# Why Genetic Testing for Familial Cancer?

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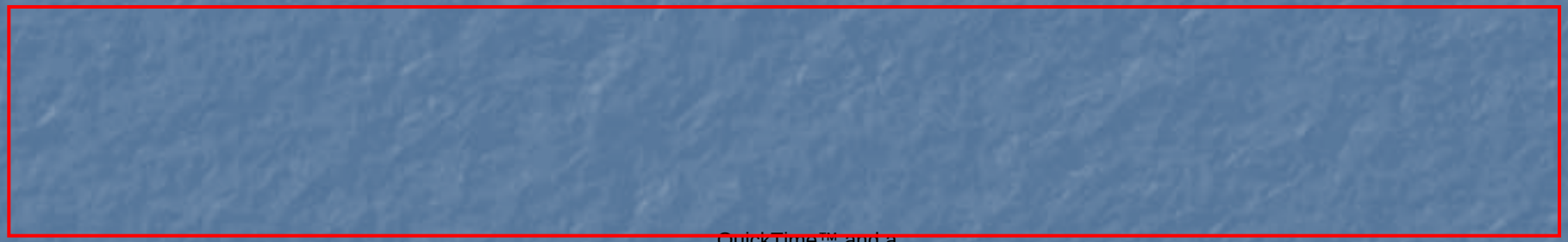
# Familial Cancer Syndromes

- Familial adenomatous polyposis-APC gene
- Hereditary Nonpolyposis Colorectal Cancer- DNA mismatch repair genes
- Multiple Endocrine Neoplasia Type 2- *ret* proto oncogene mutation
- Hereditary Breast Ovarian Cancer- BRCA1/ BRCA 2 Tumor suppressor genes

# Why genetically test familial cancers?

- Reduced cancer risk with prophylactic surgery
- Chemoprevention
- Early screening leads to earlier detection

# Prophylactic surgery reduces cancer incidence




Fatouros, M. et al. The predominant role of surgery in the prevention and new trends in surgical treatment of women with BRCA1/2 mutations. Annals of Surgical Oncology. 2007; 15 (1) :21-33.

# Reduced risk of cancer and death

- Retrospective cohort of 639 women with family history, 425 moderate risk and 214 high risk (from 203 families) with median follow-up 14 yrs
- 214 high risk patients underwent PBM had 403 sisters who did not undergo PBM
- 3 probands developed breast cancer (1.4%) and 156 of the sisters (38.7%);  2 proband deaths (0.9%) and 90 sister deaths (22.3%).
- Risk of breast cancer reduced by 90-94%
- Risk of death reduced by 81-94%

Hartman, LC et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. New England Journal of Medicine. 1999; 340: 77-84.

# Prophylactic BSO

- Prospective cohort of 666 women with BRCA1/BRCA2 from 13 US/European centers from Prevention and Observation of Surgical Endpoints (PROSE) study
- 155 had PBSO and 271 matched for age who did not have PBSO

Domchek et al. Mortality after bilateral salpingo-oopherectomy in BRCA1 and BRCA 2 mutation carriers: a prospective cohort study. Lancet Oncology. 2006; 7:223-29.

# Cancer specific deaths reduced by PBSO

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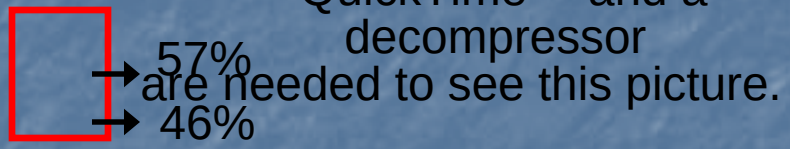
# Reduced breast cancer risk after PBO

- 4,569 patients with known BRCA1/2 were identified through a registry of mutation carriers
- 2,283 women with breast cancer and 2,286 women without breast cancer as controls
- Cases matched for age, BRCA1 or BRCA 2 status, parity, OCP use.
- 1,439 matched sets (1,060 BRCA1, 379 BRCA 2)
- 51 cases had PBO prior to breast cancer and 115 patient controls had PBO

Eisen, A et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. Journal of Clinical Oncology. 2005; 23 (30): 7491-7496.




57%

46%


- 15 yrs after PBO, in BRCA1, OR for breast cancer 0.38 but >15 yrs OR=1.27
- In BRCA2 up to 15 yrs OR for breast cancer=0.43 but >15 yrs OR=1.47

# Chemoprevention with tamoxifen

- National Surgical Adjuvant Breast and Bowel Project P1 (NSABP)
- 13,388 women age 35+ randomly assigned to tamoxifen for 5 yrs or placebo with 7 year followup

Fisher, B et al. Tamoxifen for the prevention of breast cancer: Current status of the National surgical Adjuvant Breast and Bowel Project P-1 study. Journal of the National Cancer Institute. 2005; 97 (22): 1652-1662.

QuickTime™ and a
decompressor
are needed to see this picture.

- Reduction in invasive breast cancer RR=0.57.
- Reduction in Noninvasive breast cancer RR=0.63

# Tumor characteristics

QuickTime™ and a
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decompressor
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- 62% reduction of ER + invasive breast cancers

# Specific to BRCA

- Of 288 patients who developed breast cancer, 19 were screened to have BRCA mutation

62% reduction

QuickTime™ and a
decompressor
are needed to see this picture.

83% ER -

76% ER+

King, MC et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2. Journal of American Medical Association. 2001; 286 (18) : 2251-2256.

# Surveillance in high risk groups

- Family history of breast cancer-mammogram yearly starting age 25 or 5 yrs earlier than youngest family member was diagnosed with breast cancer.
- 1,952 women from 6 familial cancer centers in Netherlands with genetic risk of breast cancer followed over 4yrs
- Clinical breast exam every 6 mos, mammogram and breast MRI every year with results blinded.
- 50 breast cancers detected

Kriege, M et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. New England journal of Medicine. 2004; 351 (5): 427-437.

# Closer surveillance

- 32 found by MRI (10 visible on mammogram), 13 missed by MRI (8 seen on mammogram) 1 detected only on clinical exam
- Mammography detected 18 (10 visible by MRI), 27 missed by mammogram (22 seen on MRI)
- Sensitivity evaluating all breast cancers of CBE, mammogram and MRI 17.0%, 40.0%, 71.1%. Specificity 98.1%, 95%, 89.8%.
- Positive predictive value: CBE 9.6% (8/83), mammogram (BIRADS 3+) 8.0% (18/225), MRI 7.1% (32/452)

# Conclusion

- Genetic testing for high risk patients who have a family history of breast or ovarian cancer.
- Reduced cancer risk with prophylactic surgery
- Chemoprevention with tamoxifen decreases incidence of ER positive cancers
- Improved surveillance for high risk patients with MRI with earlier detection of breast cancer.

# References


Domchek et al. Mortality after bilateral salpingo-oopherectomy in BRCA1 and BRCA 2 mutation carriers: a prospective cohort study. Lancet Oncology. 2006; 7:223-29.

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Guillem, JG et al. ASCO/SSO review of current role of risk-reducing surgery in common heredirary cancer syndromes. Annals of Surgical Oncology. 2006; 13 (10): 1296-1321.

Eisen, A et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. Journal of Clinical Oncology. 2005; 23 (30): 7491-7496.

Fisher, B et al. Tamoxifen for the prevention of breast cancer: Current status of the National surgical Adjuvant Breast and Bowel Project P-1 study. Journal of the National Cancer Institute. 2005; 97 (22): 1652-1662.

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Heemskerk-Gerritsen, BA et al. Prophylactic mastectomy in BRCA1/2 mutation carriers and women at risk of hereditary breast cancer: long-term experience at the Rotterdam Family Cancer Clinic. Annals of Surgical Oncology. 2007; 14 (12: 3335-3344.

Kriege, M et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. New England journal of Medicine. 2004; 351 (5): 427-437.

Rebbeck, TR et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BCRA and BRCA2 mutation carriers: the PROSE Study group. Journal of Clinical Oncology. 2004; 22: 1055-1062.

Tinelli, A et al. Hereditary ovarian cancers: from BRCA muations to clinical management. A modern apprasial. Cancer Metastasis Review. 2010; 29:339-350.