known by 1953 that DES was ineffective for this purpose (Dieckmann et al. 1953), prescription of DES continued in the U.S. until 1971 and in Europe until 1978. In the U.S., an estimated five to ten million persons were exposed either during pregnancy or while in utero (Noller and Fish 1974).

In mice, in utero DES exposure results in numerous testicular defects including cryptorchism, inflammation, hyperplasia, and adenocarcinoma of the rete testis (Newbold et al. 1985). In humans, several case reports have noted the occurrence of testicular cancer in sons of DES-exposed mothers (Loughlin et al. 1980), and a multicenter study reported a nonsignificant threefold risk of TGCT based on seven cases in the exposed group and two cases in the nonexposed group (Strohsnitter et al. 2001). Other researchers have reported conflicting results (Depue et al. 1983; Moss et al. 1986; Gershman and Stolley 1988) and reviews of the literature have concluded, in general, that the supporting data are equivocal (Giusti et al. 1995). Other disorders of the male reproductive tract, such as hypospadias, cryptorchism, and impaired fertility, have also not been strongly linked to DES exposure (Storgaard et al. 2006). The Danish experience of low exposure to DES in the 1950s, yet greatly increasing TGCT rates, argues that DES alone is unlikely to explain the increase in incidence (Buetow 1995).

2.8 Endocrine-Disrupting Chemicals

Arguably the most hotly debated topic in testicular cancer, at present, is whether there is an association with endocrine-disrupting chemicals (EDCs) (Golden et al. 1998). 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 (Kavlock et al. 1996). EDCs include compounds that are estrogenic (e.g., isoflavones, phthalates, o,p'-DDT, o,p'-DDE, bisphenol A, alkylphenols, some PCBs), antiestrogenic (e.g., dibenzo-*p*-dioxin, tributyltin, some PCBs), antiandrogenic (e.g., vinclozolin, *p,p'*-DDE, methoxychlor, dibenzo-*p*-dioxin, flutamide, linuron, natural pyrethrin, tris (4-chlorophenyl)-methanol), and antigestagenic (e.g., carbamate) (Pflieger-Bruss et al. 2004). 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).

POPs and PCBs act as either weak estrogens or antiandrogens by binding to the estrogen and androgen receptors (Toppari et al. 1996). While the early focus of attention was on the ability of these compounds to act as weak estrogens, subsequent reports highlighted the capability of some compounds to act as antiandrogens. As noted by Kelce et al. (1995), *p,p'*-DDE, a persistent metabolite of DDT, is a potent androgen receptor antagonist. Consistent with this finding is the observation that most of the EDC effects noted in animals have affected the males of experimental animal species rather than the females.

None of the EDCs appear to bind to sex-hormone-binding globulin, and thus, may be capable of increasing total estrogen activity. 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 (Golden et al. 1998). However, it can also be argued that the net combined estrogenic effects of EDCs may exceed those of DES. In support of an effect independent of the estrogen and androgen receptors, it was recently reported that two organochlorine pesticides, toxaphene and chlordane, were capable of binding to the estrogen-related receptor α -1 orphan receptor and modulating aromatase activity (Yang and Chen 1999). If EDC exposure is capable of producing the postulated spectrum of effects seen among the TDS disorders, it seems likely that the exposure would have to be early in gestational life (Parker 1997).

Thus far, only one epidemiologic study of EDCs and TGCT has been reported (Hardell et al. 2003). In an examination of 58 TGCT cases and 61 controls and their respective mothers ($n=35$ case mothers, 22 control mothers) in Sweden, Hardell et al. found that cases had significantly higher levels of *cis*-Nonachlor than did controls. Mothers of cases had significantly higher levels of *cis*-nonachlor, as well as *trans*-nonachlor, hexachlorobenzene and the sum of polychlorinated biphenyl congeners. When the mothers' levels were examined separately by the histology of the sons' tumors (seminoma, nonseminoma), all four of the noted results remained significant in the nonseminoma group, but not in the seminoma group (Hardell et al. 2004). Whether histologic differences truly exist, however, is uncertain as there were small numbers of tumors in each group after stratification.

In addition to the one TGCT study, several, mostly small, studies of EDCs and cryptorchism and/or hypospadias have been reported from around the world. One study of cryptorchism reported that hexachlorobenzene was significantly associated with risk (Hosie et al. 2000), though the finding was not supported by two subsequent studies (Waliszewski et al. 2005; Pierik et al. 2007). Heptachloroepoxide has been associated with risk in one study (Hosie et al. 2000), but not in another (Pierik et al. 2007). In addition, *trans*-Nonachlor (Damgaard et al. 2006), but not β hexachlorocyclohexane (Waliszewski et al. 2005; Pierik et al. 2007) has been associated with risk of cryptorchism. Little support for an association of DDT or DDE with risk of cryptorchism and hypospadias has been offered by four studies (Longnecker et al. 2002; Flores-Luevano et al. 2003; Bhatia et al. 2005; Waliszewski et al. 2005). In sum, the evidence to support a link between EDCs and testicular cancer or cryptorchism in humans is equivocal. Larger studies of both outcomes will be required to determine whether an association exists.

2.9 Postnatal Risk Factors

2.9.1 *Anthropometry*

A number of studies have examined associations between body mass index (BMI) and/or height and TGCT. While two studies found an inverse relationship with BMI (Petridou et al. 1997; Akre et al. 2000) and one study found a direct relationship (Garner et al. 2003) most studies have reported no association (Whittemore et al. 1984; Davies et al. 1990; Thune and Lund 1994; United Kingdom Testicular Cancer Study Group 1994a; Gallagher et al. 1995; Srivastava and Kreiger 2000; Dieckmann and Pichlmeier 2002; Rasmussen et al. 2003; Richiardi et al. 2003; Bjorge et al. 2006; McGlynn et al. 2007). Height, in contrast, has been positively associated with risk in the majority of studies in which it has been examined. Of at least 13 studies reported in the English language literature, seven reported significant positive associations (Gallagher et al. 1995; Akre et al. 2000; Dieckmann and Pichlmeier 2002; Rasmussen et al. 2003; Richiardi et al. 2003; Bjorge et al. 2006; McGlynn et al. 2007). An additional two studies reported nonsignificant positive associations (Swerdlow et al. 1989; United Kingdom Testicular Cancer Study Group 1994a), while four studies reported no association (Whittemore et al. 1984; Davies et al. 1990; Thune and Lund 1994; Petridou et al. 1997). Overall, the bulk of the evidence suggests that taller men are at increased risk of TGCT. As height is a complex trait determined by both genetic and environmental influences, the reason that height is related to TGCT remains to be elucidated. It has been suggested, however, that the association may be related to childhood nutrition (Gallagher et al. 1995), age at puberty (Akre et al. 2000), and/or individual variation in the insulin-like growth factor I system (Zavos et al. 2004).

2.9.2 *Age at Puberty*

While younger age at puberty has been reported to increase TGCT risk (Moss et al. 1986; United Kingdom Testicular Cancer Study Group 1994a), most studies have found, conversely, that older age at puberty decreases risk (Swerdlow et al. 1989; United Kingdom Testicular Cancer Study Group 1994a; Gallagher et al. 1995; Moller and Skakkebaek 1996; Weir et al. 1998; Coupland et al. 1999). 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.

2.9.3 *Nutrition*

A nutritional etiology of TGCT has not been examined extensively; however associations have been reported for diets high in fat and total calories (Armstrong and Doll 1975; Sigurdson et al. 1999), and high in consumption of dairy foods, particularly

milk and cheese (Decarli and La Vecchia 1986; Davies et al. 1996; Ganmaa et al. 2002; Garner et al. 2003). It has been suggested that the dairy food-TGCT association might arise from naturally occurring or synthetic hormones in dairy products (Ganmaa et al. 2002). No relationship, however has been found between dietary phytoestrogen intake and TGCT (Walcott et al. 2002). 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 association between taller stature and TGCT, suggests that any association with diet is likely to be with diet in early life.

2.9.4 Endogenous Hormones in Men

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 (Petersen et al. 1999). 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 (Lee et al. 1998). 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 (Petridou et al. 1997; Walcott et al. 2002). Similarly, evidence that severe acne during adolescence may be inversely related to TGCT, has suggested that higher testosterone levels are protective (Depue et al. 1983; Walcott et al. 2002). 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 (Oliver 1990). 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 cryptorchism.

2.9.5 Physical Activity

Two case-control studies have reported that childhood physical activity is inversely associated with development of TGCT (United Kingdom Testicular Cancer Study Group 1994b; Gallagher et al. 1995). The United Kingdom Testicular Cancer Study Group (1994b) found that participating in various sports at age 16, 20 years, or 1 year prior to diagnosis was protective. An inverse relationship between recreational

activity and TGCT risk was also reported by a Canadian study (Gallagher et al. 1995). Three further studies found no association with TGCT (Paffenbarger et al. 1987; Dosemeci et al. 1993; Thune and Lund 1994), although two of these studies had fewer than 50 cases (Paffenbarger et al. 1987; Thune and Lund 1994) and the third study based physical activity solely on adult occupational history (Dosemeci et al. 1993) and may, therefore, have missed the exposure time window of importance for TGCT risk. Only one study has reported that physical activity and TGCT risk are positively associated (Srivastava and Kreiger 2000). Analyzing data from 212 cases, the study found that moderate and strenuous recreational activity levels during the midteens approximately doubled risk of TGCT. Overall, however, the evidence suggests that increased childhood physical activity and TGCT risk are inversely associated.

2.9.6 Socioeconomic Status and Urban/Rural Residence

Early studies indicated that higher socioeconomic status was associated with an increased risk of testicular cancer (Ross et al. 1979; Depue et al. 1983; Office of Population Censuses and Surveys (OPCS) 1993), while more current studies are indicative of no association (Moller and Skakkebaek 1996; Coupland et al. 2004). These observations may be explained by a recent study from Finland which suggests that testicular cancer rates of different socioeconomic classes are converging, causing the association of socioeconomic status and testicular cancer to diminish (Pukkala and Weiderpass 2002).

Evidence that TGCT risk shares an association with urban/rural residence is conflicting. Some studies have reported that rural residence significantly increases TGCT risk (Lipworth and Dayan 1969; Talerman et al. 1974), while other studies have found only nonsignificantly increased risk estimates for rural residence (Graham et al. 1977; United Kingdom Testicular Cancer Study Group 1994b; Petridou et al. 1997). Conversely, some studies have found no association with urban/rural dwelling (Sonneveld et al. 1999; Toledano et al. 2001) and two studies found higher TGCT risk in urban populations (Moller 1997; Huyghe et al. 2003). Although various methodologies for assigning urban/rural status have been employed by these studies, there remains a lack of consensus on whether residence is associated with risk. Quantitation of more specific exposures associated with these locales may be a better strategy to further elucidate any potential relationship.

2.9.7 Occupation

While there have been many analyses of occupation in relation to testicular cancer, no single profession has yet been unanimously endorsed as a risk factor. Occupational groups suggested to be at increased risk of TGCT, at least by some

studies, are firefighters (Stang et al. 2003; Bates 2007) metal workers (Rhomborg et al. 1995; Pollan et al. 2001), leather workers (Marshall et al. 1990), and aircraft technicians (Foley et al. 1995; Ryder et al. 1997) Agricultural workers (Moller 1997; Hardell et al. 1998) have also been reported to be at increased risk, possibly due to pesticide exposure (Fleming et al. 1999; Guo et al. 2005). Positive associations have also been found with unionized carpenters (Dement et al. 2003), paper mill maintenance employees (Andersson et al. 2003), and writers (Knight et al. 1996). A reduced risk among concrete workers has also been observed (Knutsson et al. 2000).

Occupational exposure to extreme temperatures (Zhang et al. 1995) has been associated with increased testicular cancer risk. The evidence remains unclear whether exposure to dimethylformamide (Ducatman et al. 1986; Levin et al. 1987; Calvert et al. 1990; International Agency for Research on Cancer 1999) or magnetic fields (Floderus et al. 1999; Baumgardt-Elms et al. 2002) increases risk. Occupational exposure to cellular or cordless telephones (Hardell et al. 2007), ionizing radiation (Sont et al. 2001), PVC plastics (Westberg et al. 2005), or diesel or gasoline exhaust fumes (Guo et al. 2004) does not appear to alter risk. In general, white collar workers have been found to be at higher risk of TGCT than blue collar workers; thus, observed occupational associations may be confounded by socioeconomic status (Van den Eeden et al. 1991). In summary, although some occupations and their generic hazards have been associated with TGCT risk, the evidence has been too inconsistent and sparse to identify any specific exposure of importance.

2.9.8 *Viruses*

An infectious etiology of testicular cancer was first suggested based on epidemiologic similarities with Hodgkin disease (Newell et al. 1984). Using paralytic polio as a model, the authors hypothesized that viral infections in late childhood or adolescence might induce adverse tissue responses that would lead to these cancers in young adulthood. Further support for a viral etiology has been the observation that men infected with human immunodeficiency virus (HIV) have an increased risk of testicular cancer (Logothetis et al. 1985; Gabutti et al. 1995; Lyter et al. 1995; Goedert et al. 1998; Frisch et al. 2001) and that other cancers over-represented in HIV(+) individuals are linked to viral infections (e.g., Kaposi sarcoma and human herpes virus 8 (HHV-8); non-Hodgkin lymphoma and Epstein-Barr virus (EBV)). While a number of studies have examined viral antibody titers in TGCT, few have had adequate power to test the hypotheses (Algood et al. 1988; Mueller et al. 1988; Akre et al. 1999). Though infection with the mumps virus is known to cause orchitis in 20–30% of postpubertal males and sterility in a smaller subset, a relationship with testicular cancer has not been clearly demonstrated (Brown et al. 1987; Mueller et al. 1988). Candidate viruses implicated by several studies are EBV and cytomegalovirus (CMV) (Algood et al. 1988; Mueller et al. 1988; Akre et al. 1999). Both viruses are members of the herpes family and are known to cause p53

overexpression, a common finding in TGCT (Muganda et al. 1994). In addition, both viruses have been demonstrated to have oncogenic potential (Morris et al. 1995) and CMV infection during pregnancy, in several case reports, has been associated with cryptorchism. Conversely, at least one study reported that mononucleosis, a manifestation of EBV infection, had an inverse association with TGCT risk (Moss et al. 1986).

One of the more intriguing findings in TGCT has been the observation that many TGCTs express endogenous retroviruses. Human endogenous retroviruses (HERVs), with similarities to exogenous retroviruses known to cause disease in animals, constitute approximately 0.1–0.6% of the human genome (Leib-Mosch et al. 1990). Although most HERVs are defective due to multiple stop codons, recent research indicates that some members of the class II HERV family retain some of their original retroviral functions. For example, HERV sequences are expressed in several tissues and cell lines (Lower et al. 1996) and some encode particles released from teratocarcinoma cell lines (Lower et al. 1993). In addition antibodies specific for the HERV-K10 *gag* and *env* proteins have been identified in patients with seminomas (Sauter et al. 1995). HERV-K transcripts have now been detected in most types of testicular germ cell tumors, as well as in CIS and in the gonocytes of dysgenetic gonads (Herbst et al. 1998). The reason that HERV-K is turned on and the significance of HERV-K expression in TGCT are not understood. It may simply be an epiphenomenon, as suggested by the stimulation of HERV expression by female steroid hormones in a breast cancer cell line (Ono et al. 1987). Immunodeficiency of the host does not appear to be adequate to induce HERV-K10 expression, however, as HIV(+) men are no more likely to have HERV-K antibodies than HIV(–) men (Goedert et al. 1999). As has been demonstrated with other TGCT tumor markers (i.e., human chorionic gonadotropin and alphafetoprotein), HERV-K expression resolves on excision of the tumor. Whether the 60% of TGCT patients who have antibodies to HERV-K10 (Goedert et al. 1999) have different risk factor patterns than the TGCT patients who do not have antibodies has not been previously examined.

2.9.9 Other Factors

Increased TGCT risk has also been reported in association with testicular trauma (Brown et al. 1987; Haughey et al. 1989; Coupland et al. 1999). Some early evidence that increased scrotal temperatures, perhaps due to tight outer- or underwear, might be related to risk (Haughey et al. 1989), has not received wide support by most studies (Brown et al. 1987; Karagas et al. 1989; United Kingdom Testicular Cancer Study Group 1994a). It remains unclear whether testicular torsion (Chilvers et al. 1987; Moller et al. 1996) or having had a history of at least one sexually transmitted disease (United Kingdom Testicular Cancer Study Group 1994b; Moller and Skakkebaek 1999; Husson and Herrinton 2003) are risk factors for TGCT.

2.10 Histologic Difference 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 (1993), it is unlikely that substantial differences in risk factors exist between tumors of various histologies because of the similarity in incidence trends. In addition, mixed tumors composed of both seminoma and nonseminoma elements are not uncommon. The majority of risk factor analyses stratified by histologic group also appear to support a shared etiopathogenesis for seminomas and nonseminomas (Moss et al. 1986; Pike et al. 1987; Prener et al. 1992, 1996; Moller and Skakkebaek 1997; Hardell et al. 1998; Sabroe and Olsen 1998; Weir et al. 2000). 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 (Morrison 1976a; Stone et al. 1991; Prener et al. 1996; Coupland et al. 1999), low birth weight (Wanderas et al. 1998; English et al. 2003), and low birth order (Sabroe and Olsen 1998; Richiardi et al. 2004) are factors predominantly associated with an increased risk of seminoma. Moreover, participation in specific sporting activities (Coupland et al. 1999) and long gestational duration (Richiardi et al. 2002) may be more protective against seminoma (Coupland et al. 1999). Risk factors primarily associated with an increased risk of nonseminoma include testicular trauma (Stone et al. 1991; Coupland et al. 1999), history of at least one sexually transmitted disease (Coupland et al. 1999), younger age at shaving initiation (McGlynn et al. 2007), and short gestational duration (Richiardi et al. 2002). In addition, later puberty may have a stronger protective effect against nonseminoma than seminoma (Moss et al. 1986; Moller and Skakkebaek 1996; Coupland et al. 1999). The literature as a whole, however, is not congruent for any one of these histologic dissimilarities.

2.11 Family and Twin Studies

Study of familial clustering of testicular cancer has been somewhat limited by the relative rarity of the disease. Nevertheless, it has been reported that in comparison with men in the general population, the risk of testicular cancer is eightfold higher in brothers and fourfold higher in sons of affected men (Dieckmann and Pichlmeier 1997; Hemminki and Li 2004; Hemminki and Chen 2006). In order for an environmental exposure to fully account for such an observation, the exposure would have to be perfectly shared among siblings and to increase risk by more than tenfold (Khoury et al. 1988). The higher familial risk among 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 (Heimdal et al. 1997). A similar inference was derived from an analysis of bilateral disease

(Nicholson and Harland 1995). 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 1970s (Einhorn and Donohue 1977) 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 (1994a). Regardless of whether a greater risk is associated with an affected brother or an affected father, a relative risk of 6–10 is consistent with the involvement of predisposing genes (Hopper and Carlin 1992).

Compared to the general population, it has been reported that testicular cancer risk is increased among twins (Dieckmann et al. 2001; Hemminki and Li 2002b). The standardized incidence ratio of risk in men with an affected cotwin is estimated to be 37.5 (95%CI: 12.3–115.6), which is dramatically higher than the eightfold risk cited for men with an affected brother (Swerdlow et al. 1997a). When comparing monozygous vs. dizygous twins, studies have consistently reported that the risk of TGCT, particularly of seminoma, is higher in dizygous twins (Braun et al. 1995; Swerdlow et al. 1997a; Hemminki and Chen 2005). Such a finding argues against a genetic etiology and may support the “estrogen hypothesis” as maternal estrogen levels may be higher in dizygous births due to the existence of two placentae (Sharpe 2003). 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 (Lambalk and Boomsma 1998). In support of this postulate, it has been demonstrated that some men undergoing surgery for testicular cancer have higher FSH levels than unaffected men (Satge et al. 1997). In addition, men with Down syndrome (Satge et al. 1997), a condition associated with testicular cancer (Patja et al. 2006), have higher FSH levels, as do their mothers (van Montfrans et al. 1999). For a detailed discussion of the contribution of genetic factors to the etiology of testicular cancer, see the chapter in this volume by Rapley.

Despite the evidence that testicular cancer clusters in families, 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 1–2.8% of the total (Heimdal et al. 1996; Westergaard et al. 1996; Dieckmann and Pichlmeier 1997; Hemminki and Czene 2002; Hemminki and Li 2004). Secondly, testicular cancer risks are higher in brothers whose ages differ by fewer than 5 years (SIR = 10.81; 95%CI: 7.29–15.45) than in brothers whose ages differ by 5 years or greater (SIR = 6.69; 95%CI: 4.19–10.15) (Hemminki and Li 2004). Thirdly, testicular cancer was reported to have the highest proportion of childhood environmental effects in a familial study of all main cancers (Czene et al. 2002), although part of this estimate may be a consequence of the inability of the model to account for nonadditive (recessive) genetic effects. These studies emphasize the environmental component of testicular cancer pathogenesis and underscore the need to identify such factors, lest they confound the heritable estimates of risk derived from family and linkage studies.

In addition to supporting clustering of testicular cancers, family studies have also reported associations with several other tumors. Record linkage studies of family data from Sweden and Norway have found significant clustering of parental lung cancer with testicular cancer in sons (Stone et al. 1991; Zheng et al. 1996; Petridou et al. 1997; Ekblom and Akre 1998; Pharris-Ciurej et al. 1999), though studies from Denmark have not found similar associations (Kroman et al. 1996; Westergaard et al. 1996). However, one of the Swedish studies noted that although TGCT was significantly associated with parental lung cancer, the association was stronger for late-onset TGCT, which argues against a prenatal exposure (Hemminki and Chen 2006). The extent to which the family clusters can be attributed to smoking is uncertain. For example, a study from the U.K. reported a borderline significantly increased risk of lung cancer among mothers of testicular cancer patients (OR=5.0, 95%CI=0.9–29.6), but found no association between maternal smoking and risk of TGCT among the same individuals (Swerdlow et al. 1987a). Perhaps even more telling is the result of a recent study in the U.S. that examined cancer in the families of nonsmoking lung cancer probands. The study found that there was a significantly increased risk of testicular cancer among the relatives of the non-smoking lung cancer cases (Gorlova et al. 2007). This result may suggest that the lung cancer-testicular cancer association is due to common genetic susceptibility rather than to smoking. If this is the case, it presents opportunities for identifying susceptibility genes that may not have been previously considered. Evidence of an increased incidence of breast cancer in mothers of testicular cancer patients (Moss et al. 1986; Anderson et al. 2000; Hemminki and Li 2004) has been reported by some, but not all studies (Kroman et al. 1996; Broman et al. 2004). Testicular cancer has also been reported to be associated with leukemia, distal colon and kidney cancers, melanoma and connective tissues tumors in a report from the Swedish Family-Cancer Database (Hemminki and Chen 2006).

As with other familial cancer syndromes, there is evidence that both the age of onset and the laterality of the tumor differ in familial vs. sporadic cases. Forman et al. (1992) found that testicular cases with a family history had a significantly earlier age of onset (29 years) when compared with cases who reported no family history (32.5 years). The same researchers also found that the incidence of bilateral disease was 7.3% in the familial cases versus 2.6% in the nonfamilial cases.

2.12 Cancer Risks Among Testicular Cancer Survivors

Testicular cancer survivors have been reported to be at increased risk of developing second cancers, the highest risk of which is a metachronous tumor of the contralateral testis (Fossa et al. 2005; McMaster et al. 2006). Regarding extratesticular malignancies following testicular cancer, an analysis of 14,984 two-month testicular cancer survivors found increased risks for cancers of the rectum, bladder, thyroid, kidney, pancreas, and acute nonlymphocytic leukemia, the latter three of

which were also increased in those who did not receive radiotherapy (McMaster et al. 2006).

An analysis of European cancer registries, which included 29,511 testicular cancer patients, presented similar results (Richiardi et al. 2006). Increased risks, which the authors postulate may have arisen from shared risk factors with TGCT, included esophageal, lung, gall bladder, and bile duct cancers (Richiardi et al. 2006). Increased risks for myeloid and nonlymphoid leukemias were considered a consequence of leukemogenic toxicity, while observed excesses of pancreatic, urinary tract, connective- and soft-tissue sarcoma, and certain gastrointestinal malignancies were thought to pertain to radiotherapy (Richiardi et al. 2006).

The largest study conducted to date, which partially overlaps both geographically and temporally with both the previously discussed studies (McMaster et al. 2006; Richiardi et al. 2006), included 40,576 one-year testicular cancer survivors (Travis et al. 2005). Increased risks were observed for cancers of the stomach, pancreas, pleura, bladder, colon, esophagus, and lung, although there was evidence that the increased risk was associated with radiotherapy, chemotherapy, and combined therapy of the initial testicular cancer (Travis et al. 2005).

New malignancies following testicular cancer may vary by histology of the initial cancer, although many of these second tumor differences are likely the result of the specific therapeutic regimens for the first tumor. In an analysis of SEER data, increased risk of pancreatic cancer following seminoma and increased risk of kidney cancer following nonseminoma were observed, and these excesses remained after exclusion of patients who received radiotherapy (McMaster et al. 2006). An analysis of combined European cancer registry data, however, found risks differed by histology for larynx, small intestine, soft-tissue sarcoma, bladder, myeloid leukemia, brain and nervous system cancers (Richiardi et al. 2006). Lastly, compared to nonseminoma patients, seminoma patients have been found to have an increased risk of metachronous contralateral testicular cancer, an observation considered to be unrelated to radiotherapy (Fossa et al. 2005).

2.13 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 testicular TGCT. The association with perinatal risk factors and congenital anomalies, as well as young age of onset, suggests 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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