Why Genetic Testing for Familial Cancer?

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Grand Rounds
January 10, 2011
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

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%

**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

Cancer specific deaths reduced by PBSO
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 BRCA2 status, parity, OCP use.
- 1,439 matched sets (1,060 BRCA1, 379 BRCA2)
- 51 cases had PBO prior to breast cancer and 115 patient controls had PBO

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

Reduction in invasive breast cancer RR=0.57.
Reduction in Noninvasive breast cancer RR=0.63
Tumor characteristics

- 62% reduction of ER + invasive breast cancers
Of 288 patients who developed breast cancer, 19 were screened to have BRCA mutation.

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

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


