

Hereditary Breast Cancer Testing and Prevention

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Breast Cancer

- One in eight women will develop breast cancer.
- 5-10% of all breast cancers are "hereditary".
- 15-20% of all breast cancers are "familial".

Hereditary Breast Cancer Syndromes

- BRCA 1 & 2
- Li Fraumeni syndrome (p53)
 - Breast cancer, sarcoma, brain tumors, leukemia, lymphoma, laryngeal cancer and adrenal cortical cancer.
- Cowden's syndrome (pTEN)
 - Breast cancer, benign/malignant thyroid disease, meningioma, leiomyoma and endometrial.
- Peutz –Jeghers syndrome (STK11/LKB1)
 - Breast cancer, duodenal, gastric and pancreatic cancers, melanoma.

BRCA 1 & 2

- BRCA 1 – chromosome 17
- BRCA 2 – chromosome 13
- Both are believed to function in concert as tumor suppressor genes.
- Autosomal dominant inheritance pattern.
- Variable penetrance.

BRCA 1 & Cancer Risk

- 56-87% risk of breast cancer by age 70.
- 60-70% risk of contralateral breast cancer by age 70 and 25% within 5 years of a diagnosis.
- 28-44% risk of ovarian cancer by age 70.
- Colorectal cancer (~ 3-fold increased risk).
- Melanoma.
- Prostate.
- Leukemia/lymphoma.

BRCA 2 & Cancer Risk

- 56-87% risk of breast cancer by age 70
- 60-70% risk of contralateral breast cancer by age 70 and 25% within 5 years of diagnosis.
- Male breast cancer 6%.
- 10-30% risk of ovarian cancer by age 70.
- Prostate (RR-4.6).
- Pancreatic (RR-3.5).
- Stomach (RR-2.59).
- Melanoma, colorectal and laryngeal.

Characteristics of BRCA 1 & 2 Related Breast Cancers

- BRCA 1 related tumors more likely to be ER/PR negative and Her-2/neu negative; higher grade lesions with higher proliferative rates, and p53 mutations.
- BRCA 2 related tumors are more likely to be ER/PR positive .
- Once you control for stage and tumor characteristics, outcomes and survival no different than non-hereditary tumors.

Features Suggestive of Hereditary Syndrome

- Early age at onset (< 45).
- Bilateral breast cancers.
- Breast and ovarian cancer in a single individual.
- Male breast cancer.
- Multiple affected relatives.
- History of both ovarian and breast cancer in a family.
- Ashkenazi Jewish descent.

When Should We Test?

- Individual being tested has strong family history of or very early age of onset.
- Results can be interpreted correctly.
- Test results will influence medical management.**

Potential Benefits of Genetic Testing

- Intervene at an earlier age.
- Develop personalized strategy for cancer surveillance and prevention.
- Identify individuals who have not inherited the gene and can follow routine screening guidelines.
- Identify additional cancers for which patient is at risk.

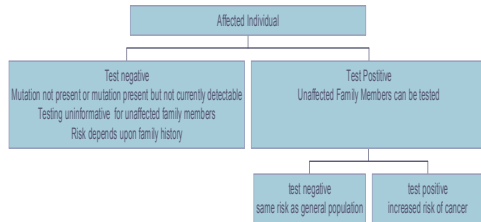
Who Should Be Tested

- Preferably an affected individual.
- Affected individual with youngest age of onset.
- Individual with two or more primary cancers.

Interpretation Of Test Results

- "Positive for a deleterious mutation"
- "Genetic variant, suspected deleterious"
- "Genetic variant, favor polymorphism"
- "Genetic variant of uncertain significance"
- "No deleterious mutation"

Interpretation Of Test Results



Options For Patients With Known Mutation

- ☞ Heightened surveillance
- ☞ Prophylactic surgery
- ☞ Chemoprevention

Proposed Surveillance Guidelines

- ☞ Breast
 - Monthly self-breast exams starting at age 18.
 - Clinician breast exams 2-4 times a year.
 - Mammography at age 25 and q6-12 months after that.
 - Breast MRI

Proposed Surveillance Guidelines

- ☞ Breast MRI
 - Two recent studies compared screening of "high risk" women with mammography versus breast MRI on an annual basis.
 - Sensitivities for mammography were 26-43% with specificity of 95%.
 - Sensitivities for breast MRI were 71-96% with specificity of 88-96%.
 - One study also looked at US and sensitivity was 47% with specificity of 88%.

Proposed Surveillance Guidelines

- ☞ Ovarian cancer
 - Annual pelvic exams.
 - CA125 q 6-12 months.
 - Transvaginal ovarian sonograms q 6-12 months.

Efficacy of Enhanced Screening Guidelines

- ☞ Two recent prospective studies of breast cancer screening as detailed above resulted in a sensitivity of 50% (did not include regular MRI's in all patients).
- ☞ Recent prospective study of ovarian cancer screening with CA125 and transvaginal sonogram every 6 months
 - Concordance between two markers only 40%
 - Sensitivity was 71% but only 10 of 22 with abnormal screening test underwent surgery

Prophylactic Surgery

☛ Breast

- Prophylactic bilateral mastectomy results in reduction in incidence of breast cancer of at least 90%.
- Reduction in risk of death from breast cancer 81-94%.

☛ Ovarian

- Prophylactic bilateral salpingoopherectomy (BSO) reduces risk of ovarian cancer by over 90%.
- 2-11% risk of primary peritoneal carcinoma after undergoing prophylactic BSO.
- If prophylactic BSO is completed prior to menopause, also decrease risk of breast cancer by

Chemoprevention

☛ Breast

- Tamoxifen reduces risk of developing breast cancer by 49%.
- Tamoxifen only effective in reducing risk of hormone dependent cancer (therefore not as effective for patients with BRCA 1 mutations).
- Aromatase Inhibitors ?

☛ Ovarian

- Oral contraceptive pill ?