TESTICULAR GERM-CELL TUMORS - EPIDEMIOLOGY AND ETIOLOGY

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SUMMARY

Testicular cancer is one of the most common malignancies among young men in the age group 15-40 with peak of incidence in the third decade. Testicular germ cell carcinoma accounts for about 95-97 % of all malignant testicular cancers. Around half of this group is presented by seminomas and the other half is mixed group named as nonseminomas including choriocarcinomas, teratomas, embryonal cell carcinoma, tumor yolk sac. This group of tumors is not evenly spread around the world. It has highest density in North Europe and Denmark and Slovenia in particular. Many risk factors have been blamed to be responsible for cancerogenesis in this group but for the time being there are few proven theories. Along with the epidemiological statistic data new scientific revelations shown and proved heredity of testicular carcinoma in specific genetic lines. In other studies indirect evidence supports that hormonal misbalance even "in utero" can cause conditions for developing malignant cells in the testicular parenchyma. There is still an open issue the reason for deference in density among different countries shearing neighbor territories.

Key words: testicular cancer, germ-cell, etiology, epidemiology, seminoma, nonseminoma

Testicular tumors primarily affect men of age between 15 and 40 years, in this age population is the most common malignant disease. Testicular tumors occupy fourth place in neoplasms of the urogenital system and represent about 0.5 to 3% of all malignancies. In Bulgaria annually register 120-180 new cases according to the register of National Oncology Center /NOC/. The testicular cancer is a successfully treated solid tumors, the survival in the last thirty years is a result of new and more sensitive diagnostic methods - specific tumor markers, new efficient schemes for multi-agent chemotherapy, better equipment for radiotherapy, which together lead to a reduction in mortality from 50% in 1970 to 5% in 1997 (Bosl et al, 1997). Effective therapy even in advanced stages led to considerable improvement in the quality of life. Testicular tumors are among the few cancers with a reliable tumor markers, β -fraction of human horeongonadotropin hormone (β ChHG) and α -fetoprotein. These tumor markers allow monitoring of disease.

Classification of germ cell tumors (GCT):

The recommended pathological classification (modified from the 2004 version of the World Health Organization).

1. Germ cell tumours

- Intratubular germ cell neoplasia, unclassified type (IGCNU)
- Seminoma (including cases with syncytiotrophoblastic cells)

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- Spermatocytic seminoma (mention if there is sarcomatous component)
- Embryonal carcinoma
- Yolk sac tumour
- Choriocarcinoma
- Teratoma (mature, immature, with malignant component)
- Tumours with more than one histological type (specify percentage of individual components).

2. Sex cord/gonadal stromal tumours

- Leydig cell tumour
- Malignant Leydig cell tumour
- Sertoli cell tumour
 - lipid-rich variant
 - sclerosing
 - large cell calcifying
- Malignant Sertoli cell tumour
- Granulosa cell tumour
 - adult type
 - juvenile type
- Thecoma/fibroma group of tumours
- Other sex cord/gonadal stromal tumours
 - incompletely differentiated
 - mixed
- Tumours containing germ cell and sex cord/gonadal stromal (gonadoblastoma).

3. Miscellaneous non-specific stromal tumours

- Ovarian epithelial tumours
- Tumours of the collecting ducts and rete testis
- Tumours (benign and malignant) of non-specific stroma.

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Testicular Cancer (C62), World Age-Standardised Incidence and Mortality Rates, World Regions, 2008 Estimates

World Region	Incidence Rate	Mortality Rate
Western Europe	7,8	0,2
Australia/New Zealand	6,7	0,2
Northern Europe	6,7	0,2
Northern America	5,1	0,2
Southern Europe	4,2	0,3
Central America	3,7	0,7
Central and Eastern Europe	2,6	0,6
South America	2,4	0,4
Western Asia	1,5	0,6
World	1,5	0,3
South-Central Asia	0,8	0,4
South-Eastern Asia	0,8	0,3
Caribbean	0,7	0,2
Southern Africa	0,7	0,4
Northern Africa	0,6	0,3
Eastern Africa	0,5	0,3
Eastern Asia	0,5	0,1
Middle Africa	0,2	0,1
Western Africa	0,2	0,2

Fig (1) Prepared by Cancer Research UK ,Original data sources:

Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer, 2010. Available from: <http://globocan.iarc.fr>

Fig (2). The age-standardized incidence of testicular cancer increased over time in all countries, although patterns for the three Baltic countries are less clear due to the small number of cases. The increasing trend was evident both for seminomas and nonseminomas. The highest incidence was found in Denmark followed by Norway and Sweden.

-Testicular cancer incidence in eight northern European countries: secular and recent trends. Richiardi L, Bellocco R, Adami HO, Torrang A, Barlow L, Hakulinen T, Rahu M, Stengrevics A, Storm H, Tretli S, Kurtinaitis J, Tyczynski JE, Akre O. Department of Medicine, Karolinska Hospital, Stockholm, Sweden

97% of testicular tumours are germ-cell tumours (GCT), 4% are lymphomas and the remaining 1% is composed of various rare histologies. Lymphomas are nearly always found in men aged over 50 and are generally treated as a different disease entity from GCTs.

GCTs can be divided into two main groups: about 40–45% are seminomas and a similar percentage are nonseminomas.

Testicular Cancer (C62), European Age-Standardised Incidence and Mortality Rates, EU-27 Countries, 2008 Estimates

Country	Incidence Rate	Mortality Rate
Denmark	10,7	0,5
Slovenia	9,2	0,5
Czech Republic	8,9	0,7
Luxembourg	8,9	0
Slovakia	8,9	0,7
Germany	8,8	0,3
Ireland	8,1	0,2
The Netherlands	8,1	0,3
Hungary	7,9	0,8
Austria	7,8	0,4
France (Metropolitan)	7,3	0,2
Cyprus	7	0,2
UK	6,9	0,2
Italy	6,4	0,3
Sweden	6,3	0,3
EU-27	6,1	0,4
Bulgaria	5,7	1
Belgium	5,3	0,2
Finland	5	0,2
Malta	4,1	0,5
Poland	3,5	0,7
Latvia	3,4	0,8
Spain	2,9	0,1
Estonia	2,9	0,8
Lithuania	2,4	0,5
Portugal	2,3	0,4
Romania	1,9	0,5
Greece	1,3	0,3

Prepared by Cancer Research UK

Original data sources:

European age-standardised rates were calculated by the Statistical Information Team at Cancer Research UK, 2011 using data from GLOBOCAN, IARC, version 1.2. <http://globocan.iarc.fr/>

Testicular Cancer (C62), European Age-Standardised Incidence and Mortality Rates, EU-27 Countries, 2008 Estimates

The nonseminoma group contains a variety of histological subtypes including malignant teratoma differentiated (MTD), malignant teratoma intermediate (MTI) and malignant teratoma undifferentiated (MTU), embryonal cell carcinoma, tumor yolk sac and chorion carcinoma

Nonseminomas tend to occur on average ten years earlier than seminomas. Incidence of nonseminomas peaks in the 20-35 age group while incidence of seminomas peaks in the 30-45 age group. Some GCTs (10-15%) are a mixture of seminoma and nonseminoma and have a peak age incidence halfway between the nonseminomas and seminomas. They are usually classified and treated as nonseminomas.

GCTs are thought to develop from a non-invasive lesion called carcinoma *in situ* (CIS) of the testis (also called intratubular germ-cell neoplasia unclassified (IGCNU) and testicular intraepithelial neoplasia (TIN)), whose malignant transformation is likely to be influenced by hormones at or after puberty.

Epidemiology and Etiology:

Annually in the U.S. are diagnosed approximately 6900 new cases of testicular cancer (Greenlee et al, 2000). Average annual incidence, corrected for age is about 3.7 per 100,000, which is two-fold increase compared to the early twentieth century. Similar trend is observed in Denmark, where the incidence increased from 3.4 to 6.4 per 100 000 between 1945 and 1970. (Slemmesen, 1974).

Average annual incidence rate is highest in white caucasians Denmark and Norway, Switzerland, Germany. It has intermediate values in the U.S. and UK, and is lowest in Africa and Asia. The only exception to this is the New Zealand Maoris, who have a high rate of testicular cancer. The peak of incidence of testicular cancer occur in late adolescence and young age (20 to 40 years), elderly (over 60 years) and childhood (0 to 10 years). highest incidence of testicular cancer occurs in young men making these neoplasms most common solid malignancies in the age group between 20 and 34 and the second frequency band from 35 40 years. Testicular seminoma is rare before the age of 10 and after 60 years. It is the most common histological type of carcinoma of the testis with a peak incidence between 35 and 39 years. Spermatocyte seminoma (approximately 10% of all seminoma) most commonly seen in patients over 50's. Embryonal and teratocarcinoma affects mostly aged between 25 and 35 years. Horiocarcinoma (1% to 2% of total GCT) occurs most often between 20 and 30 years. Yolk sac tumors are the predominant histologic variant in infants and children, but often found in the mixture GCT in adults. Histological benign variant of pure teratoma of the testis occurs in children, but often found in the composition of mixed GCT in adults. Only 1-2% of cases are bilateral at diagnosis. The histological type varies, although there is a clear predominance (90-95%) of germ cell tumours. Peak incidence is in the third decade of life for nonseminoma, and in the fourth decade for pure seminoma.

Familial clustering has been observed, particularly among siblings.

Experimental and clinical data confirm the importance of various congenital and acquired factors in the etiology of GCT. During differentiation the primary germ cells can be damaged by these factors, leading to disturbances in differentiation. Epidemiological risk factors for the development of testicular tumours are: a history of cryptorchidism or undescended testis (testicular dysgenesis syndrome), Klinefelter's syndrome, familial history of testicular tumours among first-grade relatives (father/brothers), the presence of a contralateral tumour or Tin, and infertility. Tallness was associated with a risk of germ cell cancer, although further confirmation is needed. Major role in the etiology of cancer of the testicles play cryptorchidism, gonadal dysgenesis, disbalance of the sex hormones, the hereditary predisposition. LeComete (1851) was the first to make the relationship between frequency of maldescensus testis testicular cancer. The frequency of disease incidence is over 20 to 40 times higher in cryptorchidism or after orchidopexy. Around 7% to 10% of patients with testicular tumors had a previous history of cryptorchidism (Whitaker, 1970). Mostofi (1973) describes five possible factors that may play a causal role in cryptorchidism: abnormal morphology of germ cells, raising the ambient temperature, disturbance of blood circulation, endocrine dysfunction and gonadal dysgenesis.

An increase in the incidence of testicular cancer was detected during the 1970s and 1980s, particularly in Northern European countries, and there is a clear trend towards an increased testicular cancer incidence in the last 30 years in the majority of the industrialised countries in North America, Europe and Oceania, although surprising differences in incidence rates are seen between neighbouring countries (4,5). Data from the Surveillance Epidemiology and End Results Program during the years 1973 to 1998 show a continuing increased risk among Caucasian men in the USA only for seminoma

The dramatic increase in the incidence of testicular cancer has led to an intense search for its causes, but, as yet, no preventable risk factors have been found. Both environmental and genetic factors are likely to be involved.

Some groups of men are at increased risk of developing testicular cancer (Table 4.1).

Testicular cancer

Known risk factors for testicular cancer

Demographic	Age 20-49
	Race – Caucasian
Medical conditions	Previous testicular cancer
	Carcinoma <i>in situ</i> of testis
	Cryptorchidism
	Inguinal hernia
	Subfertility
Genetic	Close family relative with testicular cancer

Previous testicular cancer

A previous diagnosis of testicular cancer increases the risk of developing a subsequent (metachronous) testicular tumour by around 12-fold (1). Men with a previous extragonadal germ cell tumour (GCT) have a 60-fold higher risk.

Untreated carcinoma *in situ* (CIS) of the testis will almost certainly progress to malignancy: around half of all men diagnosed with CIS of the testis where it is not treated will develop invasive testicular cancer within five years.

Cryptorchidism

Cryptorchidism, a common congenital abnormality in males - at birth 6% of all male babies have undescended testes but most of these descend spontaneously by 3 months by which time only 1.6% of babies still have one or more undescended testes, or maldescent testicle (MDT), is one of a range of testicular abnormalities known to increase the risk of testicular cancer. Correction of cryptorchidism is possible through a procedure known as orchiopexy.

About 5-10% of GCT patients have a history of cryptorchidism. According to a large Swedish study, cryptorchidism is associated with a two-fold increased risk of testicular cancer in men who underwent orchiopexy before the age of 13, but risk of testicular cancer is more than five times higher for men treated at the age of 13 or later. A meta-analysis showed that, for men with unilateral cryptorchidism, risk of testicular cancer in the other testis is almost doubled, while risk for testicular cancer in the same testis is six times higher.

Cryptorchidism is also associated with CIS of the testis, with around 2-3% of men with a history of cryptorchidism at risk of developing CIS (6). Cryptorchidism is more common in low birth weight babies, a characteristic which may be associated with an increased risk of testicular cancer.

Other medical conditions

Inguinal hernia has been associated with a 63% increased risk of testicular cancer (9). Hypospadias has been associated with an 88% increase in risk.

More recently the diagnosis of microlithiasis (micro-calcifications in the testis detected by ultrasound) has been associated with an increase in risk of testicular cancer, though the precise relationship remains to be determined.

It has been suggested that population trends for problems with male reproductive health (including an increase in MDT, decreasing sperm quality, and increasing rates of testicular cancer) may have a common, but as yet unproven, aetiology. Low fertility in general has been linked to a two-three-fold higher risk of testicular cancer. There is some evidence that brothers of men with testicular cancer have reduced fertility.

Hormonal causes. The fluctuation in levels of the sex hormones and disruption of the axis hypothalamus-pituitary-gonads can help carcinogenesis in experimental animals and humans. Application of estrogen in pregnant mice resulted in maldescent and dysgenesis of the testes in the

offspring (Nomura & Kanzak, 1977). Similar changes were seen in children of women who received diethylstilbestrol (Cosgrove et al, 1977) or oral contraceptives (Rothman & Louik, 1978) in the early stages of pregnancy. Exogenous administration of estrogen is associated with increased incidence of Leydig cell tumors.

Inherited risk

Family history of testicular cancer has long been recognized as a significant risk factor. It is still the strongest known risk factor for testicular germ cell tumors. Genetic effects have been estimated to account for about 25% of susceptibility to testicular cancer (see Czene et al, 2002), putting it in third place with regard to heritability among all cancers. Men with a father diagnosed with testicular cancer have a four-fold risk increase and those with a brother diagnosed with the disease have a nine-fold risk increase. Having a brother with a testicular germ cell tumor increases a man's risk 10 to 13-fold. This is higher than for any other cancer. Having a father with testicular cancer increases the risk 4-fold. Twin data also show a greatly increased risk between both dizygotic (35-fold) and monozygotic (75-fold) twins. In spite of this considerable familial risk of testicular cancer, there has been little progress in the identification of specific genetic risk factors for this type of cancer - until the recent discovery of the genetic variants used in the deCODEme genetic test.

It is thought that germ cell tumours are initiated during foetal development, most likely in the first trimester, and that they progress to invasive cancer under the influence of adult hormones. Research has focused on maternal factors which could influence foetal development.

Of particular interest is the relationship between high levels of circulating oestrogen and a number of male reproductive disorders that are increasing in frequency, including cryptorchidism, urethral abnormalities, poor semen quality and testicular cancer. Indirect evidence supports this oestrogen over-exposure hypothesis. Conditions that increase foetal exposure to oestrogen, including first pregnancy, twins, and severe maternal nausea, are also associated with increased risk of testicular cancer. However, epidemiological studies do not consistently confirm this association and more research is needed to clarify the role of in utero hormonal exposure.

Low birth weight babies and babies who are small for gestational age may be at increased risk of testicular cancer, supporting the theory that prenatal influences are important. However, there appears to be an "s-shaped" relationship between birth weight and testicular cancer risk, with men that weigh more than 4 kilos at birth also at an increased risk. This may be related to adult height (see below).

Genetic changes have been described in patients with testicular cancer. A specific genetic marker (an isochromosome of the short arm of chromosome 12 - i(12p) - has been described in all histological types of germ cell tumours (7). Intratubular germ cell neoplasia (testicular intraepithelial neoplasia, Tin) shows the same chromo-

somal changes, and alterations in the p53 locus have been found in 66% of cases of testicular Tin (8).

A deregulation in the pluripotent programme of fetal germ cells (identified by specific markers such as M2A, C-KIT and OCT4/NANOG) is probably responsible for the development of Tin and germ cell neoplasia. There is overlap in the development to seminoma and embryonal carcinoma as shown by genomewide expression analysis and detection of alpha-fetoprotein (AFP) mRNA in some atypical seminoma (9,10).

Continued genome wide screening studies and gene expression analysis data suggest testis cancer specific gene mutations on chromosomes 4,5,6 and 12 (namely expressing SPRY4, kit-Ligand and Synaptopodin)

European ancestry. Testicular cancer is more common in some ethnic and social groups than others. In the U.S. for example, men of European ancestry are about five times more likely than men of African American descent to develop testicular cancer, and their risk is more than three times that of Asian American and American Indian men (according to SEER statistics). However, ethnic differences do not tell the whole story. Even among males of European descent, surprising differences have been found in the incidence of testicular cancer. Within Scandinavia, for example, the incidence rates were considerably higher in Denmark than in Finland (according to a studies by Huyghe et al, in 2003 and 2007).

Smoking

Evidence on maternal smoking is conflicting. A strong correlation has been identified between female smoking trends and rates of testicular cancer in Nordic countries and a positive association with maternal lung cancer has been observed in Sweden.

However, one case-control study showed a significant reduction in risk of testicular cancer in offspring of women who smoke heavily while others report no association.

Other risk factors

Increased adult height is associated with risk of testicular cancer. Risk ratios have varied from 17% for men over 180 cm compared to 170-179 cm, to a three-fold risk increase for 195 cm or taller, compared to 175-79 cm, and a reduction in risk for men who are shorter than average. This factor may be connected to hormonal and dietary factors. Population trends towards increasing adult height are consistent with the rising trends of testicular cancer incidence.

Trauma. Despite that injury is generally considered as a possible etiologic factor for carcinogenesis relationship is not proven. Most of the authors believe that trauma to the enlarged testicle is rather leading reason towards an early search for medical help than cause.

Testicular atrophy. Nonspecific or parotitis associated testicular atrophy is considered as a potential causative factor for cancer of testis. Despite this there is room for speculation on the role of testicular atrophy in carcinogenesis suggests that it is the result of hormonal imbalance with local subsequent malignant transformation.

White men have a higher risk of testicular cancer than men of other ethnicities, according to a Thames Cancer Registry study. The higher risk in white men has also been shown in America, particularly in comparison to incidence rates in black men.

Many occupations have been linked to increased testicular cancer risk, but the specific risks are not clear (5).

There is evidence that men with HIV or AIDS have a 35% increased risk of testicular cancer (45).

REFERENCES

1. Fossa, S.D., et al., Risk of contralateral testicular cancer: a population-based study of 29,515 U.S. men. *J Natl Cancer Inst*, 2005. **97**(14): p. 1056-66.
2. Hartmann, J.T., et al., Incidence of metachronous testicular cancer in patients with extragonadal germ cell tumors. *J Natl Cancer Inst*, 2001. **93**(22): p. 1733-8.
3. Giwercman, A., J. Muller, and N.E. Skakkeboek, Cryptorchidism and testicular neoplasia. *Horm Res*, 1988. **30**(4-5): p. 157-63.
4. Jorgensen, N., et al., Clinical and biological significance of carcinoma in situ of the testis. *Cancer Surv*, 1990. **9**(2): p. 287-30E2.
5. Garner, M.J., et al., Epidemiology of testicular cancer: an overview. *Int J Cancer*, 2005. **116**(3): p. 331-9.
6. Giwercman, A., et al., Prevalence of carcinoma in situ and other histopathological abnormalities in testes of men with a history of cryptorchidism. *J Urol*, 1989. **142**(4): p. 998-1001: discussion 1001-2.
7. Coupland, C.A., et al., Maternal risk factors for testicular cancer: a population-based case-control study (UK). *Cancer Causes Control*, 2004. **15**(3): p. 277-83.
8. English, P.B., et al., Parental and birth characteristics in relation to testicular cancer risk among males born between 1960 and 1995 in California (United States). *Cancer Causes Control*, 2003. **14**(9): p. 815-25.
9. Cook, M.B., et al., A systematic review and meta-analysis of perinatal variables in relation to the risk of testicular cancer--experiences of the son. *Int J Epidemiol*, 2010.
10. Miller, F.N., et al., Testicular calcification and microlithiasis: association with primary intra-testicular malignancy in 3,477 patients. *Eur Radiol*, 2007. **17**(2): p. 363-369.
11. Bennett, H.F., et al., Testicular microlithiasis: US follow-up. *Radiology*, 2001. **218**(2): p. 359-63.
12. Ganem, J.P., Testicular microlithiasis. *Curr Opin Urol*, 2000. **10**(2): p. 99-103.
13. Boisen, K.A., et al., Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries. *Lancet*, 2004. **363**(9417): p. 1264-9.
14. Carlsen, E., et al., Evidence for decreasing quality of semen during past 50 years. *Bmj*, 1992. **305**(6854): p. 609-13.
15. Skakkebaek, N.E., E. Rajpert-De Meyts, and K.M. Main, Testicular dysgenesis syndrome: an increasingly common developmental disorder with

- environmental aspects. *Hum Reprod*, 2001. **16**(5): p. 972-8.
16. Skakkebaek, N.E., Testicular dysgenesis syndrome: new epidemiological evidence. *Int J Androl*, 2004. **27**(4): p. 189-91.
17. Jacobsen, R., et al., Risk of testicular cancer in men with abnormal semen characteristics: cohort study. *Bmj*, 2000. **321**(7264): p. 789-92.
18. Doria-Rose, V.P., M.L. Biggs, and N.S. Weiss, Subfertility and the risk of testicular germ cell tumors (United States). *Cancer Causes Control*, 2005. **16**(6): p. 651-6.
19. Walsh, T.J., et al., Increased risk of testicular germ cell cancer among infertile men. *Arch Intern Med*, 2009. **169**(4): p. 351-6.
20. Richiardi, L. and O. Akre, Fertility Among Brothers of Patients with Testicular Cancer. *Cancer Epidemiol Biomarkers Prev*, 2005. **14**(11): p. 2557-2562.
21. Hemminki, K. and X. Li, Familial risk in testicular cancer as a clue to a heritable and environmental aetiology. *Br J Cancer*, 2004. **90**(9): p. 1765-70.
22. Horwich, A., J. Shipley, and R. Huddart, Testicular germ-cell cancer. *The Lancet*, 2006. **367**(9512): p. 754.
23. Oosterhuis, J.W. and L.H. Looijenga, Current views on the pathogenesis of testicular germ cell tumours and perspectives for future research: highlights of the 5th Copenhagen Workshop on Carcinoma in situ and Cancer of the Testis. *Apmis*, 2003. **111**(1): p. 280-9.
24. Sharpe, R.M. and N.E. Skakkebaek, Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet*, 1993. **341**(8857): p. 1392-5.
25. Westergaard, T., et al., Testicular cancer risk and maternal parity: a population-based cohort study. *Br J Cancer*, 1998. **77**(7): p. 1180-5.
26. Swerdlow, A.J., et al., Risks of breast and testicular cancers in young adult twins in England and Wales: evidence on prenatal and genetic aetiology. *Lancet*, 1997. **350**(9093): p. 1723-8.
27. Richiardi, L., et al., Body Size at Birth and Adulthood and the Risk for Germ-cell Testicular Cancer. *Cancer Epidemiol Biomarkers Prev*, 2003. **12**(7): p. 669-673.
28. Pettersson, A., et al., Women smoking and testicular cancer: One epidemic causing another? *Int J Cancer*, 2004. **109**(6): p. 941-4.
29. Kaijser, M., et al., Maternal lung cancer and testicular cancer risk in the offspring. *Cancer Epidemiol Biomarkers Prev*, 2003. **12**(7): p. 643-6.
30. Weir, H.K., et al., Pre-natal and peri-natal exposures and risk of testicular germ-cell cancer. *Int J Cancer*, 2000. **87**(3): p. 438-43.
31. Moller, H. and N.E. Skakkebaek, Risks of testicular cancer and cryptorchidism in relation to socio-economic status and related factors: case-control studies in Denmark. *Int J Cancer*, 1996. **66**(3): p. 287-93.
32. Chen, Z., et al., Risk of childhood germ cell tumors in association with parental smoking and drinking. *Cancer*, 2005. **103**(5): p. 1064-71.
33. Dieckmann, K-P., et al., Tallness is associated with risk of testicular cancer: evidence for the nutrition hypothesis. *Br J Cancer*, 2008.
34. Richiardi, L., et al., Body size at birth and adulthood and the risk for germ-cell testicular cancer. *Cancer Epidemiol Biomarkers Prev*, 2003. **12**(7): p. 669-73.
35. Dieckmann, K.P. and U. Pichlmeier, Is risk of testicular cancer related to body size? *Eur Urol*, 2002. **42**(6): p. 564-9.
36. Weir, H.K., N. Kreiger, and L.D. Marrett, Age at puberty and risk of testicular germ cell cancer (Ontario, Canada). *Cancer Causes Control*, 1998. **9**(3): p. 253-8.
37. Aetiology of testicular cancer: association with congenital abnormalities, age at puberty, infertility, and exercise. United Kingdom Testicular Cancer Study Group. *Bmj*, 1994. **308**(6941): p. 1393-9.
38. Garner, M.J., et al., Dietary risk factors for testicular carcinoma. *Int J Cancer*, 2003. **106**(6): p. 934-41.
39. Davies, T.W., et al., Adolescent milk, dairy product and fruit consumption and testicular cancer. *Br J Cancer*, 1996. **74**(4): p. 657-60.
40. Ganmaa, D., et al., Incidence and mortality of testicular and prostatic cancers in relation to world dietary practices. *Int J Cancer*, 2002. **98**(2): p. 262-7.
41. Pettersson, A., et al., Age at surgery for undescended testis and risk of testicular cancer. *N Engl J Med*, 2007. **356**(18): p. 1835-41.
42. Stang, A., et al., Adolescent Milk Fat and Galactose Consumption and Testicular Germ Cell Cancer. *Cancer Epidemiol Biomarkers Prev*, 2006. **15**(11): p. 2189-95.
43. McGlynn, K.A., et al., Body size, dairy consumption, puberty, and risk of testicular germ cell tumors. *Am J Epidemiol*, 2007. **165**(41): p. 355-63.
44. Michos, A., et al., Birth weight and the risk of testicular cancer: A meta-analysis. *Int J Cancer*, 2007.
45. Grulich, A.E., et al., Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet*, 2007. **370**(9581): p.59-67
46. Akre, O., et al., Risk of contralateral testicular cancer among men with unilaterally undescended testis: a meta analysis. *Int J Cancer*, 2009, **124**(3): p.687-9
47. Dieckmann, K-P., and Skakkebaek, N.E., Carcinoma in situ of the testis: review of biological and clinical features. *Int J Cancer*, 1999. **83**(6): p.815-22
48. Neale, R.E., et al., Testicular cancer in twins: a meta-analysis. *Br J Cancer*, 2008. **98**(1): p.171-3
49. Jack, R.H., et al., Testis and prostate cancer incidence in ethnic groups in South East England. *Int J Androl*, 2007. **30**(4): p.215-20
50. SEER Stat Fact Sheets: Testis. SEER/NCI, 2010.
51. Cook, M.B., et al., A systematic review and meta-analysis of perinatal variables in relation to the risk of testicular cancer-experiences of the mother. *Int J Epidemiol*, 2009. **38**(6): p.1532-42
52. Schnack, T.H., et al., Familial coaggregation of cryptorchidism, hypospadias, and testicular germ cell

- cancer: a nationwide cohort study. *J Natl Cancer Inst*, 2009. **102**(3): p.187-92
53. Bjorge, T. et al., The impact of height and body mass index on the risk of testicular cancer in 600,000 Norwegian men. *Cancer Causes Control*, 2006. **17**(7)
54. Czene K, Lichtenstein P, Hemminki K. Environmental and heritable causes of cancer among 9.6 million individuals in the Swedish Family-Cancer Database. *Int J Cancer*. 2002 May 10; **99**(2):266
55. Katherine A. McGlynn and Michael B. Cook., Etiologic factors in testicular germ cell tumors. *Future Oncol*. 2009 November; **5**(9): 1389-1402.