Inherited and familial breast cancer: delination, tumour biologies and effects of interventions

Pål Møller

BRCA1 penetrance

Summary
'Inherited breast cancer' development of concept since 1990

Family history

Genetic testing slowly starting

Replacing educated guesses with empirical facts

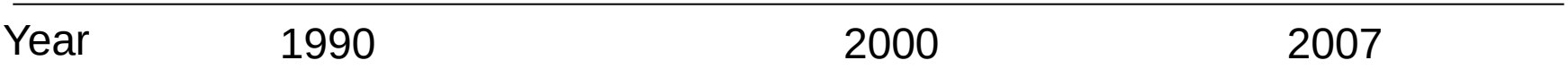
BRCA2

BRCA1

Genetic stratification
Effect of intervention

Familial breast cancer
Familial ovarian cancer

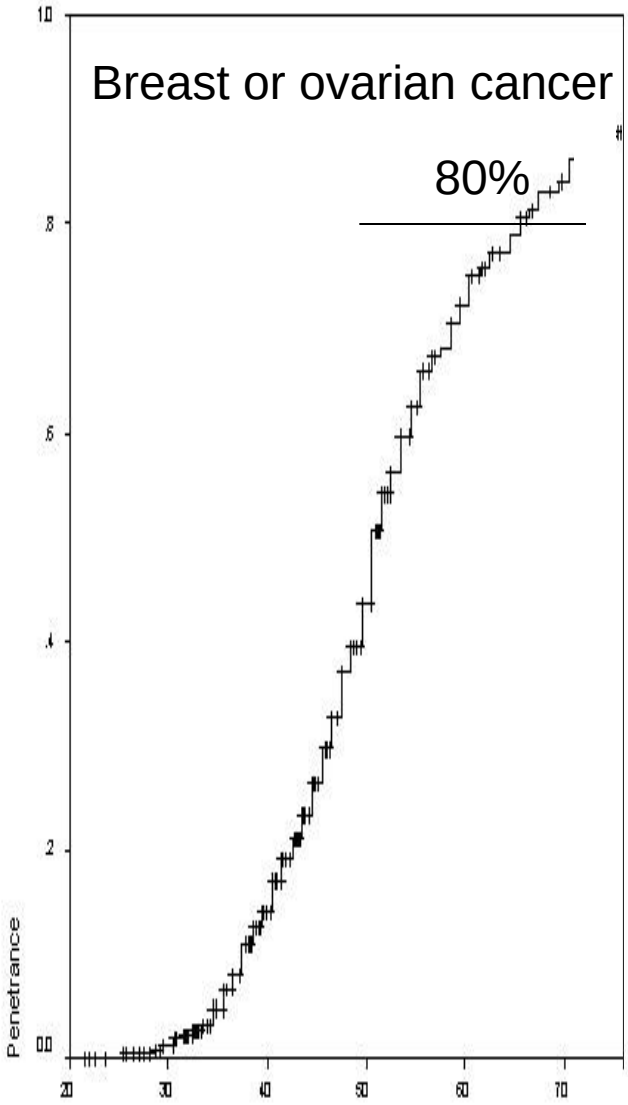
FBOC re-invented

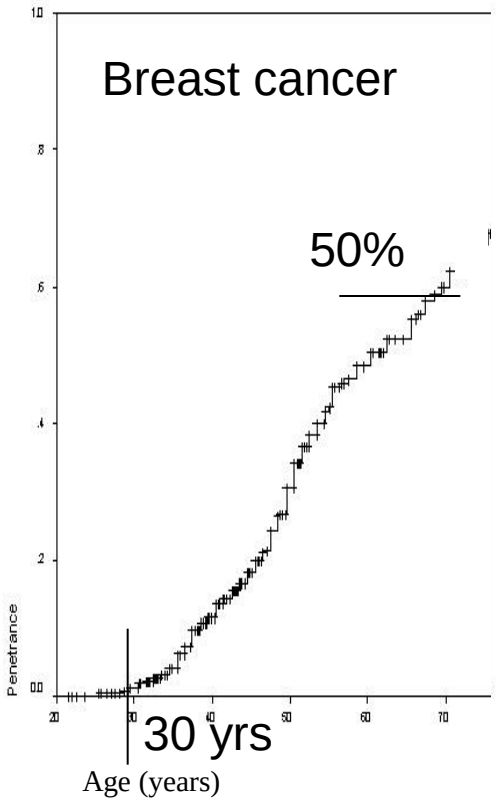


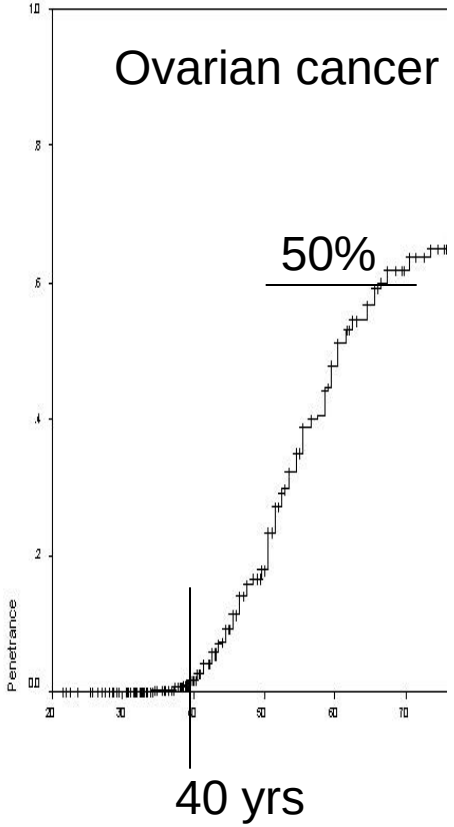
BRCA1 mutation carriers. Retrospective series = no intervention

Cumulative incide rates by age

Pål Møller OnkoLis Feb 13th 2015







Norwegian BRCA1 founder mutations Time to first cancer. Retrospective segregation analysis.

Eur J Cancer. 2003 Oct;39(15):2205-13.

Prospectively observed cumulative incidence of BRCA1 breast cancer by age

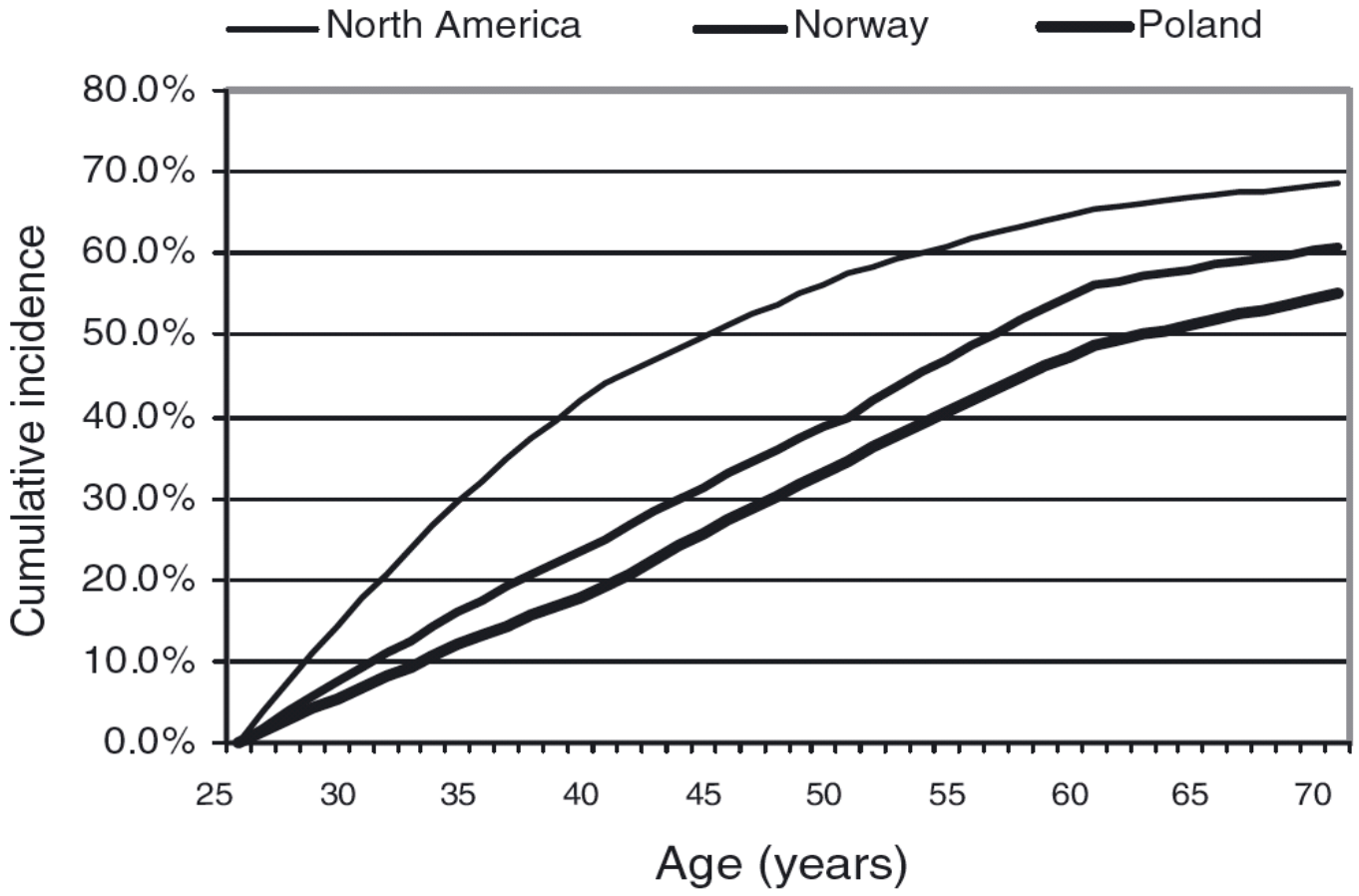


Fig. 2. Cumulative incidence of breast cancer in female BRCA1 mutation carriers by country.

Møller et al. Clin Genet 2013: 83: 88–91

Modifiers of risk in BRCA mut carriers
Genetic modifiers

- A number of normal (frequent) DNA variants in the population have RR ~ 1.1 to contract breast cancer.
- Some of these have a similar RR to modify BRCA1/2 penetrance
- Clinical utility??

Modifiers of risk in BRCA mut carriers
Environment

- (Early) **pregnancy** is not protective against breast cancer risk in BRCA carriers (Cullinane et al 2005)
- **Breast-feeding** protects against breast cancer in BRCA carriers (Kotsopoulos et al 2012)
- **Alcohol** does not increase breast cancer risk in BRCA carriers (Dennis et al 2010).
- **HRT** does not increase breast cancer risk in BRCA carriers (Eisen et al 2008)
- Possibly modest increased risk for breast cancer of **smoking** in BRCA carriers (Ginsburg et al 2008)
- **Oral contraceptives** ~ halves the risk for ovarian cancer in BRCA (McLaughlin 2007)
- **Oral contraceptives** may increase breast cancer risk in BRCA carriers (Narod et al 2002).
- Endometrial cancer is associated with **tamoxifen** use, not with BRCA (Segev et al 2013)
- Clinical utility ??

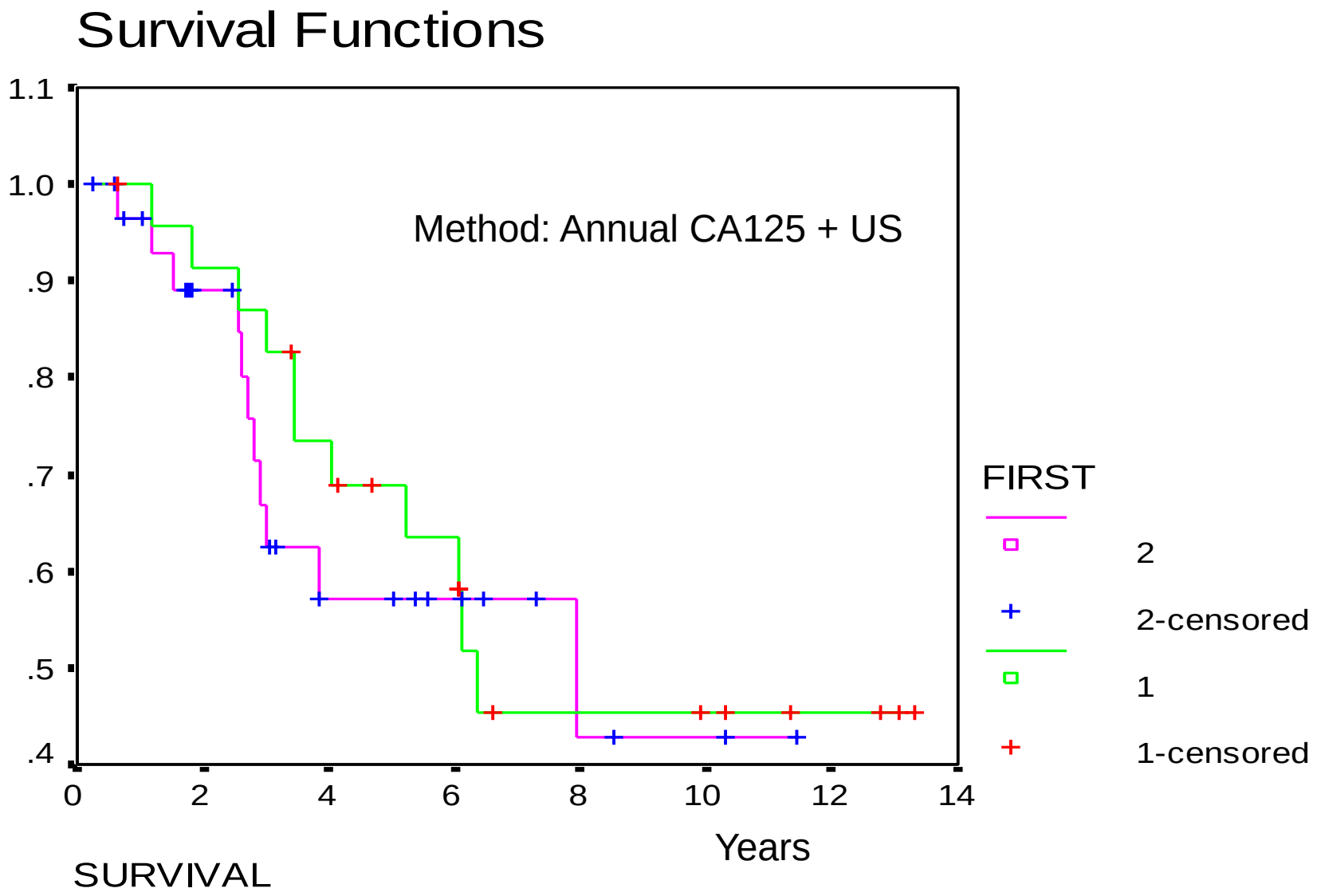
Modifiers of risk
Chemoprevention

- Chemoprevention for breast cancer by tamoxifen or aromatase inhibitors commonly used (in BRCA2 carriers) but forbidden in Norway.
- Should oral anticonceptives be advocated as chemoprevention prior to salpingo-oophorectomy? (Possibly forbidden to do so in Norway).

BRCA1 survival

Survival of prospectively detected BRCA-associated ovarian cancer

Evans et al. J Med Genet 2009



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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Impact of Oophorectomy on Cancer Incidence and Mortality in Women With a *BRCA1* or *BRCA2* Mutation

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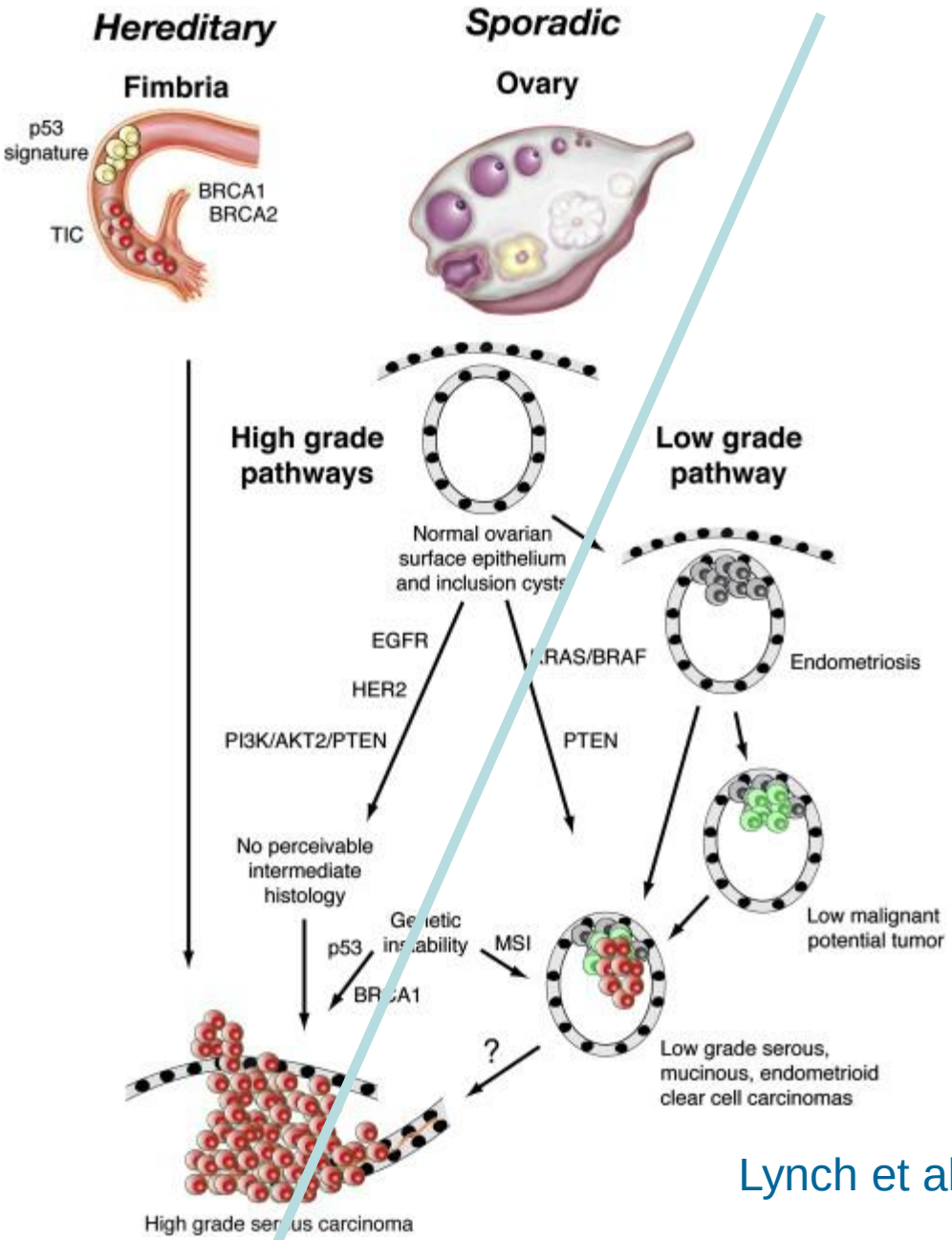
Conclusion

Preventive oophorectomy was associated with an 80% reduction in the risk of ovarian, fallopian tube, or peritoneal cancer in *BRCA1* or *BRCA2* carriers and a 77% reduction in all-cause mortality.

BRCA1
BRCA2

High Grade Pathway

PSO



MSH2
MLH1

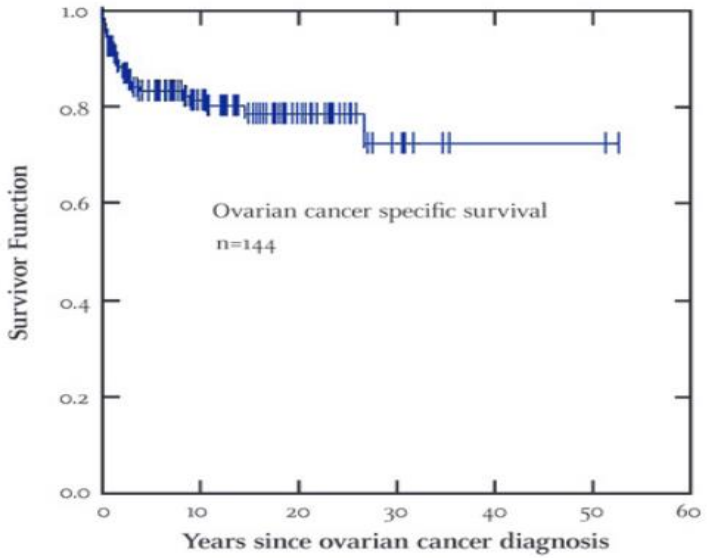
Low Grade Pathway

Early diagnosis

Lynch et al., *Mol Oncol* 2009

Ovarian cancer survival in Lynch syndrome

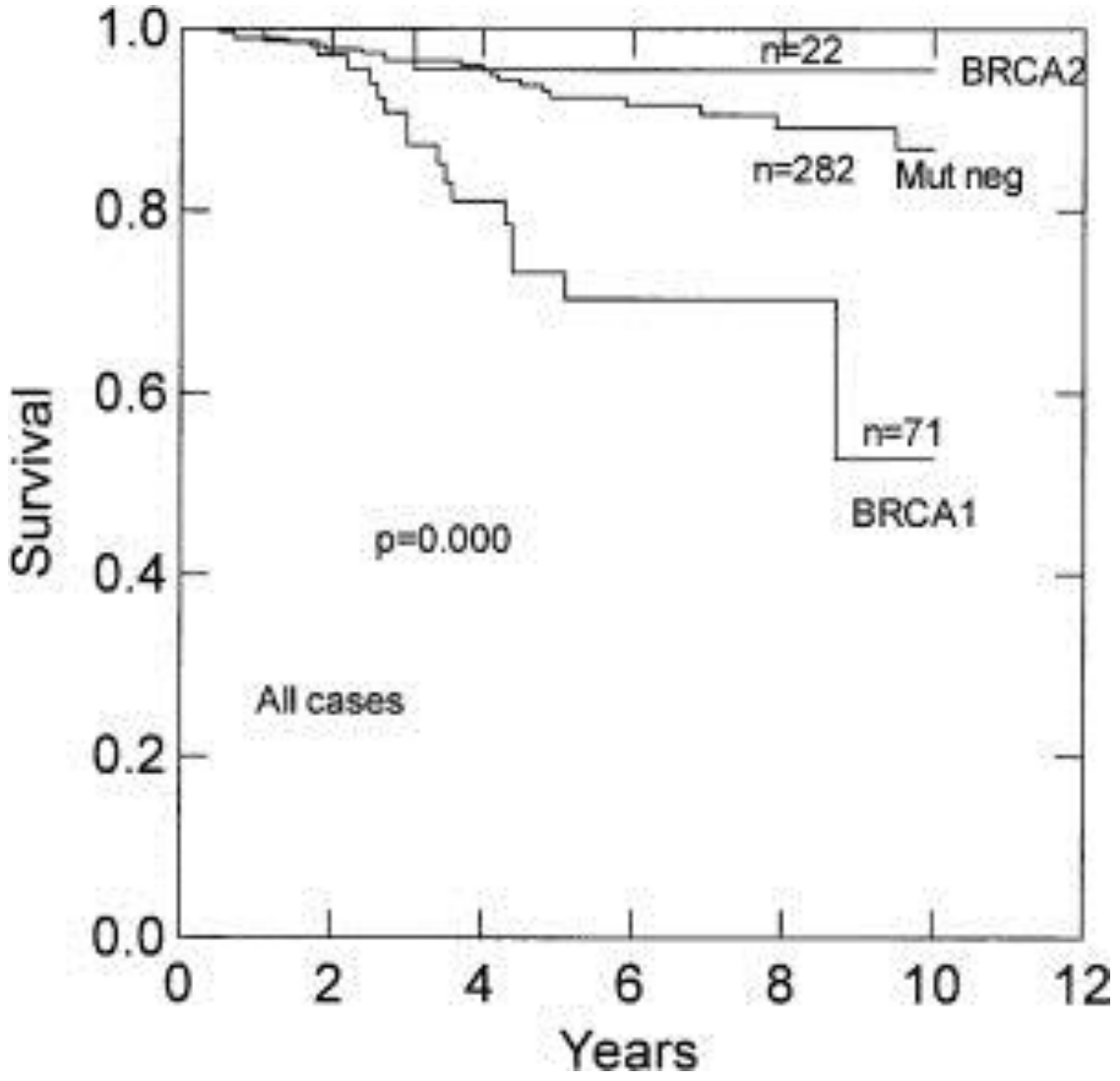
Infiltrating epithelial cancer in Lynch syndrome (MMR mutation carriers)
Retropsepctive series
Grindedal et al 2010 doi:10.1136/jmg.2009.068130



MRI for secondary prevention in BRCA1 mutation carriers

Møller et al International Journal of Cancer
Volume 121, Issue 5, pages 1017-1020 **2002**

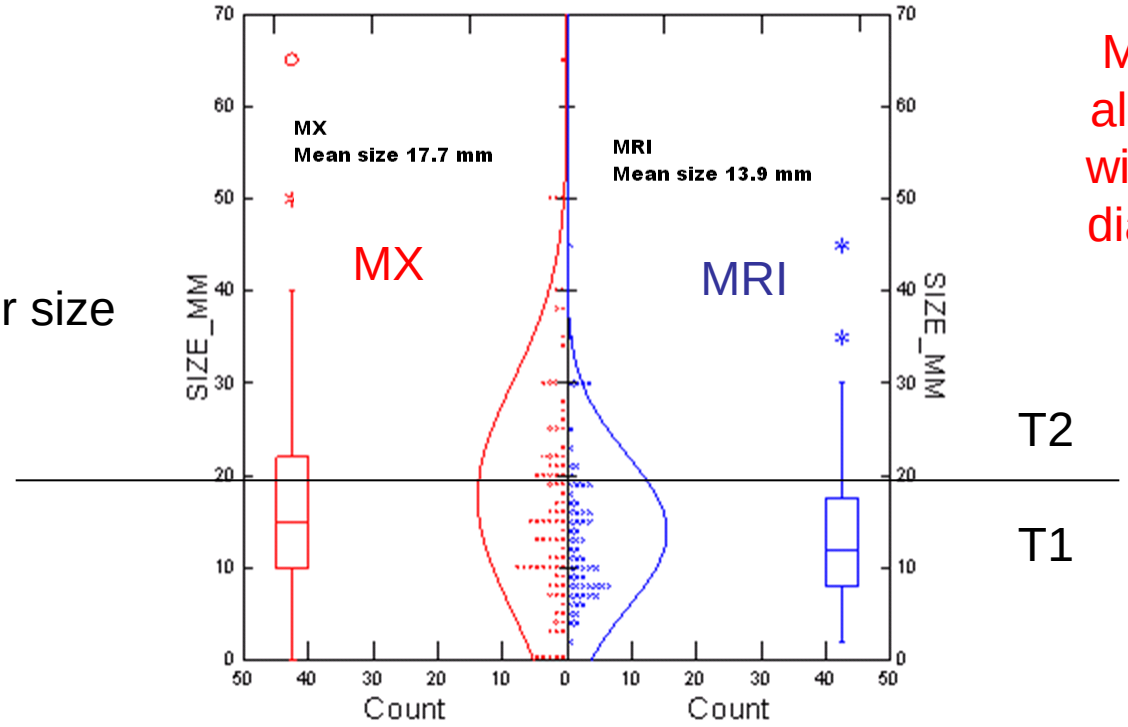
Surveillance for familial breast cancer with annual mammography: Differences in outcome according to *BRCA* mutation status



Since 2001, all BRCA1 mut carriers > 25 years have been offered annual MRI

802 healthy BRCA1 mut carriers follwed by annual breast MRI for mean 4.2 yrs.
64 prospectively detected cancers
Tumour size reduced to 13.9 mm
- -80% node negative
- -68% grade 3

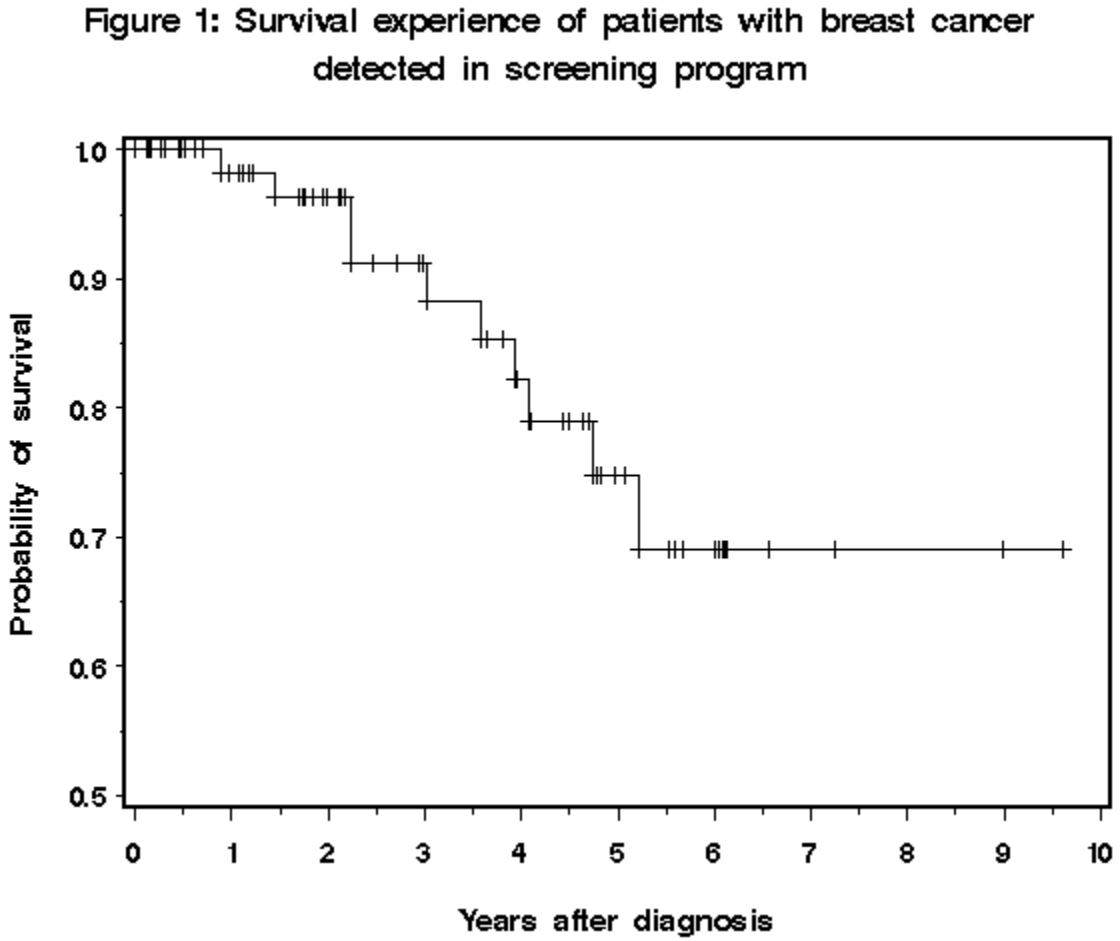
Tumour size



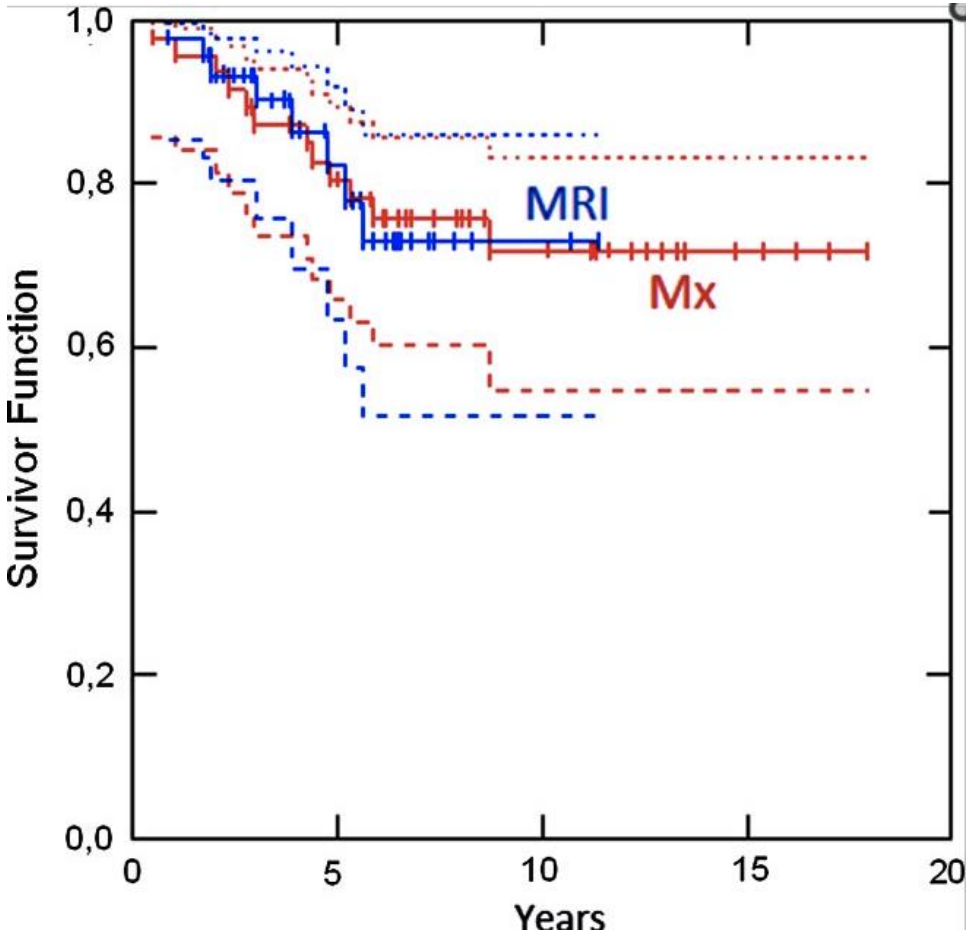
MRI detected close to all tumours at stage T1 without nodal spread at diagnosis, but they had high grade

Møller et al 2013

Survival BRCA1 breast cancer subjected to annual MRI
Moller et al BCRT 2013.
http://www.ncbi.nlm.nih.gov/pubmed/23615785



BRCA1 mut carriers.
Effect of screening with annual mammography (MX) versus MRI on survival.
Kaplan-Meier analysis on time from diagnosis to death.
Tharmaratnam K et al BCRT 2014
http://www.ncbi.nlm.nih.gov/pubmed/25398653



Who has a BRCA1 mutation?

- **75% of mutation carriers do not have family history indicative of inherited cancer.**
- **75% of those having a family history of breast cancer, do not have BRCA1 mutation.**

↓

- **Family history is insufficient to identify BRCA1 mutation carriers.**

BRCA1 breast cancer epidemiology

In round figures:

1 mill women in EU carriers a pathogenic BRCA1 gene

- 80% will contract breast or ovarian cancer
- Median age at disease 55 years
- 10-year survival ~ 50%
- Median age at death 65 years
- Number deaths pr year 7,500 in EU
- 1,125 per year die before 50 years of age
- For Norway, figures are 1% of EU

Who should be entitled to a BRCA1 genetic test?

- **Because it is necessary if you want to take part in decision of own future (principle of autonomy), every woman should be entitled to a BRCA1 test – if she wants to.**
- **But**
  - **what is the cost?**
  - **what about social justice?**

Social justice

1. **With the the falling prices of genetic testing**
2. **offering testing to all**
3. **will be balanced by the reduced cost of less dying patients with BRCA1 cancer due to uptake of preventive means.**

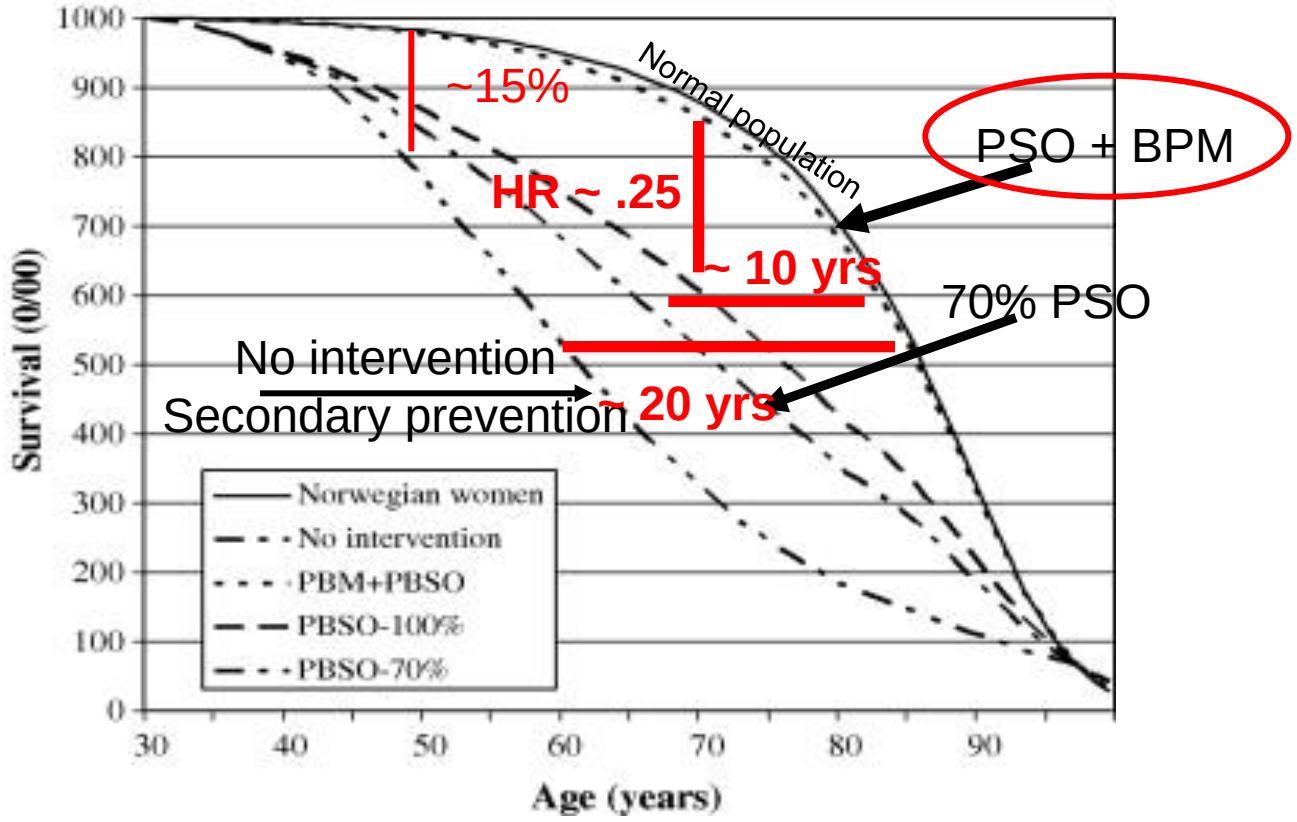
European Journal of Cancer Volume 44, Issue 7 2008 963 - 971

Cost is not interesting as such – the balance is interesting because you deprive nobody from nothing, there is no conflict with respect to social justice.

We are left with the principle of autonomy – the right to know.

European Best Practice Guidelines for Use of Genome-based Information and Technologies (EU Project No. 20081302)
http://www.phgen.eu/typo3/fileadmin/downloads/Use_Report.pdf

Expected survival of female BRCA1 mut carriers
according to intervention strategies
Risks as of today projected upon figure from Norum et al 2008
http://www.ncbi.nlm.nih.gov/pubmed/18362067

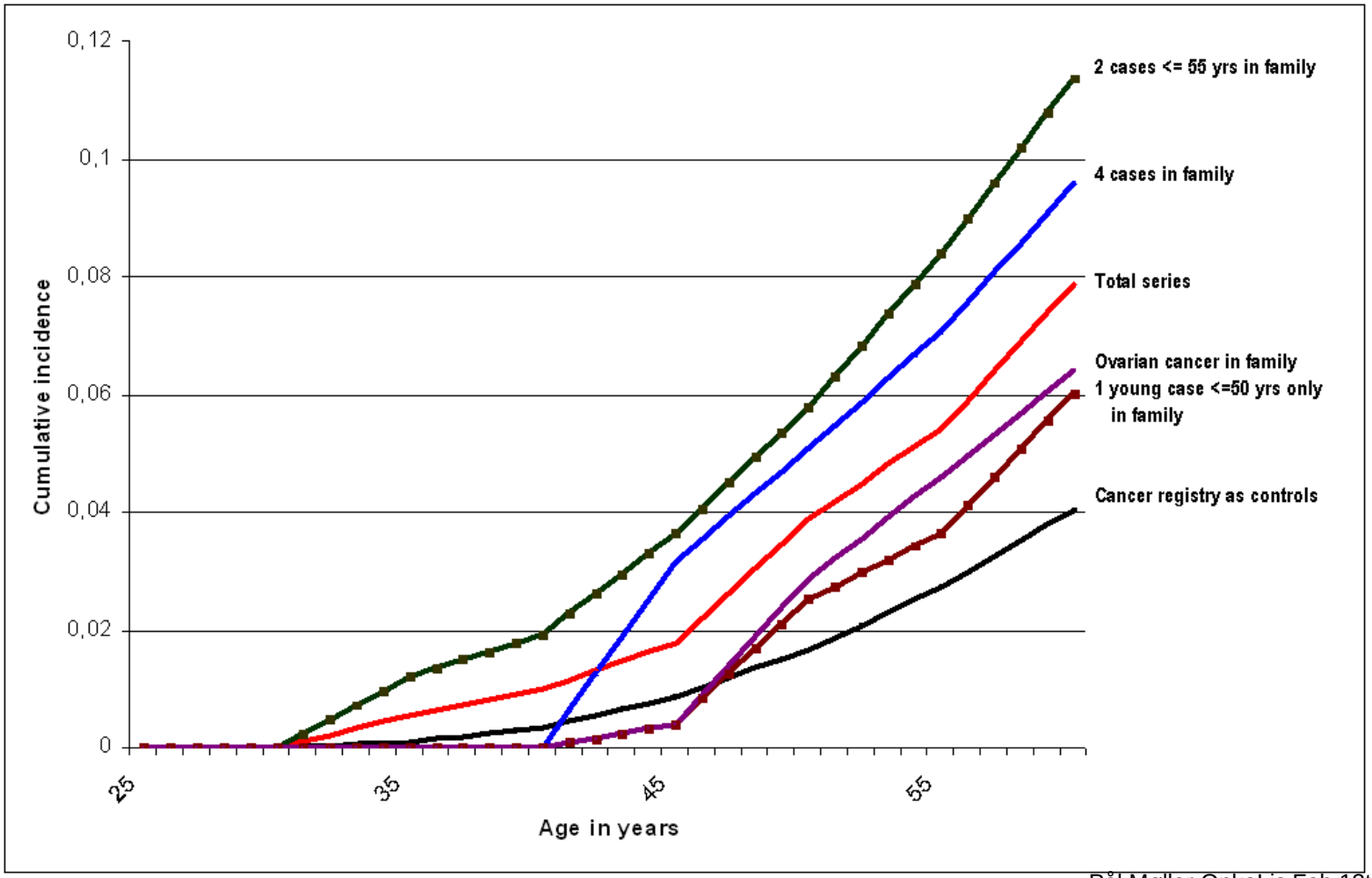


Personalized medicine for female BRCA1 mutation carriers. Scientific arguments

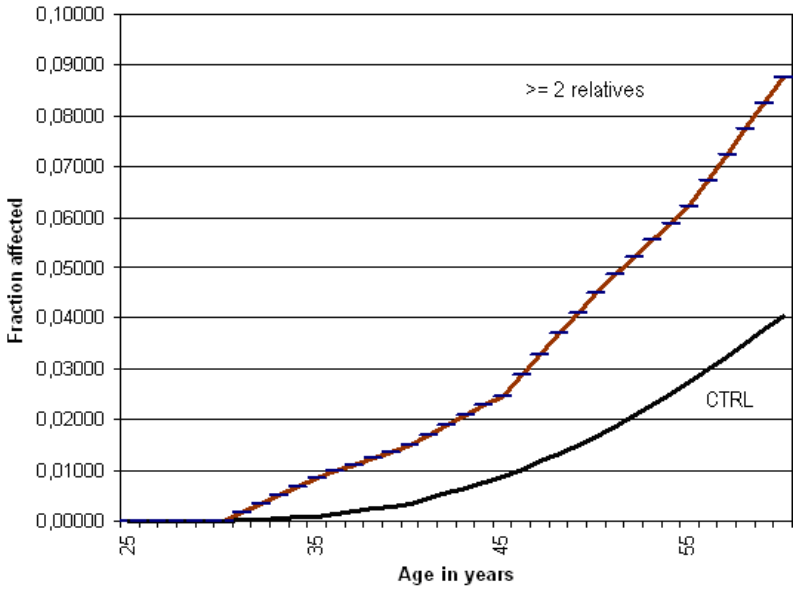
- Risk for cancer >80%
- Mortality when cancer: 50% dead in 10 years.
- Effect of secondary prevention: None
- Effect of surgical primary prevention. Good
- Cost per life year gained if offering testing to all and preventive means to carriers: close to zero.
- 1.25 BRCA1 carriers to treat per cancer prevented
- 2.5 BRCA1 carriers to treat per death prevented.
- Uptake and patient satifaction: Good.

Familial breast cancer without a demonstrable genetic cause

Cumulative risk by age and family history in breast cancer kindreds without a demonstrable BRCA1/2 causative mutation
Moller et al BCRT 2014
http://www.ncbi.nlm.nih.gov/pubmed/24619173



Familial breast cancer with no demonstrable BRCA mutation.
Risk for breast cancer in sisters and daughters of breast cancer cases and survival when prospectively detected with annual Mammography



Familial breast cancer
Cumulative risk by age
compared to population
Breast Cancer Res Treat. 2014

Clinical summary

- **Familial breast cancer – no BRCA mutation**
  - **Risk = 10 year older woman in population**
  - **Annual mammography from 30 years > good prognosis**
  - **MRI?**

- **BRCA2 mutation**
  - **High risk**
  - **Annual mammography good, better with annual MRI**
  - **PSO past chilbearing ages**

- **BRCA1 mutation**
  - **Highest risk**
  - **Mammography some effect?, no additional effect MRI**
  - **PSO past chilbearing ages**
  - **PM**