Cancer Risks for People with Non-BRCA Mutations

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October 20, 2018
No conflicts to disclose
Cancer genes are NEEDED for DNA repair and cell cycle control

When a suppressor gene has a mutation and does not work properly, cells collect DNA damage and can overgrow into cancers
DNA mutation
Controlled cell death

Normal Cell Division

Normal cells

Cancer Cell Division

First mutation
Second mutation
Third mutation
More mutations
Uncontrolled cell growth

Tumor develops
How Much Breast and Ovarian Cancer Is Hereditary?

Breast cancer
- 15%–20%
- 5%–10%

Ovarian cancer
- ~20%

Legend:
- Sporadic
- Family clusters
- Hereditary
<table>
<thead>
<tr>
<th>Company</th>
<th>Test</th>
<th>Website</th>
<th>Genes Included†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambyr Genetics</td>
<td>BreastNext</td>
<td><a href="http://www.ambyrygen.com/tests/breastnext">www.ambyrygen.com/tests/breastnext</a></td>
<td>ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, TP53</td>
</tr>
<tr>
<td>BreastHealth UK</td>
<td>BreastGene</td>
<td><a href="http://www.breasthealthuk.com/screening-services/genetic-testing/breastgene">www.breasthealthuk.com/screening-services/genetic-testing/breastgene</a></td>
<td>ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, PALB2, PTEN, STK11, TP53</td>
</tr>
<tr>
<td>Centogene</td>
<td>Breast Ovarian Cancer Panel</td>
<td><a href="http://www.centogene.com/centogene/centogene-test-catalogue.php">www.centogene.com/centogene/centogene-test-catalogue.php</a></td>
<td>ATM, BARD1, BRIP1, CDH1, CHEK2, MEN1, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PM51, PM52, RAD50, RAD51C, RAD51D, STK11, TP53, XRCC2</td>
</tr>
<tr>
<td>Emory Genetics Laboratory</td>
<td>High Risk Breast Cancer Panel</td>
<td><a href="http://geneticslab.emory.edu/tests/MM201">http://geneticslab.emory.edu/tests/MM201</a></td>
<td>PTEN, STK11, TP53</td>
</tr>
<tr>
<td>Fulgent Diagnostics</td>
<td>Breast Ovarian Cancer NGS Panel</td>
<td><a href="http://fulgentdiagnostics.com/test/breast-ovarian-cancer-NGS-panel/">http://fulgentdiagnostics.com/test/breast-ovarian-cancer-NGS-panel/</a></td>
<td>APC, ATM, ATR, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, CTNNB1, EPCAM, FANCC, HOXB13, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PALLD, PM52, PTEN, RAD50, RAD51, RAD51C, RAD51D, SMAD4, STK11, TP53, VHL, XRCC3, XRCC3</td>
</tr>
<tr>
<td>GeneDx</td>
<td>OncoGeneDx</td>
<td><a href="http://www.genedx.com/test-catalog/available-tests/breastovarian-cancer-panel">www.genedx.com/test-catalog/available-tests/breastovarian-cancer-panel</a></td>
<td>ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, NBN, PALB2, PM52, PTEN, RAD51C, RAD51D, STK11, TP53, XRCC2</td>
</tr>
<tr>
<td>Illumina</td>
<td>TruSight Cancer</td>
<td><a href="http://www.illumina.com/clinical/translational-genomics/panels/kits.html">www.illumina.com/clinical/translational-genomics/panels/kits.html</a></td>
<td>94 Genes plus 287 SNPs reported to be associated with risk of breast cancer</td>
</tr>
<tr>
<td>Myriad Genetics†</td>
<td>myRisk</td>
<td><a href="http://www.myriad.com/products-services/hereditary-cancers/myrisk-hereditary-cancer/">www.myriad.com/products-services/hereditary-cancers/myrisk-hereditary-cancer/</a></td>
<td>ATM, BARD1, BRCA2, BRIP1, CDH1, CHEK2, NBN, PALB2, PTEN, RAD51C, STK11, TP53</td>
</tr>
<tr>
<td>University of Washington†</td>
<td>BROCA – Cancer Risk Panel</td>
<td><a href="http://web.labmed.washington.edu/tests/genetics/BROCA">http://web.labmed.washington.edu/tests/genetics/BROCA</a></td>
<td>AKT1, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FAM175A, GEN1, MRE11A, MUTYH, NBN, PALB2, PIK3CA, PTEN, RAD50, RAD51C, RAD51D, STK11, TP53, XRCC2</td>
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</table>
MULTI-GENE PANEL TESTING

- Gene panels are effective methods for germline mutation screening of predisposition genes
- The relevance of all genes on panels specific to cancer is not fully understood
- Different genes confer different levels of risk and for different cancers
- Different mutations in the same gene may confer different levels of risk
- The phenotypes (pathology, hormone status, treatment response, recurrence) associated with specific mutations are not well understood
- Many variants of unknown significance (VUS) are being identified
GENES ASSOCIATED WITH BREAST CANCER
and their associated risk ranges

- BRCA1: 46-87%
- BRCA2: 43-84%
- PTEN: 77-85%
- PALB2: 17-58%
- CDH1: 39-52%
- ATM: 17-52%
- STK11: 45-50%
- CHEK2: 23-48%
- NBN: 10.2-30%

General population risk to age 80: 10.2%

ELEVATED RISK OF BREAST CANCER, BUT NO DEFINED NUMBER AVAILABLE

TP53
BARD1
PALB2

- Partner and localizer of BRCA2, assists in DNA repair
- 2 to 4-fold increased lifetime risk of female breast cancer (17-58%) may be higher with stronger family history
- Increased risk of male breast, pancreas and prostate cancer though exact magnitude is unknown
- Possible increased risk of ovarian cancer
PALB2 c.509delGA
Checkpoint kinase 2; activated by DNA damage to regulate cell division

~2-3 fold increased lifetime risk of female breast cancer, 25-35%, may be higher with stronger family history

Mutations are more common in Northern and Eastern European ancestries

Different mutations have different risks:
- 1100delC - most common, higher risk, more ER+ br ca
- S428F - founder mutation of AJ ancestry, moderate risk
- I157T - less common, less br ca risk ~1.5 fold, prostate ca risk

Likely/possible risk of male breast, colon, thyroid, kidney, and prostate cancers and sarcoma; not associated with ovarian cancer
B Mutation in CHEK2

Cumulative Risk

Age (yr)

0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00

0 20 40 60 80
CHEK2 c.1100delC
CHEK2 p.S428F
ATM

- Kinase for repairing double-strand breaks in DNA
- Inheriting two mutations leads to Ataxia Telangiectasia - CNS/muscle impairment, dilated blood vessels in eyes, immunodeficiency, radiation sensitivity, increased cancer risk especially leukemia/lymphoma
- ~1% of general population carries one ATM mutation
- Female carriers have 2-3 fold increased risk of breast cancer, 25-35% lifetime risk; some mutations may confer higher risk
- Carriers may have risks of melanoma, thyroid, stomach, pancreas, lung, bladder, prostate, ovarian cancers; no significant radiation impact for carriers
BARD1

- BRCA1 associated RING domain 1; binds to N-terminal of BRCA1, assists cell growth regulation
- Co-inherited with breast cancer and with ovarian cancer in multiple severely affected families in King Lab series
- Possible 2-fold lifetime risk of breast cancer, ~ 25%
- Magnitude of ovarian cancer risk unknown
CDH1

- Encodes E-cadherin; plays key role in epithelial cell adhesion
- Causes highly penetrant diffuse gastric cancer (HDGC) - thickening of stomach wall without an actual tumor or mass
- CDH1 mutations seen in 30-50% of HDGC
- 67% stomach cancer risk for men, 83% for women, most cancer dx <40 yo
- Expected 3-4 fold increased risk of lobular breast cancer, 39-52% lifetime risk
CDH1 p.W156X
TP53

- Tumor suppressor gene regulating cell cycle and cell death
- Mutations cause Li-Fraumeni Syndrome, associated with multiple young onset cancers; 50% risk by age 30; 90% risk by age 60
- Rare; 1 in 5,000-20,000 individuals are carriers
- High breast cancer risk - up to 85% by age 60, often dx < age 30
- Increased risk of soft tissue sarcoma and brain tumors in childhood, bone cancer, cancer of connective tissue, adrenal glands, pancreas, colon, liver and leukemia
TP53 p.P223L

- Pro 80
- Pro
- Pro
- Br 75 1915-2001

- Ut 68 1930-2003
- 70s
- d. 82
- d. 60

- d. 45

- Bil Br 48/52 1954-

- CsU 55 67

- VN

- Br 26 1986-

- Broca -
NBN

- Nibrin protein involved in DNA repair and stability
- NBN/RAD50/MRE11A complex fixes double-strand breaks in DNA
- Autosomal Recessive Nijemen breakage syndrome - microcephaly, poor growth, immunodeficiency and cancer susceptibility
- Female carriers: increased risk of breast cancer, 2-3 fold (30%), often dx < age 55
- Male carriers: increased risk of prostate cancer
- Uncertain risk of ovarian cancer
- Different mutations more common among people of different ancestries and may confer different levels of risk
NBN c.675del5

- Bone? 80s (1872-1958)
- Pro 70, Skin 60s (1918-2002)
- Ov 70s (1883-1961)
- Stroke (1920-2013)

- Pro 66 (1945-)
- col polyps (1945-NN)

- Ov 56 (1956-VN)

- B cell Lymph 73 (1943-NN)

- Lung

- 67

- 1982-VN

- 1982-NN
BRIP1

- BRCA1 Interacting Protein; influences DNA repair and tumor suppressor functions of BRCA1
- Co-inherited with breast cancer and ovarian cancer in multiple severely affected families in King lab series
- Increased lifetime risk of ovarian cancer, ~ 5.8%
- Suspected moderate breast cancer risk, some groups question any risk
- Possible increased risk of prostate cancer
BRIP1 c.1871C>A
RAD51C/RAD51D

- Part of RAD51 protein family, important in fixing double-stranded DNA breaks from replication or damaging agents
- 6-fold lifetime risks of ovarian cancer, 10-15%; RAD51C ovarian risks may be higher than RAD51D
- Recent studies suggest increased risk of breast cancer especially with RAD51D; possible TNBC
- Possible increased risks of prostate cancer
RAD51C del 7511bp (del ex 8-9)
Mismatch repair genes causing Lynch Syndrome, the most common hereditary colon/uterine cancer syndrome; 1 in 370 are carriers.

Other cancers include stomach, ovarian, hepatobiliary tract, urinary tract, small bowel, CNS, skin, pancreas cancers; different genes confer different levels of risk.

New data suggests breast cancer risk with MSH6 and PMS2; possible 2-3 fold lifetime risk (24-36%).

New data suggests prostate cancer risk with MSH6, MSH2 and MLH1; possible 2-3 fold lifetime risk (22-33%).
<table>
<thead>
<tr>
<th>Cancer type</th>
<th>MLH1/MSH2 Mutations</th>
<th>PMS2 Mutations</th>
<th>MSH6 Mutations</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>52-82%</td>
<td>15-20%</td>
<td>10-22%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Endometrium (uterus)</td>
<td>25-60%</td>
<td>15%</td>
<td>16-26%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Stomach</td>
<td>6-13%</td>
<td></td>
<td>&lt;3%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ovary</td>
<td>Up to 20% (MLH1)/ Up to 24% (MSH2)</td>
<td>Combined 6% risk</td>
<td>1-11%, still being determined</td>
<td>&lt;2%</td>
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<tr>
<td>Hepatobiliary tract</td>
<td>1-4%</td>
<td></td>
<td>Not Reported</td>
<td>&lt;1%</td>
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<tr>
<td>Urinary tract</td>
<td>1-7%</td>
<td></td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Small bowel</td>
<td>3-6%</td>
<td></td>
<td>Not Reported</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Brain/central nervous system</td>
<td>1-3%</td>
<td></td>
<td>Not Reported</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Skin (sebaceous adenomas/neoplasm)</td>
<td>1-9%</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1-6%</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>&lt;1%</td>
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</table>
MSH6 c.3980-3981insTCAG
PTEN

- Tumor suppressor gene associated with PTEN Hamartoma Syndromes, Cowden Syndrome
- Increased lifetime risks of multiple cancers: female breast (50%), uterine (28%), thyroid (10%), colon (9%), kidney (5%), melanoma
- Associated with noncancerous tumors in the thyroid (goiter), uterus (fibroids) and GI tract (polyps)
- Increased incidence of autism and autism-like features
PTEN
c.1075G>T
VUS

Ut, Br 70s
1908-2004

1903-1964

Col
1909-1995

1908-1991

Liv 55
1910-1966

d. 83
d. 80s

Ut, Br 70s
1908-2004

Col
1909-1995

1908-1991

Liv 55
1910-1966

d. 83
d. 80s

1882-1964

1883-1967

1944-2004

1910-1966

2

1 w ut fibroid

Br 37
1979-

VN

1882-1964

1883-1967

1944-2004

VN

1 w ut fibroid

Br 37
1979-

VN

1 w ut fibroid

Br 63, preco col polyps
skin tags
cognitive delay
1947-

1947-

1 w ut fibroid

Br 66
1950-

int polyps, skin
cognitive delay
1947-

1947-

1 w ut fibroid

Br 66
1950-

int polyps, skin
cognitive delay
1947-

1947-

1 w ut fibroid

Br 66
1950-

int polyps, skin
cognitive delay
1947-
MANAGEMENT RECOMMENDATIONS:

BREAST CANCER

NCCN Guidelines: Perform annual mammograms +/- MRI with contrast; Consider Risk-Reducing Mastectomy based on family history

▸ From age 30 - CDH1, PALB2, PTEN, TP53 (start 20-29)
▸ From age 40 - ATM, CHEK2, NBN
▸ Insufficient evidence - BARD1, BRIP1, RAD51C, RAD51D, MSH6, PMS2

Non-NCCN Guidelines: Make screening decisions based on family history; start screening 10 years younger than the earliest diagnosis in the family; Tamoxifen may be an option after age 35 if childbearing is complete
MANAGEMENT RECOMMENDATIONS:
OVARIAN CANCER

NCCN Guidelines: Consider Risk Reducing Salpingo-Oophorectomy (ovarian and fallopian tube removal)

- From age 35 - Lynch syndrome genes
- From age 45-50 - BRIP1, RAD51C, RAD51D
- Insufficient evidence - ATM, BARD1, PALB2, NBN
- No Increased Risk - CHEK2, CDH1, PTEN, TP53

Non-NCCN Guidelines: Make RRSO decisions based on family history; Screening is not considered effective, however, consider annual CA-125 and transvaginal U/S for those who refuse RRSO
MANAGEMENT RECOMMENDATIONS:

MALE BREAST CANCER

Self-chest exams, clinical exams, consider mammography/MRI/risk-reducing mastectomy based on family history

- CHEK2, PALB2

PROSTATE CANCER

Annual PSA blood test and rectal digital exam from age 40-50 or 10 years younger than the earliest diagnosis in the family

- ATM, CHEK2, RAD51D, PALB2, NBN, PMS2, MSH2, MSH6, RAD51C, BRIP1, FH, ATR, GEN1, MRE11A, FAM175A, POLE
MANAGEMENT RECOMMENDATIONS:

PANCREATIC CANCER

Consider Magnetic Resonance Cholangiopancreatography with contrast or endoscopic U/S

- Based on family hx - ATM, PALB2, TP53

COLON CANCER

Colonoscopy

- 1-2 yrs from age 20-25 - Lynch
- 5 yrs from age 35-40 - PTEN, CHEK2, TP53, CDH1
MANAGEMENT RECOMMENDATIONS:

UTERINE CANCER

- Consider endometrial biopsy and U/S from age 30-35; Consider hysterectomy after completing childbearing - PTEN, Lynch

STOMACH CANCER

- Consider stomach removal from ages 18-40 - CDH1
- Consider endoscopy +/- biopsy
  - every 6-12 months from age 18 - CDH1
  - every 3-5 yrs from age 40 - Lynch
- Possible screening based on family hx - ATM, TP53, PTEN
Many Genes = Too Much Information?

► CANCER RISKS VARY
   How high does risk need to be before pursuing MRI, surgery or medications?
   * look at your family history

► CANCER RISKS/OPTIONS MAY BE UNCLEAR
   How to make medical decisions without precise information?
   * listen to your heart and your gut

► WE’RE STILL LEARNING
   Risks and recommendations will likely change
   * seek current information
KEEP CALM AND CALL A GENETIC COUNSELOR

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