Testicular Tumors

Epidemiological and clinical perspectives

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Thanks to

- Niels Jørgensen, Anna-Maria Andersson, Henrik Leffers, Ewa Rajpert-De Meyts, Anders Juul and several of their Ph.D. students
- Jorma Toppari, Finland
- Other European collaborators
- And many others

Some evidence that fetal exposure to exogenous hormones increases risk of testis cancer

- Henderson's estrogen hypothesis, (several papers by Henderson et al. 1972-1988)
- Exposure to sex steroids, incl. estrogens (Weir et al. 2000)
- Exposure to DES (?) (Strohsnitter et al. 2001, Relative rate of exposed: 3.05
  unexposed 0.65-22.0)

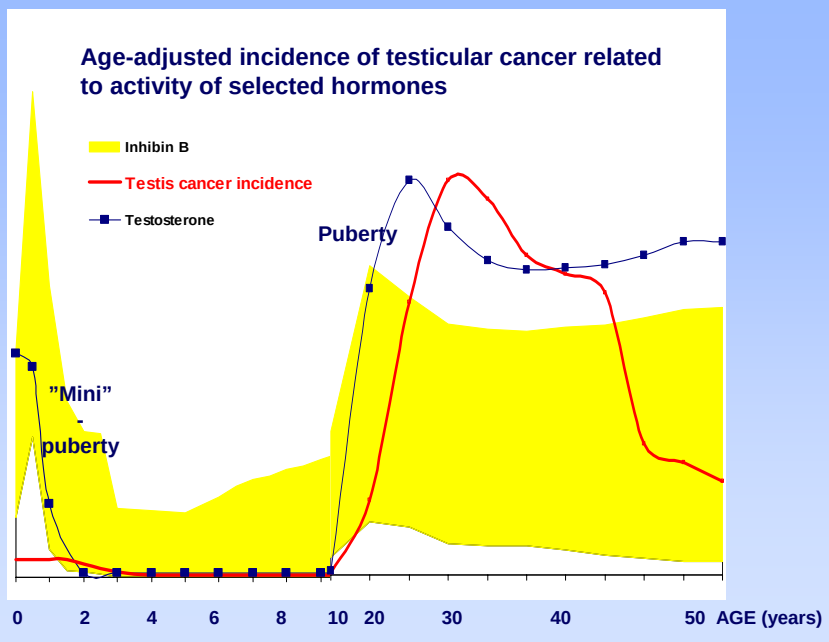
Testicular neoplasms

- Germ cell-derived tumors: >90%
  - infantile
    - Mature teratoma
    - Yolk sac tumors
  - of adolescents and young adults
    - Seminoma (Classical Seminoma)
    - Nonseminoma (Teratoma)
  - of older men
    - Spermatocytic seminoma
- Leydig-cell tumors (~2%)
- Sex cord stromal tumors (Sertoli cell tumors) and mixed germ cell-sex cord stromal tumors (~2%)
- Malignant lymphoma (~6%, but 67% in men >70 years old)
- Myosarcoma

Pike et al. 1987; Scully et al. 1995; Ulbright et al. 1999

Testicular cancer

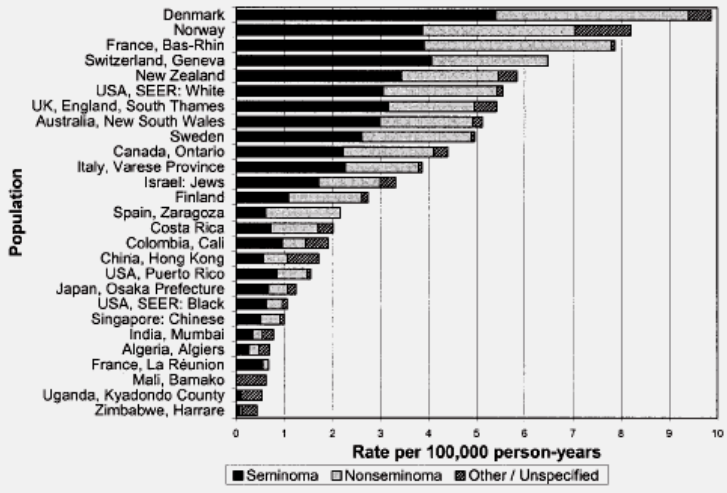
- Why are there postnatal and postpubertal peaks?



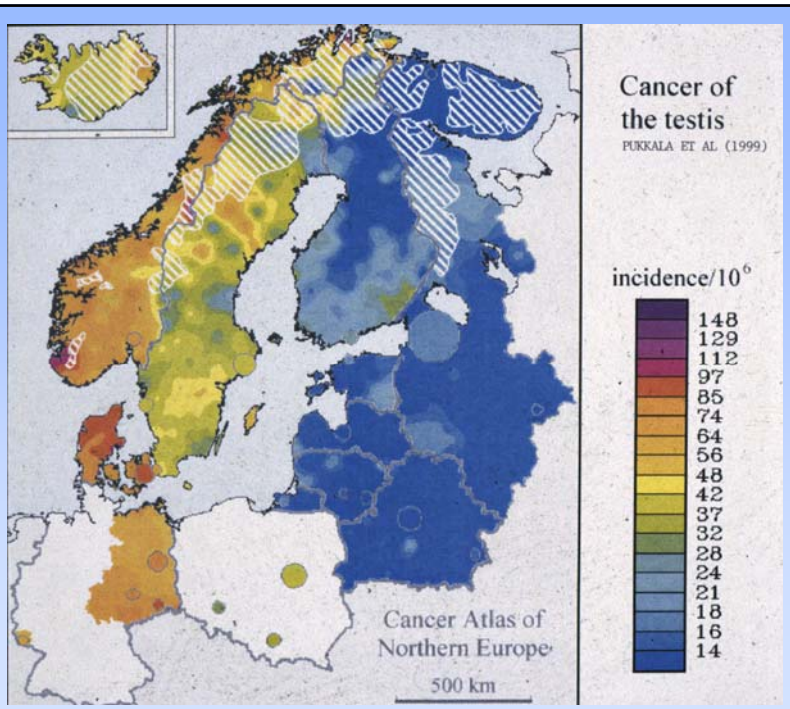
Testicular cancer

- Why are there postnatal and postpubertal peaks?
- Why so huge differences in incidence rates?

Population for selected populations for the time period 1993-1997



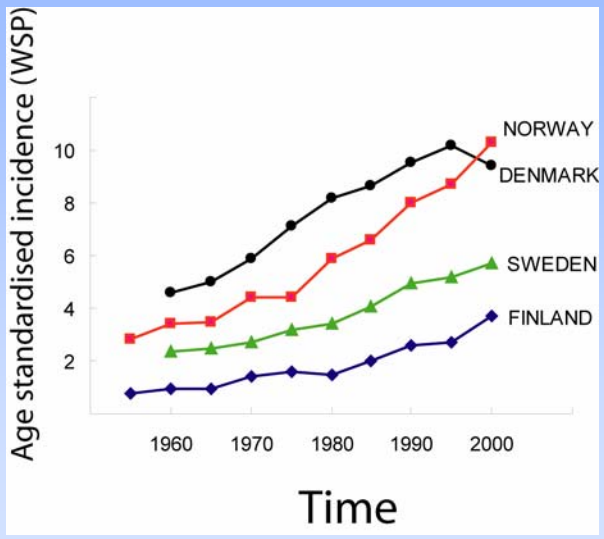
Int J Cancer. 2005



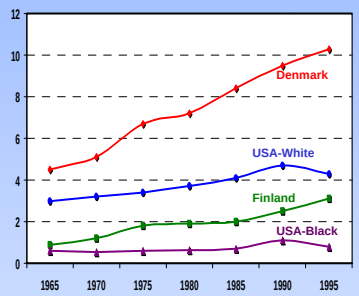
Testicular cancer

- Why are there postnatal and postpubertal peaks?
- Why so huge differences in incidence rates?
- Why are testis cancer rates increasing all over the world, particularly in Caucasians ?

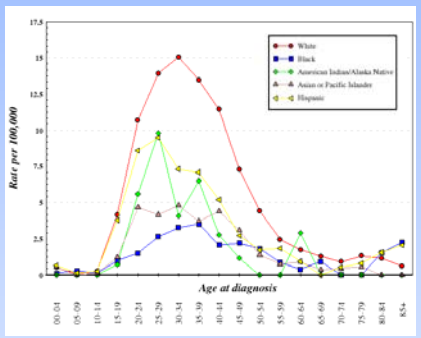
Rates in testis cancer



Testicular germ cell cancer: A growing problem



The incidence of testicular cancer has been increasing



Testicular cancer is predominantly a disease of young men

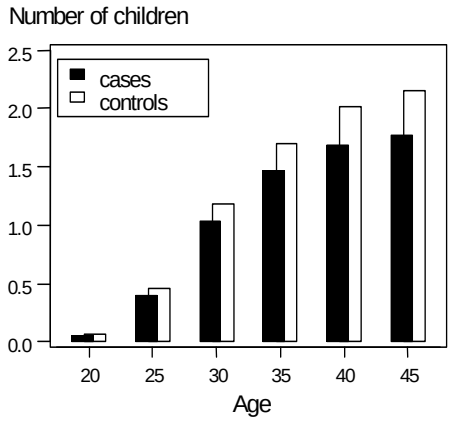
Testicular cancer

- Why are there postnatal and postpubertal peaks?
- Why so huge differences in incidence rates?
- Why are testis cancer rates increasing all over the world, particularly in Caucasians?
- Why is testis cancer more likely to occur in patients with cryptorchidism, *exept those with hypogonadotropic hypogonadism?*

Testicular cancer

- Why are there postnatal and postpubertal peaks?
- Why so huge differences in incidence rates?
- Why are testis cancer rates increasing all over the world?
- Why are testis cancer risk factors all prenatal?
- Why is testis cancer more likely to occur in patients with cryptorchidism, *exept those with hypogonadotropic hypogonadism*?
- Why do men with testis cancer often have poor semen quality at the time of diagnosis of tumor?

Evidence for decreased fertility in men who later developed testicular cancer



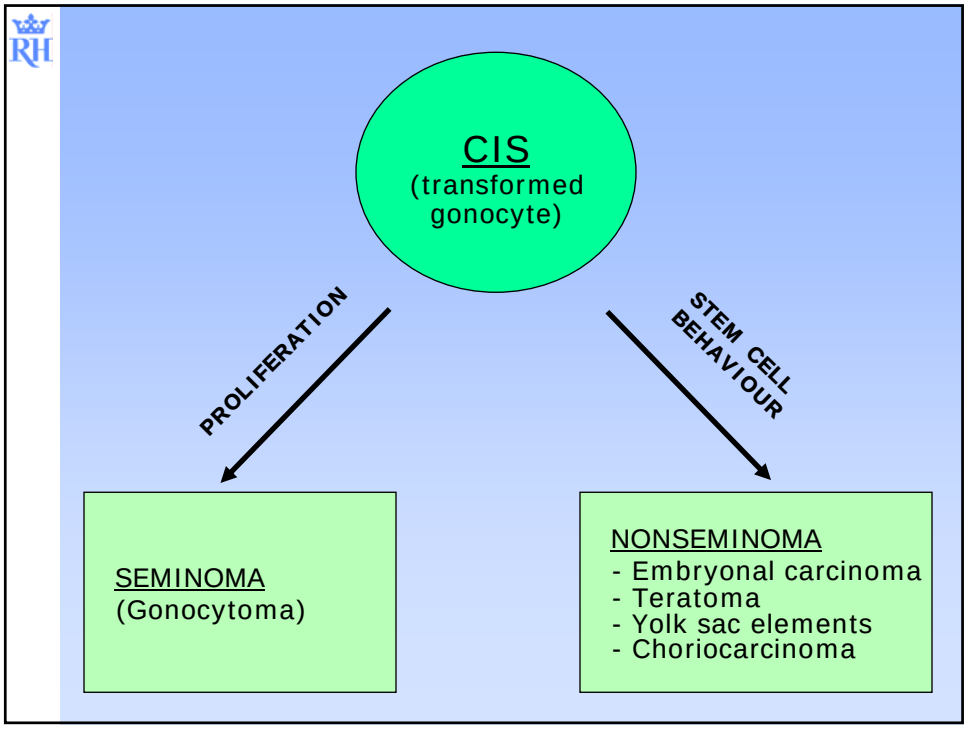
Møller & Skakkebæk, Br Med J, 1999

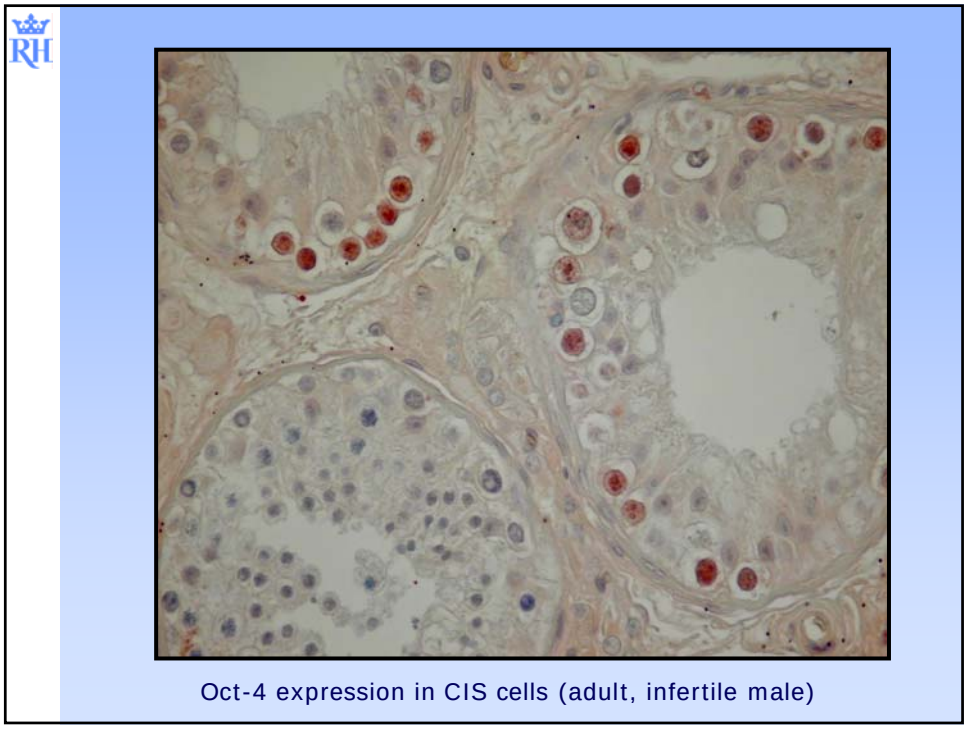
Cancer Causes and Control (2005) 16:295–299
DOI 10.1007/s10552-004-4024-2

Fertility patterns prior to testicular cancer diagnosis

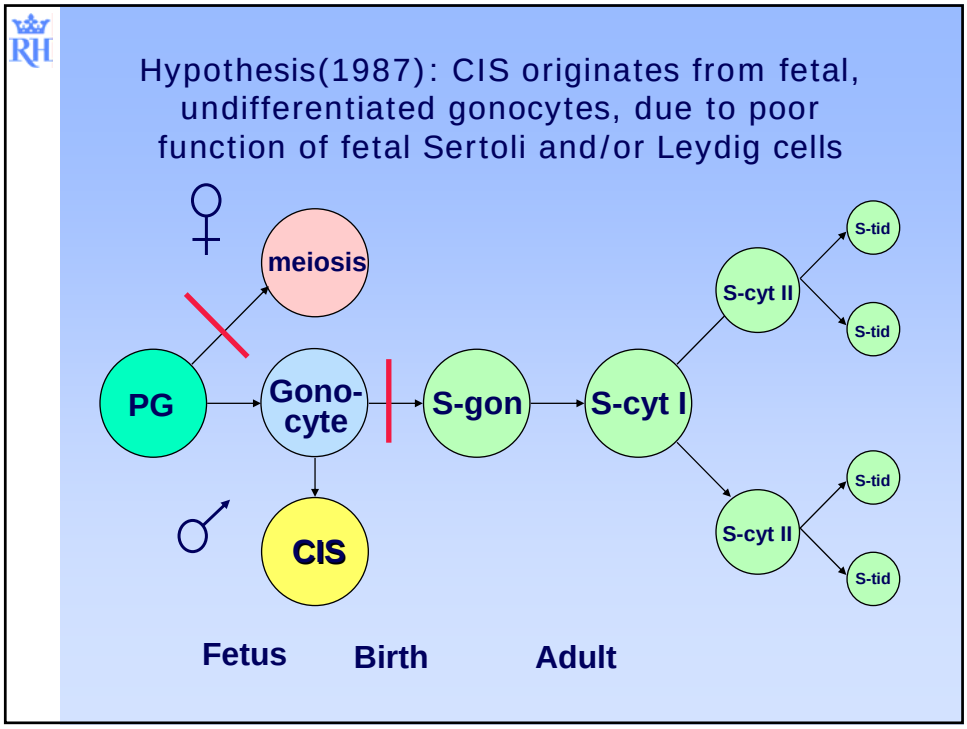
Julie A. Baker[1,*], Germaine M. Buck[2], John E. Vena[3] & Kirsten B. Moysich[1]
[1]*Division of Cancer Prevention and Population Sciences, Roswell Park Cancer Institute (JAB, KBM);* [2]*Division of Epidemiology, Statistics & Prevention, National Institute of Child Health & Human Development, National Institutes of Health (GMB);* [3]*Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina (JEV)*

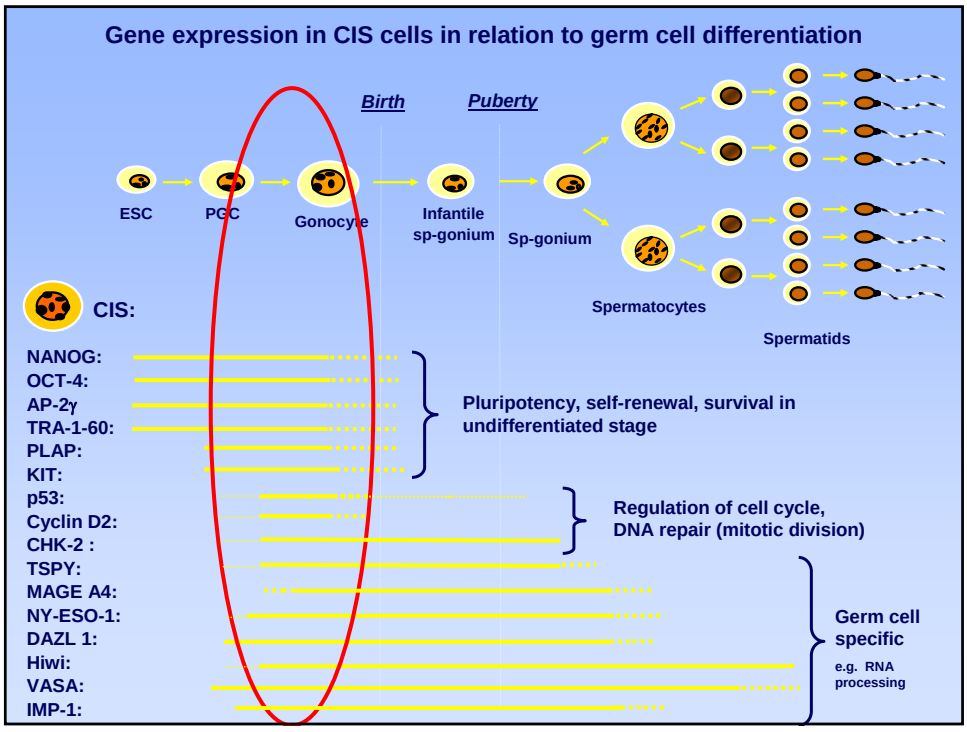
…"the current study provides additional evidence for the testicular dysgenesis hypothesis that men with testicular cancer have impaired fertility prior to diagnosis"



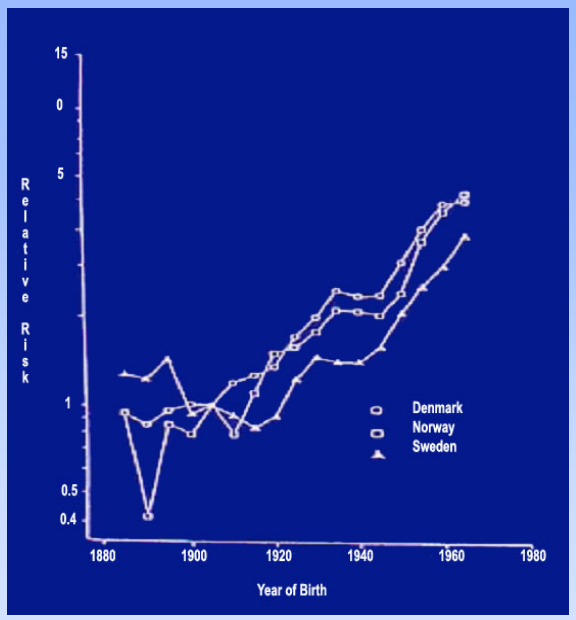


Oct-4 expression in CIS cells (adult, infertile male)


Hypothesis(1987): CIS originates from fetal, undifferentiated gonocytes, due to poor function of fetal Sertoli and/or Leydig cells
meiosis
PG
Gono-cyte
S-gon
S-cyt I
S-cyt II
S-cyt II
S-tid
S-tid
S-tid
S-tid
CIS
Fetus
Birth
Adult

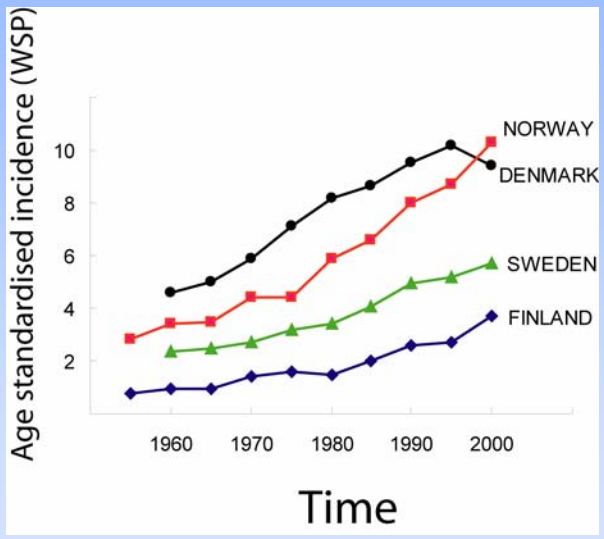

Gene expression in CIS cells in relation to germ cell differentiation
Birth
Puberty
ESC
PGC
Gonocyte
Infantile sp-gonium
Sp-gonium
Spermatocytes
Spermatids
CIS:
NANOG:
OCT-4:
AP-2γ
TRA-1-60:
PLAP:
KIT:
p53:
Cyclin D2:
CHK-2 :
TSPY:
MAGE A4:
NY-ESO-1:
DAZL 1:
Hiwi:
VASA:
IMP-1:
Pluripotency, self-renewal, survival in undifferentiated stage
Regulation of cell cycle, DNA repair (mitotic division)
Germ cell specific
e.g. RNA processing

The CIS cell seems to be a hybrid between an embryonic stem cell and a germ cell!



Bergström et al. J.N.C.L. 1988

Rates in testis cancer

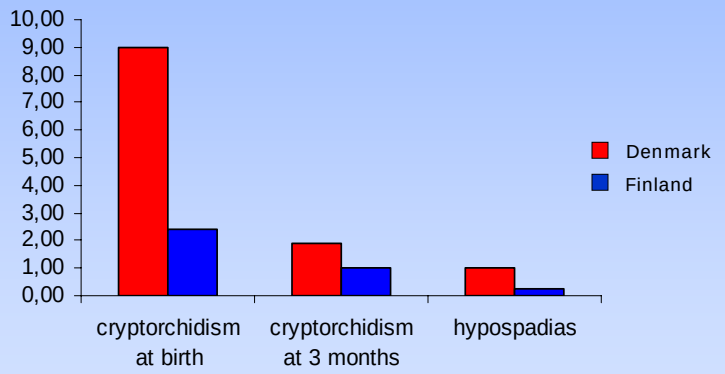


Large, prospective Danish-Finnish population studies of male reproductive health

- 2566 pregnant women
- 2566 newborn boys, followed to age 3
- 628 fertile men
- 4418 18-20 year old men from general population
- **Total: >10.178 volunteers**
- Funding: National Research Agency funds and EU (> 7 mill. Euro in DK alone)

Differences in prevalence of genital abnormalities between Denmark and Finland

(From Boisen *et al.* Lancet 2004;Boisen *et al.* JCEM 2005)



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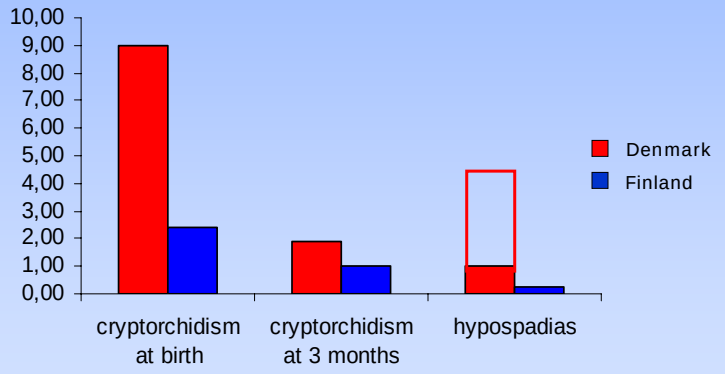
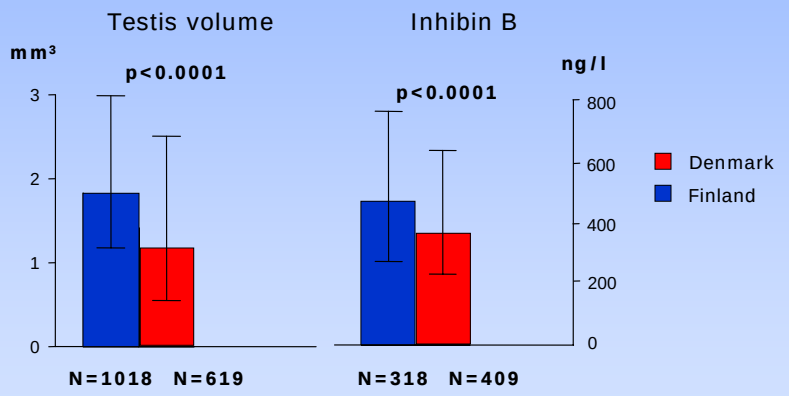


Testis volume and inhibin-B levels

(Main et al. JCEM [Epub ahead of print])



Geographic association between abnormalities in male reproductive health

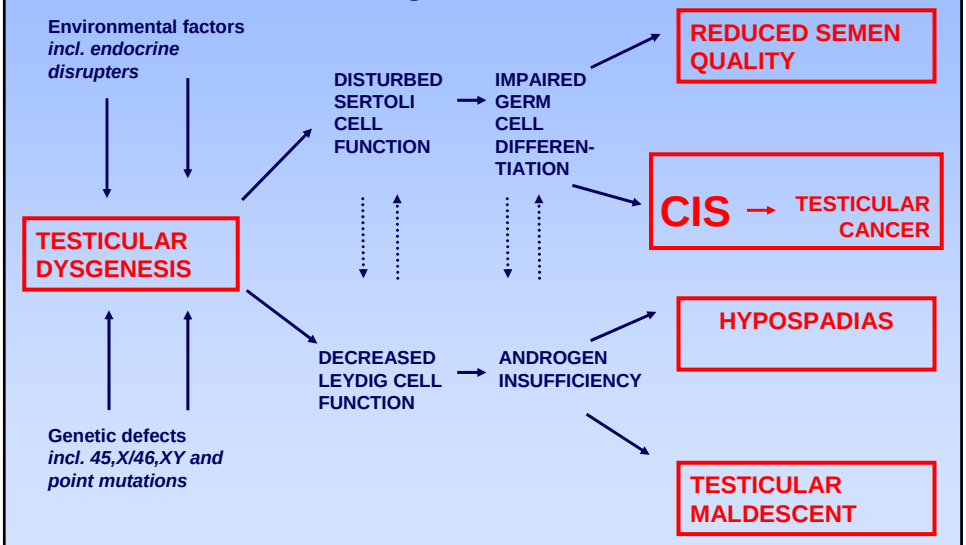
Denmark

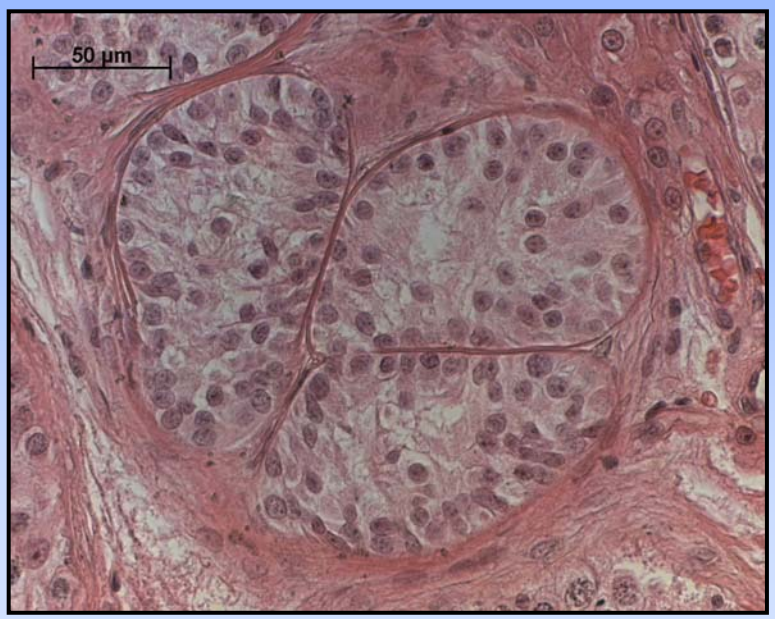
- High incidence of testicular cancer
- High prevalence of cryptorchidism
- High prevalence of hypospadias
- Low sperm counts
- Smaller testes as newborns and lower inhibin-B levels

Finland

- Low incidence of testicular cancer
- Low prevalence of cryptorchidism
- Low prevalence of hypospadias
- High sperm counts
- Bigger testes as newborns and higher inhibin-B levels

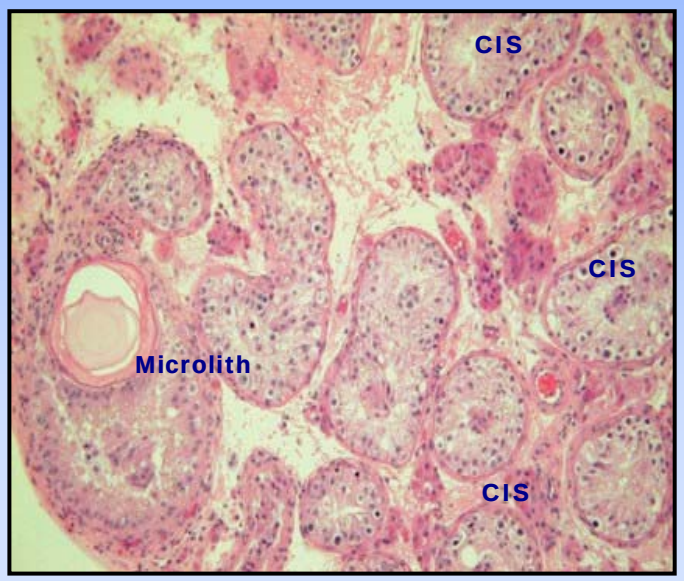
Testicular Dysgenesis Syndrome



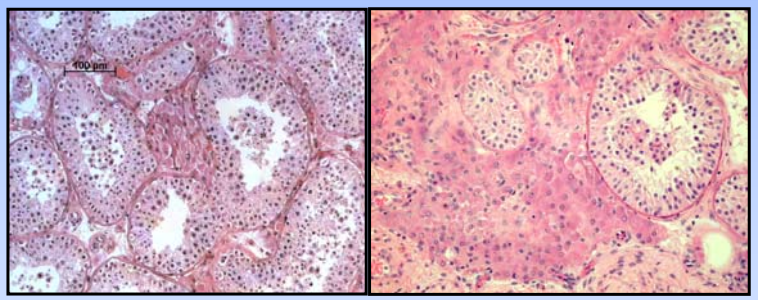


Cluster of undifferentiated SCO tubules in contralateral testis of patient with testicular cancer

Infertility: CIS associated with testicular dysgenesis



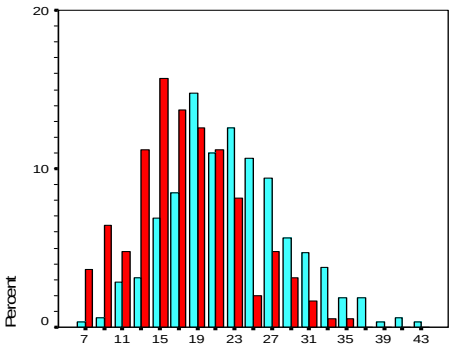
Frequent presence of Leydig cell "micronodules" (clusters >15 cells) in men with reduced spermatogenesis: 70 %



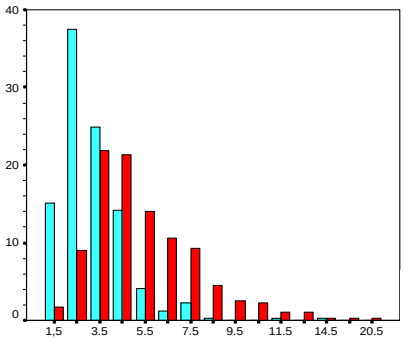
Clusters of Leydig cells (micronodules)

Holm et al. J Pathol 2003

Testosterone



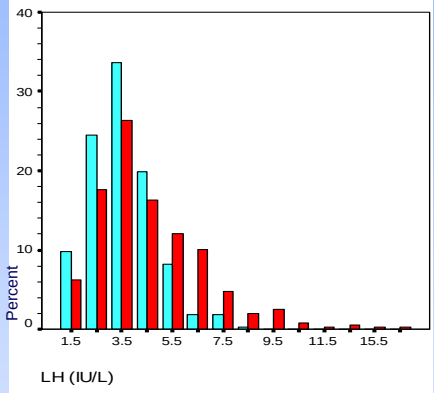
Estradiol/testosterone ratio



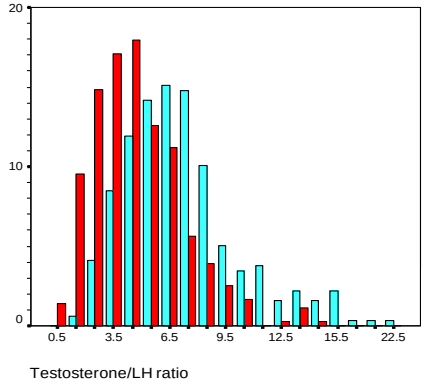
Fertile men, n = 318
Infertile men, n = 357

Andersson et al. JCEM, 2004)

LH



Testosterone/LH ratio



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Andersson et al. JCEM, 2004)

Summary

- All types of testicular germ cell cancer are derived from CIS, which has both stem cell- and germ cell properties
- Gonadotropins and/or Sertoli cell factors and/or sex steroids may be needed to drive the CIS cell into an invasive tumor
- TC shares risk factors with cryptorchidism, hypospadias and male infertility
- All confirmed TC risk factors relate to perinatal events, causing poor/delayed development of fetal testis

Conclusion

- The link between TC and poor semen quality may be testicular dysgenesis, sometimes also resulting in undescended testis, hypospadias and other signs of insufficient genital development
- However, we should not forget that male infertility have many etiologies, e.g. chemotherapy and mutations causing spermatogenic arrest in adults and such disorders are most likely not related to testicular cancer

Challenges for Testis Cancer Researchers

- No cell or tissue culture systems exist
- Animal models are lacking

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Low birth weight and testicular cancer

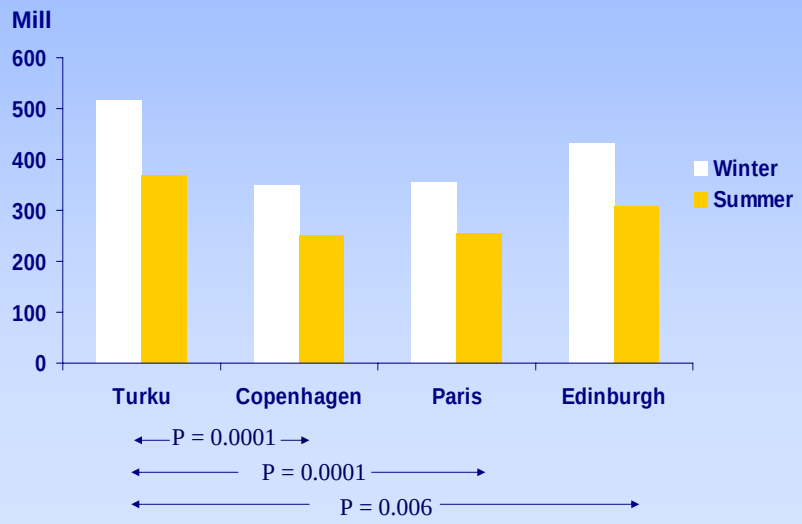
	RR
Depue et al. JNCI 71, 1151, 1983	**3.2**
Brown et al. Cancer Res. 46, 1986	**13.5**
Akre et al. JNCI 88, 883, 1996	**2.6**
Møller og Skakkebæk, Cancer causes & control, 1997	**2.6**

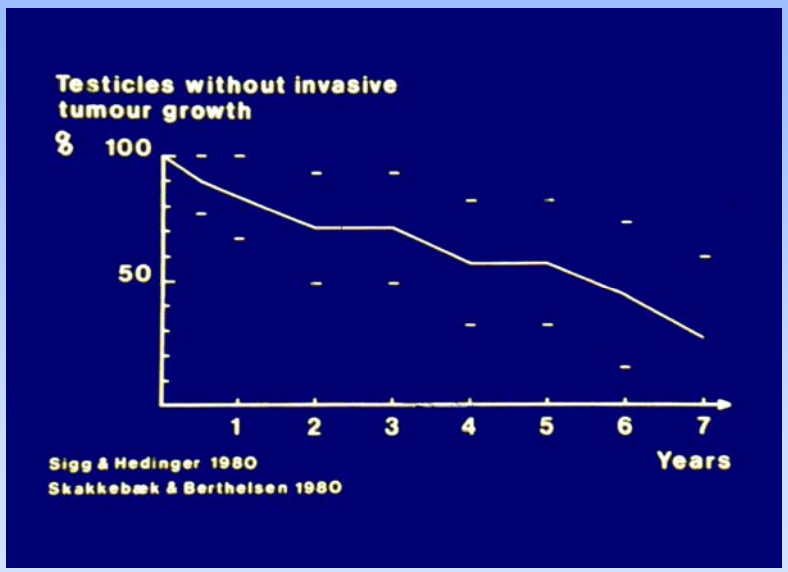
Increased risk of testis cancer in sons of mothers with increased levels of persistant organic pollutants in their blood

Hardell et al. Environmental Health Perspectives, 2003

Total Sperm Counts

30-year-old, fertile, ejaculation abstinence 4 days





TDS in Contralateral Testis in 218 Cases of Unilateral Testicular Cancer (Hoei-Hansen et al. J.Pathol. 2003)

- 19 patients, 8.7%, had CIS
- 38 patients, 13.8%, had Sertoli cell only tubules
- 11 patients, 4.6%, had immature tubules with undifferentiated Sertoli cells
- 14 patients, 6.0%, microliths
- Cumulative presence of one or more signs of TDS: 25.2%
- In addition more than 70% had Leydig cell "micronodules"

Testis cancer risks in first and second generation of Nordic immigrants to Sweden

1. generation: As in country of origin

2. generation: As in Sweden

Hemminki et al. Int J Cancer 99, 229, 2002