

Kivesten kehityshäiriö ja kivessyövän etiologia

Jaakko Koskenniemi LK, väitöskirjatutkija



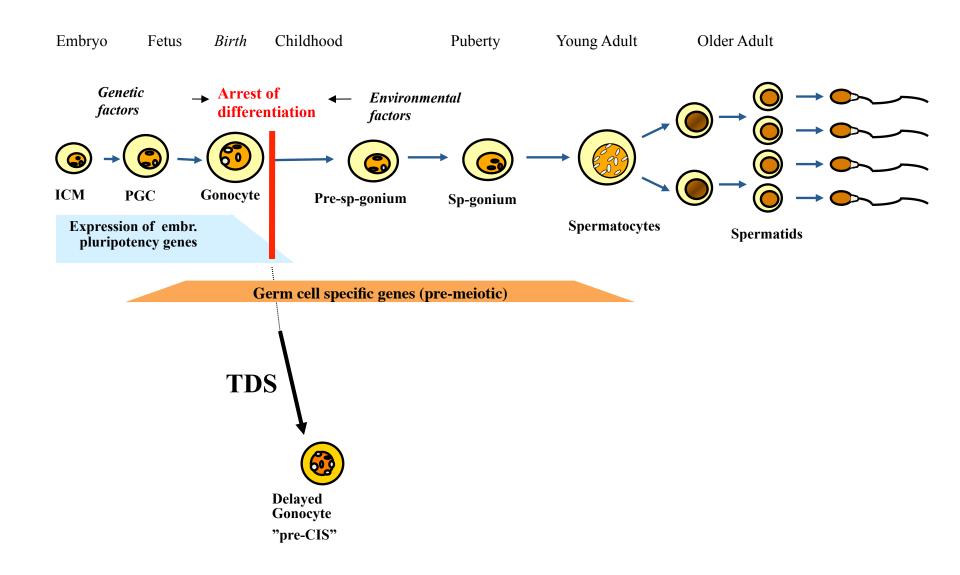


Sidonnaisuudet

 Väitöskirja-apuraha: Lastentautien tutkimussäätiö, Suomen kulttuurirahasto

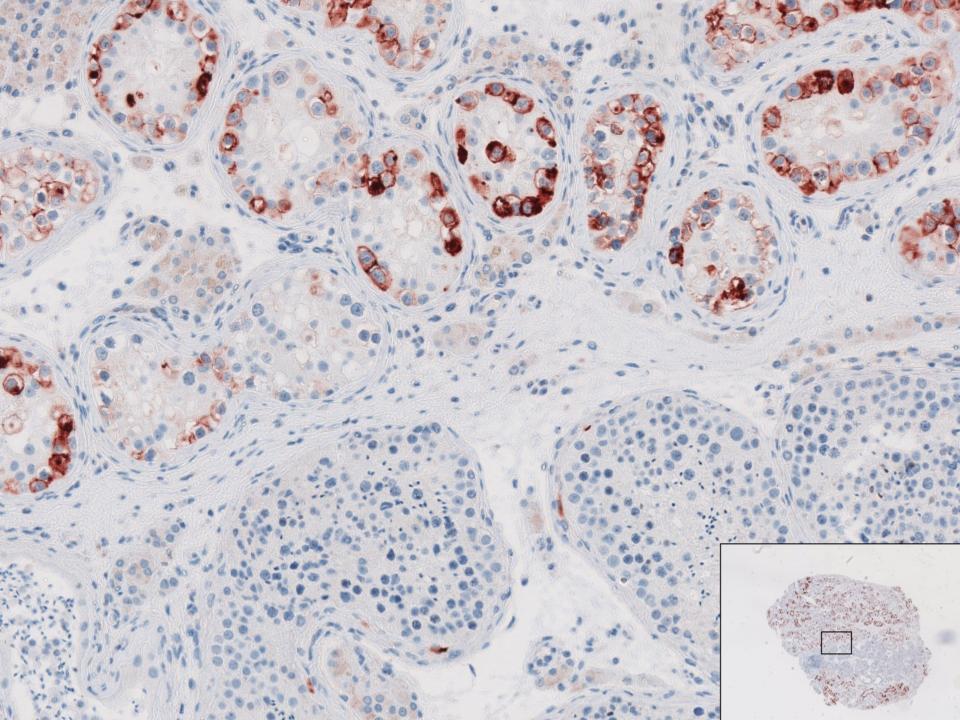
Sisältö

- Kivessyövän etiologinen malli
- Kiveksen kehityshäiriö
- Ympäristön hormonihäiritsijäkemikaalit kehityshäiriön aiheuttajana

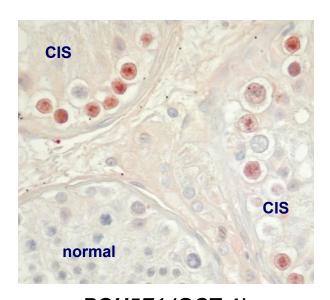


CIS = ITGCN = TIN = GCNIS (germ cell neoplasia in situ)

Rajpert-De Meyts 2006 Hum Reprod



Stem-cell pluripotency-related factors are highly expressed in CIS

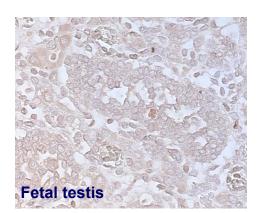


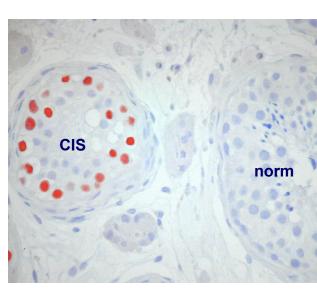
POU5F1 (OCT-4)
Looijenga et al. 2003
Rajpert-De Meyts et al. 2004
Jones et al. 2004



CIS

NANOG Høi-Hansen et al. 2005 Hart et al. 2005

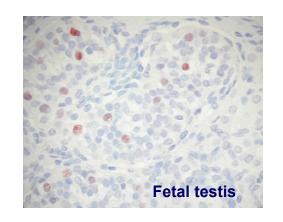




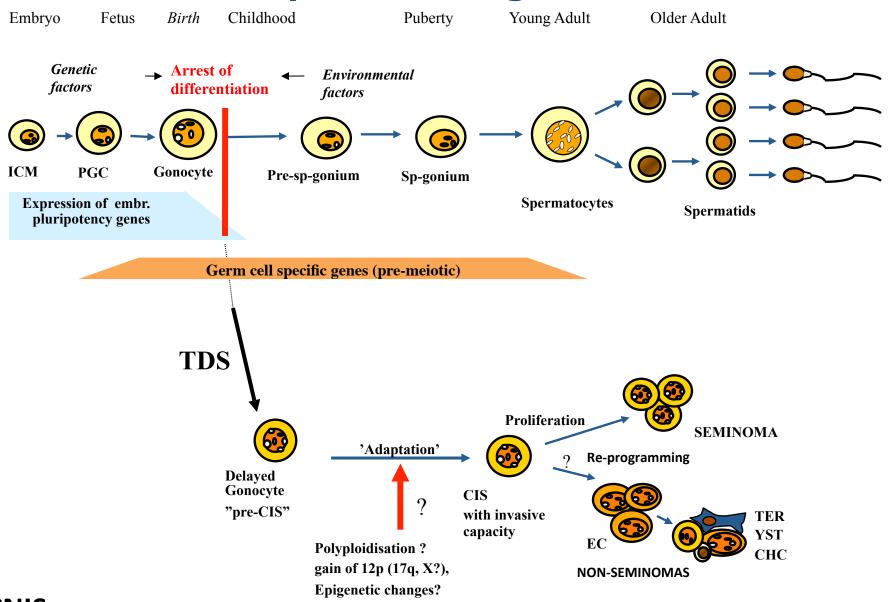
TFAP2C (AP2 gamma)

Høi-Hansen et al. 2004

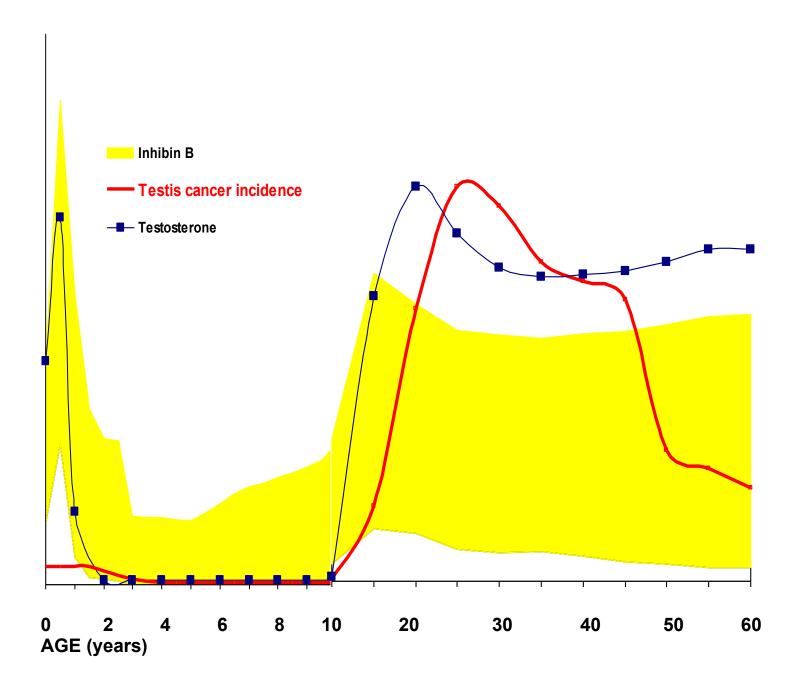
Pauls et al. 2005



Kivessyövän etiologinen malli

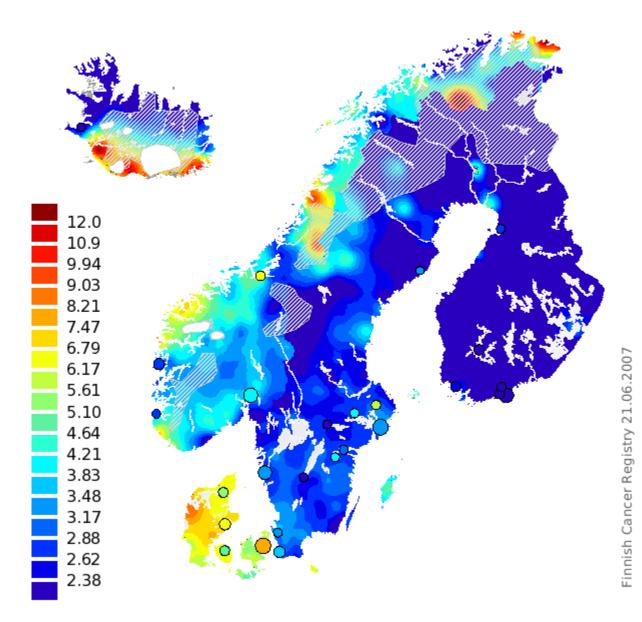


GCNIS

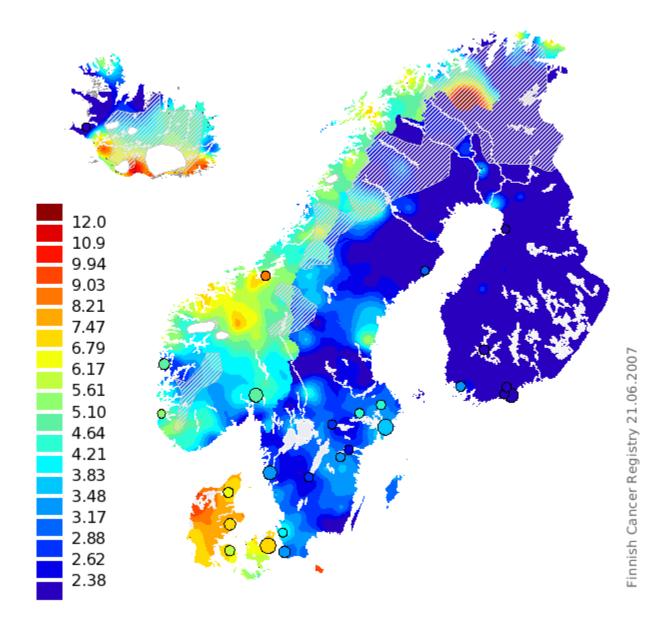


Ympäristö ja perimän rooli kivessyövän synnyssä?

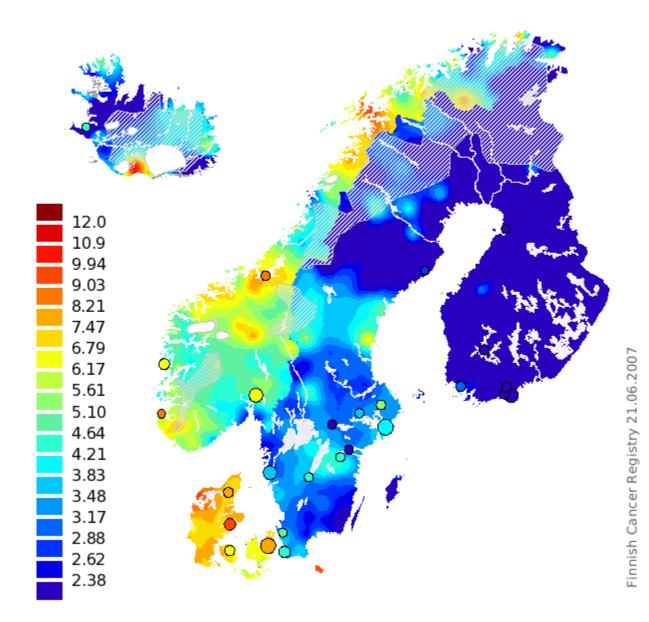
Testicular cancer, 1970-1976



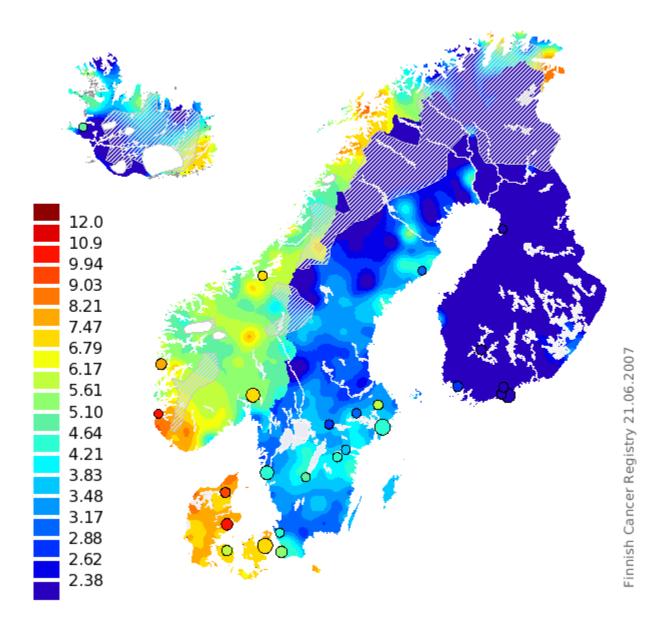
Testicular cancer, 1974-1979



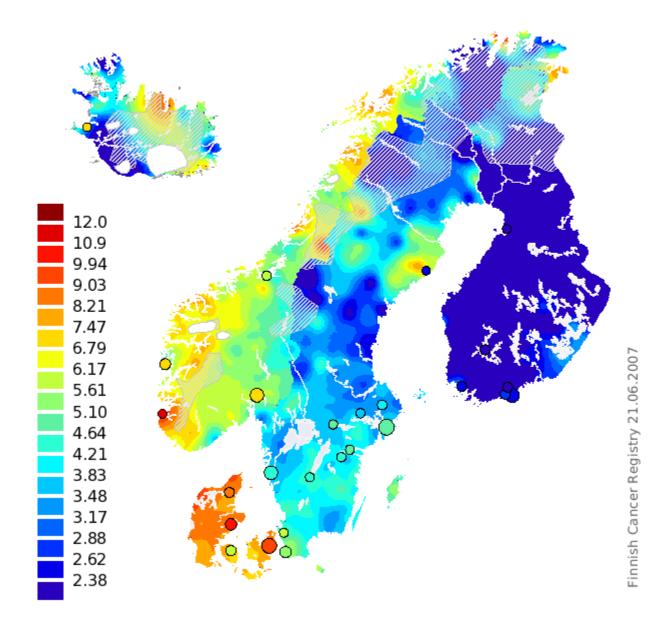
Testicular cancer, 1977-1982



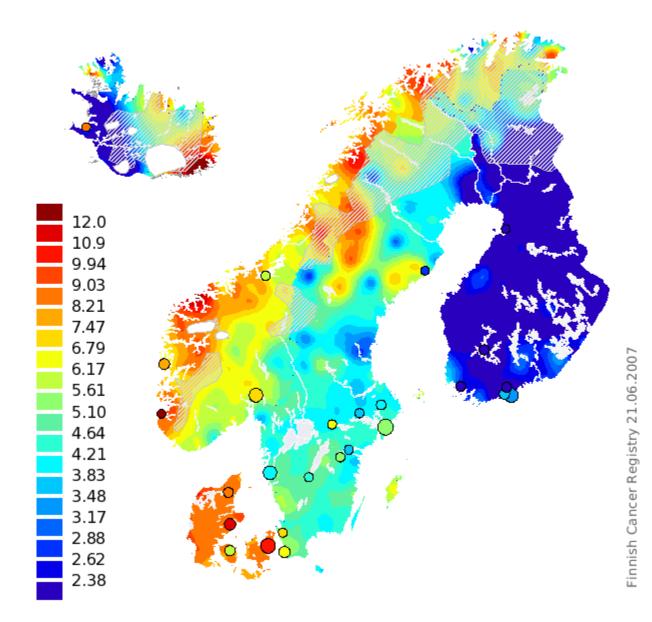
Testicular cancer, 1980-1985



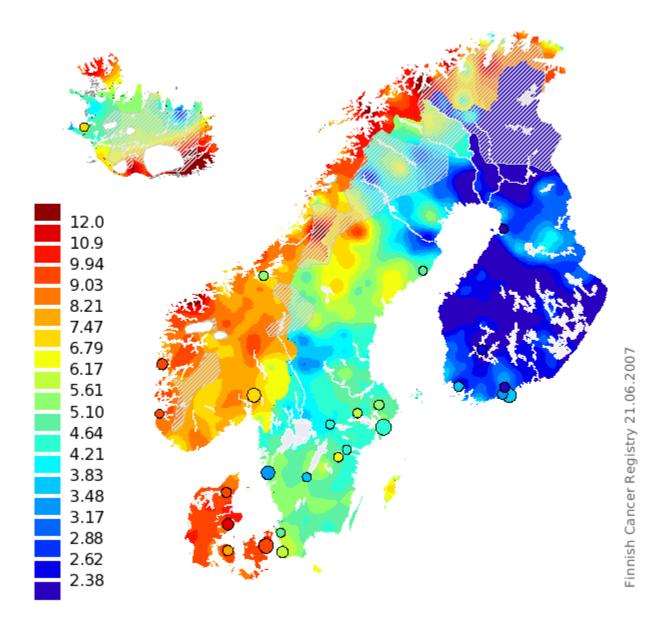
Testicular cancer, 1983-1988



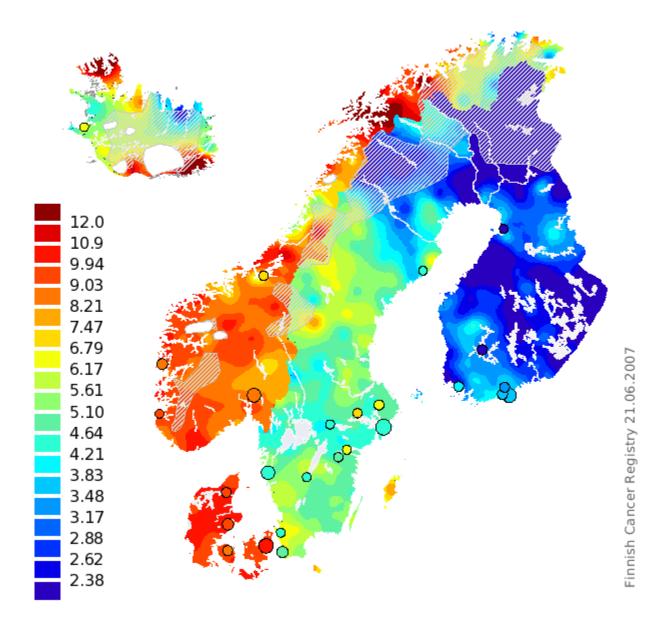
Testicular cancer, 1986-1991



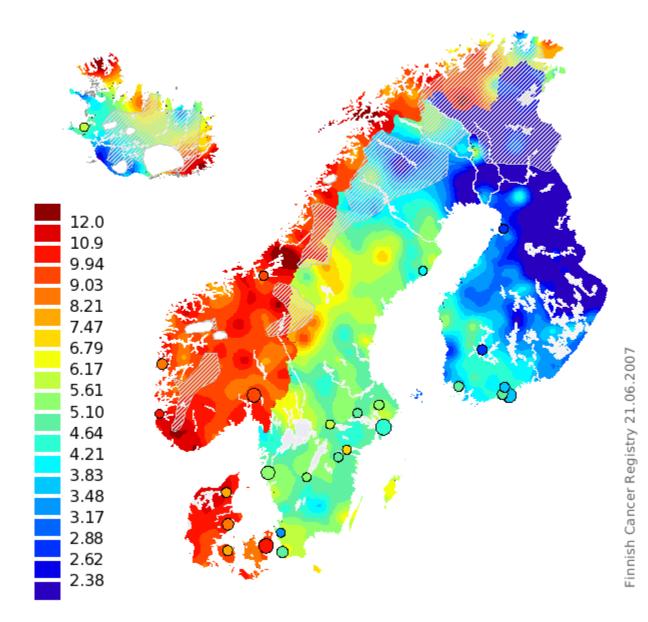
Testicular cancer, 1989-1994



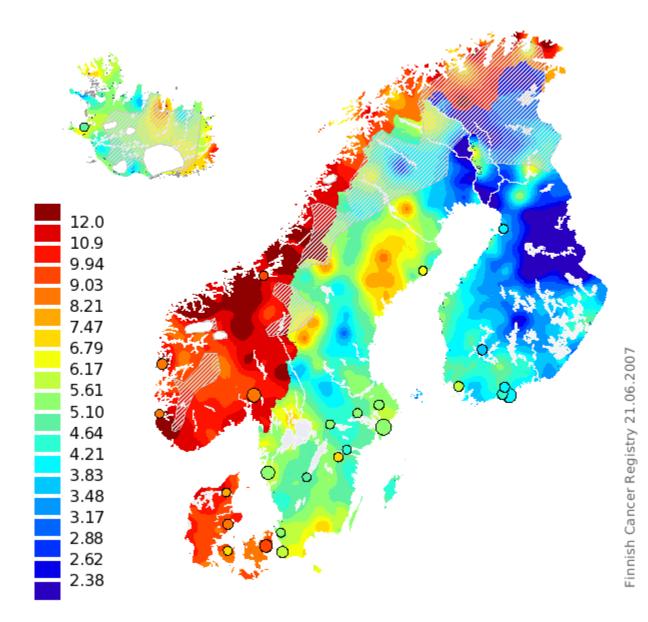
Testicular cancer, 1992-1997

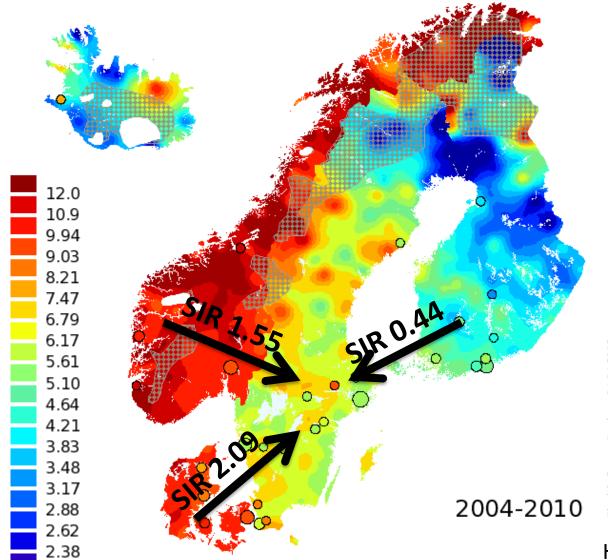


Testicular cancer, 1995-2000



Testicular cancer, 1998-2003

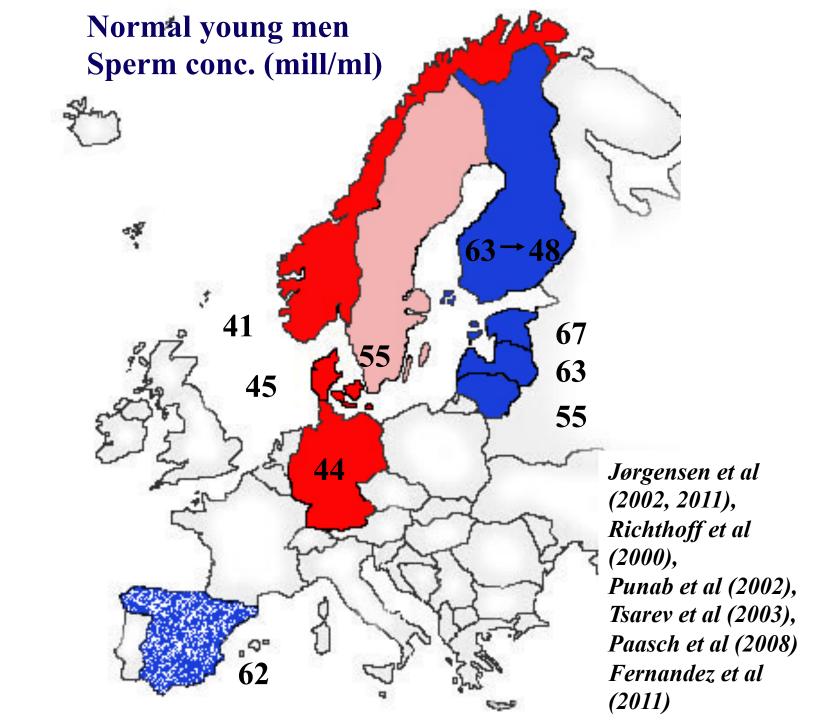




Finnish Cancer Registry 04.0

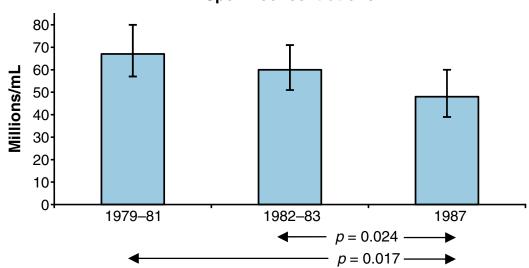
Hemminki et al. 2002 Eur J Cancer

Cancer incidence / 100,000

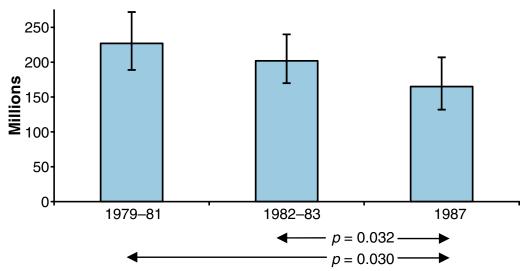


Young men from the Finnish general population

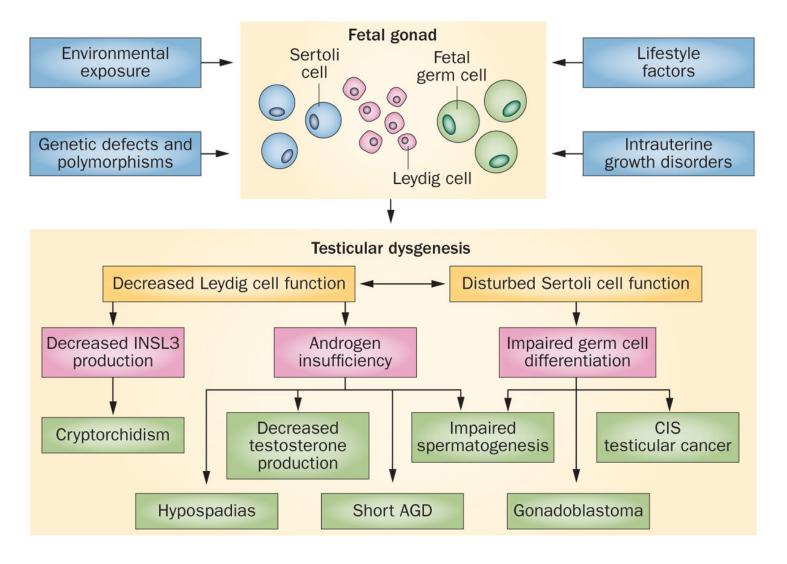




Total sperm counts

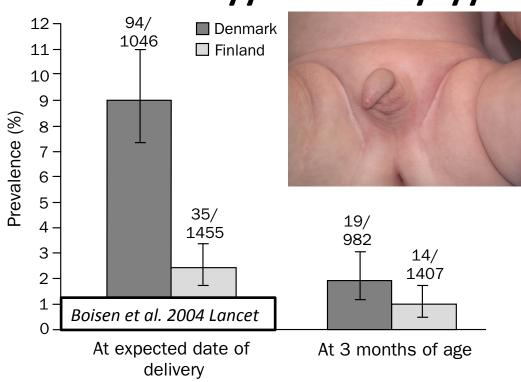


Kiveksen kehityshäiriö

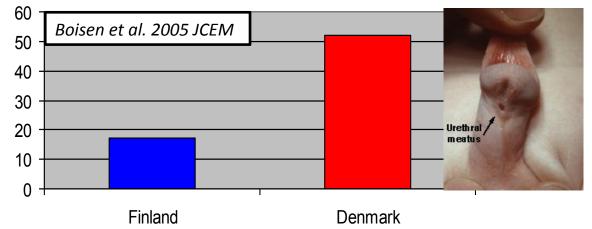


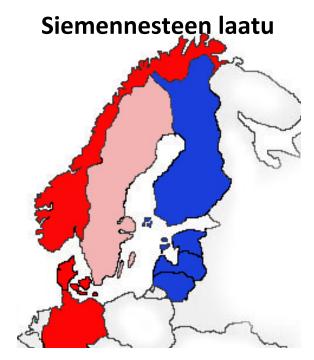
Juul et al. 2014 Nat Rev Endocrinol, modifed from Skakkebæk et al. 2001

Piilokiveksisyyden esiintyvyys

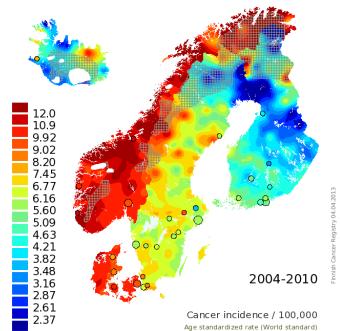


Hypospadiatapauksia / 10 000 elävänä syntynyttä











Working group

- Georg Becher, Norway
- Åke Bergman, Sweden (Leader)
- Poul Bjerregaard, Denmark
- Riana Bornman, South Africa
- Ingvar Brandt, Sweden
- Jerrold J. Heindel, USA
- Taisen Iguchi, Japan
- Susan Jobling, England
- Karen A. Kidd, Canada
- Andreas Kortenkamp, England
- Derek C.G. Muir, Canada
- Roseline Ochieng, Kenya
- Niels E. Skakkebaek, Denmark
- Jorma Toppari, Finland
- Tracey J. Woodruff, USA
- R. Thomas Zoeller, USA

Endocrine Disrupting Chemicals have many sources



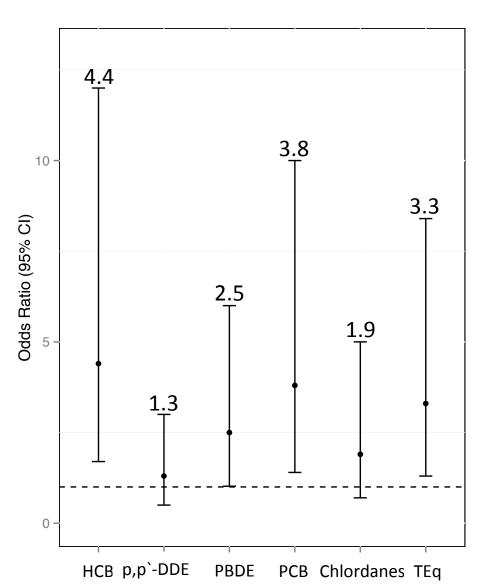
800 –2560

Androgeenireseptoriin sitoutuvaa kemikaalia (Vinggaard et al. 2008)



WHO State of Science of Endocrine Disrupting Chemicals - 2012

Kivessyöpä

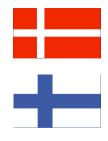


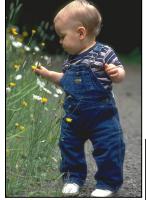
- 61 kivessyöpäpotilaan äitiä
 + 61 samanikäisen miehen äitiä
- PCB, p,p´-DDE, klordaanin, ja PBDE:n määritys äidin seerumista lapsen diagnoosin jälkeen
- PBDE, PCB, HCB, PCB-TEq yhteyksissä kohonneeseen piilokiveksisyyden riskiin







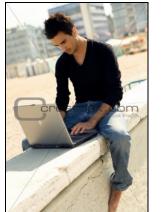




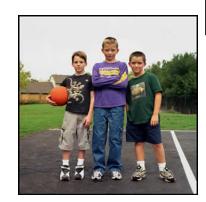




4957 families 2562 boys



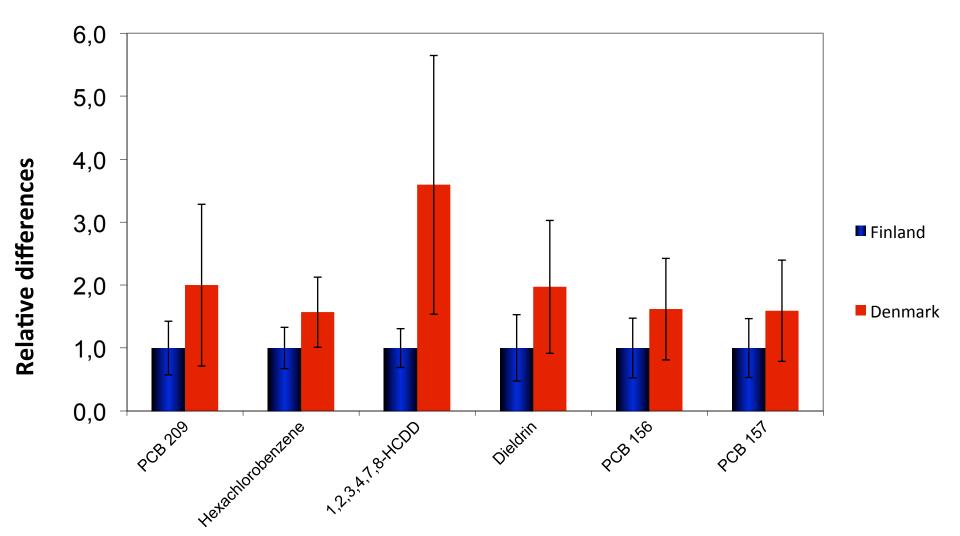




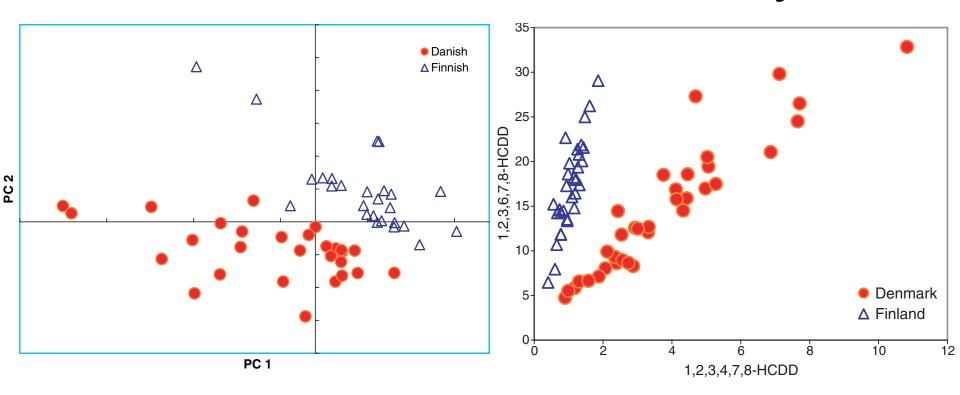
2006-2007

Katharina Main 2008 -

Tanskalaispojat altistuvat suuremmalle kemikaalipitoisuudelle



Suomalaisten ja tanskalaisten kemikaalialtistuksessa on eroja



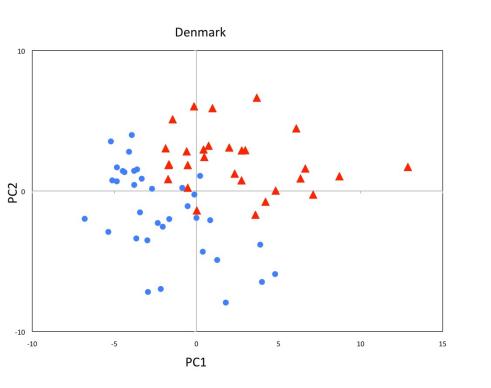
The top 10 most important chemicals in each of the two principal components:

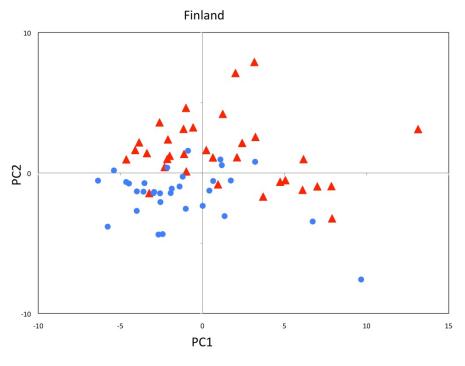
PC 1: 1,2,3,4,7,8-HCDD, PCBs (81,156, 157, 170, 180, 189, 194, 209), o.p'-DDE.

PC 2: 1,2,3,6,7,8-HCDD, 1,2,3,4,6,7,8-HepCDD, Mirex, 1,2,3,4,6,7,8-HepCDF, OCDD, PeBB,

BDE-154, 1,2,3,4,7,8-HCDD, PCB 49, Octachlorostyrene.

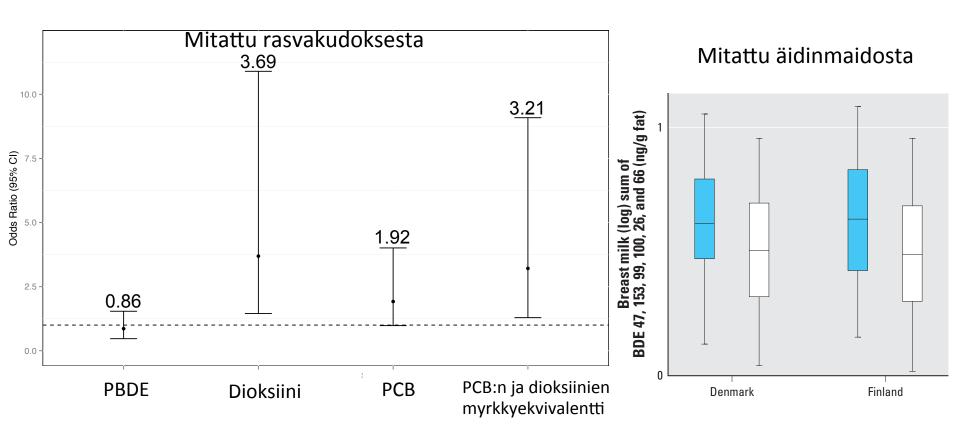
Scatter plots from the PLS (Partial Least Square): Danish and Finnish breast milk samples







Altistus PBDE:lle, dioksiineille ja PCB:lle on yhteydessä piilokiveksisyyteen



Yhteenveto

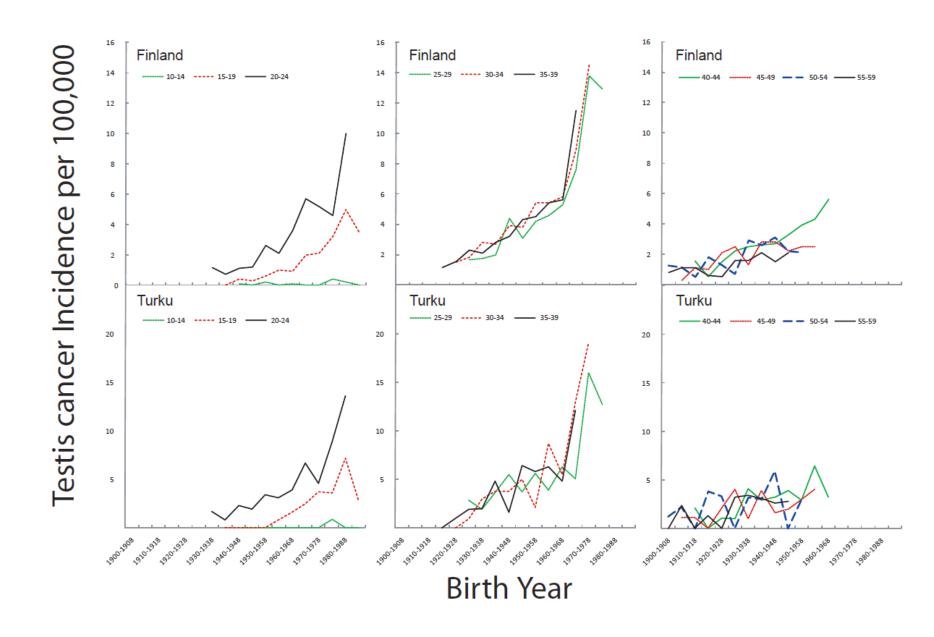
- Kivessyöpä saa alkunsa gonosyyttien puutteellisesta muuntumisesta spermatogoniaksi, jolloin solut muuttuvat GCNISsoluiksi.
- Epidemiologista näyttöä että piilokiveksisyys, kivessyöpä ja huono siemennesteen laatu johtuisivat pienistä androgeenitasoista raskauden aikana.
- Näitä sairauksia näyttää yhdistävän altistus ympäristön (anti-androgeenisille) hormonihäiritsijäkemikaaleille.



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 - Matti Vierula
 - Johanna Järvi
 - Wiwat Rodprasert
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 - Sigrid Juselius Foundation
 - Turku University Hospital
 - Danish Council for Strategic Research
 - Finnish Cultural foundation

- Rigshospitalet, Copenhagen
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 - Niels Jorgensen
 - Marlene Dalgaard
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 - Anders Juul
 - Anna-Maria Andersson
 - Ewa Rajpert-De Meyts
- Inst. Health and Welfare, Kuopio
 - Hannu Kiviranta
 - Terttu Vartiainen



Jørgensen et al 2011 IJA