Genetic counseling and testing

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ESMO Breast Cancer Preceptorship - November 2018
Disclosures

Roche: Speakers bureau, honoraria, consultancy
Astra Zeneca: Speakers bureau, honoraria, consultancy
Novartis: Speakers bureau, honoraria, consultancy
Pfizer: Speakers bureau, honoraria, consultancy
Cancer Arises From Gene Mutations

**Germline mutations**
- Mutation in egg or sperm
- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes
- All cells affected in offspring

**Somatic mutations**
- Somatic mutation (e.g., lung)
- Occur in nongermline tissues
- Are nonheritable
• Cancer can cluster in families because of shared environmental exposures (diet, lifestyle, “environment”, work related exposures)

• Those 15-20% referred to as “familial”, may be caused by the interaction of low-penetrance genes, gene-environment interaction, or both.
Hereditary cancers
- Multiple affected family members
- Early onset
- Bilateral BC or multiple primaries
- Clustering in family of diseases suggestive of a hereditary cancer syndrome
- Extensive family history

Sporadic cancers
- Age appropriate
- Common cancers

Familial Cancer
- Occurring in or affecting more members of family than would be expected by chance
- Generally, two or more family members with the same type of cancer, age appropriate

Risk for cancer is AVERAGE

Risk for cancer is MODERATE

Risk for cancer is HIGH
BRCA1/2 Mutations
BRCA1 and BRCA2

- Cloned in families with multiple cases of breast and/or ovarian cancer

Mutations in different genes can cause the same disease

BRCA1- cloned 1994

BRCA2- cloned 1995
Prevalence

In unselected populations - 1/300-1/800.

Founder mutations:
Iceland - BRCA2 999del5 - 0.6% (~1/170)
Ashkenazi Jews -
BRCA1 - 185del AG 1%
5382insC 0.1%
BRCA2 - 6174delT 1.4%

2.5% (1/40)
The prevalence of BRCA1/BRCA2 mutations: Contribution to cancer

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Non-selected population</th>
<th>Ashkenazi Jewish</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>2.5-5%</td>
<td>~11%</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>10-15%</td>
<td>~40%</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>?</td>
<td>~8%</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>?</td>
<td>~5%</td>
</tr>
</tbody>
</table>
Cancer susceptibility genes other than \textit{BRCA1/2}

### Table 1. Cancer Susceptibility Genes Other Than \textit{BRCA1/2}

<table>
<thead>
<tr>
<th>Cancer Susceptibility Gene</th>
<th>Breast Cancer RR (90% CI when available) or Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast</strong></td>
<td></td>
</tr>
<tr>
<td>\textit{ATM}</td>
<td>2.8 (2.2 to 3.7)\textsuperscript{35}</td>
</tr>
<tr>
<td>\textit{BARD1}</td>
<td>Breast cancer association reported; RR not yet determined\textsuperscript{17,46,47}</td>
</tr>
<tr>
<td>\textit{BRIP1}</td>
<td>2.0 (1.3 to 3.0)\textsuperscript{48}, ovarian cancer RR 11.2\textsuperscript{9}</td>
</tr>
<tr>
<td>\textit{CDH1}</td>
<td>6.6 (2.2 to 19.9)\textsuperscript{49}</td>
</tr>
<tr>
<td>\textit{CHEK2}</td>
<td>3.0 (2.6 to 3.5)\textsuperscript{35}; most data for 1100delC</td>
</tr>
<tr>
<td>\textit{NBN}</td>
<td>2.7 (1.9 to 3.7)\textsuperscript{35}</td>
</tr>
<tr>
<td>\textit{PALB2}</td>
<td>5.3 (3.0 to 9.4)\textsuperscript{35}</td>
</tr>
<tr>
<td>\textit{PTEN}</td>
<td>RR 2.0-5.0\textsuperscript{50,51}</td>
</tr>
<tr>
<td>\textit{STK11}</td>
<td>RR 2.0-4.0\textsuperscript{52,53}</td>
</tr>
<tr>
<td>\textit{TP53}</td>
<td>105 (62 to 165)\textsuperscript{35}</td>
</tr>
</tbody>
</table>

\textsuperscript{17,46,47}
Prevalence of BRCA1/2 mutation amongst Breast Cancer patients

**Table 4. Frequency of Deleterious Mutations by Age at Breast Cancer Diagnosis**

<table>
<thead>
<tr>
<th>Genes</th>
<th>Patients (\leq 45) Years of Age With DM (n = 180)</th>
<th>Patients 46-60 Years of Age With DM (n = 199)</th>
<th>Patients &gt; 60 Years of Age With DM (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any deleterious mutation*</td>
<td>30 (16.7 [11.1 to 22.9])</td>
<td>15 (7.5 [4.3 to 12.1])</td>
<td>7 (6.4 [2.6 to 12.8])</td>
</tr>
<tr>
<td>Genes related to breast cancer*</td>
<td>29 (16.1 [11.1 to 22.3])</td>
<td>14 (7.0 [3.9 to 11.5])</td>
<td>6 (5.5 [2.1 to 11.6])</td>
</tr>
<tr>
<td>BRCA1 or BRCA2</td>
<td>22 (12.2 [7.8 to 17.9])</td>
<td>6 (3.0 [1.1 to 6.5])</td>
<td>2 (1.8 [0.2 to 6.5])</td>
</tr>
<tr>
<td>BRCA1*</td>
<td>15 (8.3 [4.7 to 13.4])</td>
<td>2 (1.0 [0.1 to 3.6])</td>
<td>1 (0.9 [0.02 to 5.0])</td>
</tr>
<tr>
<td>BRCA2*</td>
<td>7 (3.9 [1.6 to 7.9])</td>
<td>4 (2.0 [0.6 to 5.1])</td>
<td>1 (0.9 [0.02 to 5.0])</td>
</tr>
<tr>
<td>Other genes related to breast cancer*</td>
<td>8 (4.4 [1.9 to 8.6])</td>
<td>8 (4.0 [1.8 to 7.8])</td>
<td>4 (3.7 [1.0 to 9.1])</td>
</tr>
<tr>
<td>ATM*</td>
<td>3 (1.7 [0.4 to 4.8])</td>
<td>1 (0.5 [0.01 to 2.8])</td>
<td>0 (0.0 [0.0 to 3.3])</td>
</tr>
<tr>
<td>BRIP1</td>
<td>1 (0.6 [0.01 to 3.1])</td>
<td>2 (1.0 [0.1 to 3.6])</td>
<td>1 (0.9 [0.02 to 5.0])</td>
</tr>
<tr>
<td>CHEK2*</td>
<td>4 (2.2 [0.6 to 5.6])</td>
<td>3 (1.5 [0.3 to 4.3])</td>
<td>3 (2.8 [0.6 to 7.8])</td>
</tr>
<tr>
<td>NBN</td>
<td>0 (0.0 [0.0 to 2.0])</td>
<td>1 (0.5 [0.01 to 2.8])</td>
<td>0 (0.0 [0.0 to 3.3])</td>
</tr>
<tr>
<td>PALB2</td>
<td>1 (0.6 [0.01 to 3.1])</td>
<td>0 (0.0 [0.0 to 1.8])</td>
<td>0 (0.0 [0.0 to 3.3])</td>
</tr>
<tr>
<td>PTEN</td>
<td>0 (0.0 [0.0 to 2.0])</td>
<td>1 (0.5 [0.01 to 2.8])</td>
<td>0 (0.0 [0.0 to 3.3])</td>
</tr>
<tr>
<td>Genes not clearly related to breast cancer*</td>
<td>2 (1.1 [0.1 to 4.0])</td>
<td>1 (0.5 [0.01 to 2.8])</td>
<td>1 (0.9 [0.02 to 5.0])</td>
</tr>
<tr>
<td>MSH6</td>
<td>0 (0.0 [0.0 to 2.0])</td>
<td>1 (0.5 [0.01 to 2.8])</td>
<td>0 (0.0 [0.0 to 3.3])</td>
</tr>
<tr>
<td>PMS2*</td>
<td>1 (0.6 [0.01 to 3.1])</td>
<td>0 (0.0 [0.0 to 1.8])</td>
<td>0 (0.0 [0.0 to 3.3])</td>
</tr>
<tr>
<td>RAD51C</td>
<td>0 (0.0 [0.0 to 2.0])</td>
<td>0 (0.0 [0.0 to 1.8])</td>
<td>1 (0.9 [0.02 to 5.0])</td>
</tr>
<tr>
<td>RAD51D</td>
<td>1 (0.6 [0.01 to 3.1])</td>
<td>0 (0.0 [0.0 to 1.8])</td>
<td>0 (0.0 [0.0 to 3.3])</td>
</tr>
</tbody>
</table>

Tung et al JCO 2016
When to refer for onco-genetic counseling & testing?
Who should we test for gBRCA mutations?

• From classical genetics to genetically-driven precision medicine...

• **Current guidelines** (historical target: 10% tested positive; use family history, male cancer, ovarian cancer, TNBC < 50 or 60, age < 40, askenazi descent) identify only part of the carriers

• **Risk-benefit** of testing to be re-estimated provided targeted therapeutic benefit is relevant

What is risk?? VUS, cost…

Courtesy of Karen Gelmon
CRITERIA FOR FURTHER GENETIC RISK EVALUATION

- An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene within the family, including such variants found on research testing.
- An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene found on tumor testing (See BR/OV-A 3 of 3).
- An individual diagnosed at any age with any of the following:
  - Ovarian cancer
  - Pancreatic cancer
  - Metastatic prostate cancer
  - Breast cancer or high-grade (Gleason score ≥7) prostate cancer and of Ashkenazi Jewish ancestry
- An individual with a breast cancer diagnosis meeting any of the following:
  - Breast cancer diagnosed age ≤50 y
  - Triple-negative (ER-, PR-, HER2-) breast cancer diagnosed age ≤60 y
  - Two breast cancer primaries
  - Breast cancer at any age, and
    - ≥1 close blood relative with:
      - breast cancer age ≤50 y; or
      - invasive ovarian cancer;
      - male breast cancer; or
      - pancreatic cancer; or
      - high-grade (Gleason score ≥7) or metastatic prostate cancer
    - ≥2 close blood relatives with breast cancer at any age

The criteria for further risk evaluation and genetic testing are not identical. For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

Irrespective of degree of relatedness.

Includes fallopian tube and primary peritoneal cancers. BRCA-related ovarian cancers are associated with epithelial, non-mucinous histology. Lynch syndrome can be associated with both non-mucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.

Metastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence.

Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors diagnosed either synchronously or asynchronously.

Close blood relatives include first-, second-, and third-degree relatives. (See BR/OV-B).

When possible, genetic testing should be performed first on an affected family member.

For dermatologic manifestations, see COVID-1.

For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.
BRCA1/2 TESTING CRITERIA\textsuperscript{a,b}

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known BRCA1/2 pathogenic/likely pathogenic variant, including such variants found on research testing
- Personal history of breast cancer\textsuperscript{a} + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed 46-50 y with:
    - An additional breast cancer primary at any age\textsuperscript{d}
    - ≥2 close blood relative\textsuperscript{e} with breast cancer at any age
    - ≥2 close blood relative\textsuperscript{e} with high-grade (Gleason score ≥7) prostate cancer
  - An unknown or limited family history\textsuperscript{a}
  - Diagnosed ≤60 y with:
    - Triple-negative breast cancer
    - Diagnosed at any age with:
      - ≥2 close blood relative\textsuperscript{e} with:
        - breast cancer diagnosed ≤50 y; or
        - ovarian cancer; or
        - male breast cancer; or
        - metastatic prostate cancer;\textsuperscript{g} or
        - pancreatic cancer
    - ≥2 additional diagnoses\textsuperscript{d} of breast cancer at any age in patient and/or in close blood relatives
    - Ashkenazi Jewish ancestry\textsuperscript{h}
- Personal history of ovarian carcinoma\textsuperscript{f}

\textsuperscript{a} For further details regarding the nuances of genetic counseling and testing, see BRCA-\textit{OVA}.

\textsuperscript{b} Irrespective of degree of relatedness.

\textsuperscript{c} For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

\textsuperscript{d} Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors diagnosed either synchronously or asynchronously.

\textsuperscript{e} Close blood relatives include first-, second-, and third-degree relatives on same side of family. (See BRCA-\textit{OVA}.)

\textsuperscript{f} Includes fallopian tube and primary peritoneal cancers. BRCA-related ovarian cancers are associated with epithelial, non-mucinous histology. Lynch syndrome can be associated with both non-mucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome (see NCCN Guidelines for Genetic/Hereditary High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.

- BRCA1/2 pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic/likely pathogenic variant analysis
- Regardless of family history, some individuals with an BRCA-related cancer may benefit from genetic testing to determine eligibility for targeted treatment
- An individual who does not meet the other criteria but with ≥1 first- or second-degree blood\textsuperscript{e} relative meeting any of the above criteria. The significant limitations of interpreting test results for an unaffected individual should be discussed.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
• Carrier probability at which genetic testing should be offered

• **Breast/ovarian cancer cases** with combined *BRCA1/BRCA2 mutation carrier probability of >10% (based on acceptable methods)*

• NICE 2013 guidelines indicate that research is needed on the benefits and harms of RGCT (Rapid Genetic Counseling and Testing)
Consider genetic counseling & testing for BRCA1/2 when:

- Bilateral breast cancer
- Early onset breast cancer (≤40-45)
- Histo-pathologic features including: triple negative subtype (Medullary carcinoma, lymphocytic infiltration)
- Personal or family history of – breast (incl. male breast cancer), ovarian, pancreatic or prostate cancer
- Certain ethnic groups (eg Ashkenazi Jewish ancestry)
- When there’s therapeutic implication – in all ABC?
Genetic counseling
- what, how, when?
Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease*

*Journal of Genetic Counseling, Vol. 15, April 2006.*
Who *can* give genetic counseling?

- **USA** – Physicians and genetic counselors *(relatively new profession, MSc to PhD; ABGC)*

- **Europe** – also “genetic nurses”

- **Israel** – *Genetic Information Law (2001):*
  Physicians within their specialty and genetic counselors.
Genetic counseling for inherited cancer predisposition

Affected vs. Healthy

Common issues:
- Risk assessment for specific cancers.
- Cancer surveillance and prevention.
- Familial implications: mode of inheritance, relatives at risk, reproduction.
- Genetic testing: sensitivity, clinical utility, method, result interpretation.

Issues for affected women:
- Therapeutic implications – Surgical & Medical.
- Recently diagnosed – time pressure & information overload
- Reproductive
Genetic counseling for inherited cancer predisposition

The traditional model:

• Pretest counseling (30-45 min, and more)
  Drawing a family pedigree
  Discussion – inheritance, risk assessment, etc.
  Reaching an informed decision about testing.

• Genetic testing

• Post-test counseling (variable length)
  Discussion of results
  Recommendations for patient and relatives
Genetic Counseling - Issues

- Different national requirements and institutional policies
- Could be a bottleneck to timely testing
- New studies suggesting that written information or post-testing counseling as acceptable alternative
BRCA1/ BRCA2 testing at breast cancer diagnosis:

Potential concerns

- Information overload
- Psychological distress
- Delay in treatment initiation — if testing takes too long.
## Rapid vs. Traditional BRCA testing in patients at Modena Cancer Genetics Clinic

<table>
<thead>
<tr>
<th></th>
<th>Traditional</th>
<th>Rapid</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uptake</strong></td>
<td>70% (1058/1520)</td>
<td><strong>100%</strong> (110/110)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>BRCA1/BRCA2 positive</strong></td>
<td>20% (209/1058)</td>
<td><strong>33%</strong> (36/110)</td>
<td>.003</td>
</tr>
<tr>
<td><strong>RRM in BRCA positive</strong></td>
<td>4.7% (10/209)</td>
<td><strong>42%</strong> (15/36)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Contralateral disease by pathology @ RRM</strong></td>
<td>20% (2/10)</td>
<td><strong>27%</strong> (4/15)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Psychological support usage post RRM (voluntary)</strong></td>
<td>50% (5/10) Age: 38y (SD =7y)</td>
<td><strong>53%</strong> (8/15) Age: 37y (SD =6y)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conclusions – Modena Cancer Clinic Study

Rapid genetic testing:
• Increased uptake of testing
• Identification of more carriers (higher rate)
• Increased uptake of contralateral RRM
• No increased use of psychological support services
Psychological implications - Rapid genetic testing

- Immediate effects: 54% (18/26) reported distress beyond that generated by cancer diagnosis (not associate with test results) 19% (5/26) reported rapid testing reduced their distress.
- Long term (2.5y) status: 23% (6/26) had clinically relevant breast cancer –specific distress (IES>25) (comparable to historical controls).
- Satisfaction: 96% (25/26) very/satisfied with rapid testing. 88% thought best timing was between diagnosis and surgery.
- No long term harm (Baers et al Clin Genet 2014, testing performed during radiotherapy)
How BRCA testing is changing with the introduction of specific BRCA therapies?

• More patients referred for testing

• Quicker results needed

• Testing will take place earlier - at diagnosis or during early treatment phase

• Role\timing of counselling will need to change
Hereditary breast cancer syndrome & multi-gene panel testing
Other HBOC Syndromes

- Li Fraumeni Syndrome
- $p53$ mutation
- $PTEN$/Cowden Syndrome
- $ATM$ mutation
- Lynch Syndrome
- $MLH1, MSH2, MSH6, EPCAM$ and $PMS2$ mutations
- $RAD51$ mutation
- $BRIP1$ mutation
- $PALB2$ mutation
- $CHEK2$ mutation
- $STK11$ mutation
- (Peutz-Jeghers Syndrome)
- $CDH1$ mutation

Clinical implications for prevention and screening not well understood for all these mutations…..
<table>
<thead>
<tr>
<th>BRCA-RELATED FOLLOW-UP</th>
<th>FAMILY STATUS</th>
<th>GENETIC TESTING</th>
<th>TEST OUTCOME</th>
<th>SCREENING RECOMMENDATION</th>
</tr>
</thead>
</table>
| Risk assessment and counseling:  
- Psychosocial assessment and support  
- Risk counseling  
- Education  
- Discussion of genetic testing  
- Informed consent |  
Familial BRCA1/2 pathogenic/likely pathogenic variant known | Recommend BRCA1/2 testing for specific familial pathogenic/likely pathogenic variant |  
Positive for familial BRCA1/2 pathogenic likely pathogenic variant | See BRCA-Related Pathogenic Variant-Positive Management (BRCA-A) |
|  
No known familial BRCA1/2 pathogenic/likely pathogenic variant | Consider comprehensive BRCA1/2 testing of patient or if unaffected, test family member with highest likelihood of a pathogenic/likely pathogenic variant | Pathogenic/likely pathogenic variant found |  
Pathogenic/likely pathogenic variant found | See BRCA-Related Pathogenic Variant-Positive Management (BRCA-A) |
|  
No known familial BRCA1/2 pathogenic/likely pathogenic variant | Consider multi-gene testing, if appropriate | Not tested |  
Variant of unknown significance found (uninformative) | Offer research and individualized recommendations according to personal and family history |

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For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.

If of Ashkenazi Jewish descent, in addition to the specific familial pathogenic/likely pathogenic variant, test for all three founder pathogenic/likely pathogenic variants. Additional testing may be indicated if there is also a significant family history of cancer on the side of the family without the known pathogenic/likely pathogenic variant.

For both affected and unaffected individuals of Ashkenazi Jewish descent with no known familial pathogenic/likely pathogenic variant, first test for the three common pathogenic variants. Then, if negative for the three pathogenic/likely pathogenic variants and ancestry also includes non-Ashkenazi Jewish relatives or other BRCA-related criteria are met, consider comprehensive genetic testing. For both affected and unaffected individuals who are non-Ashkenazi Jewish and who have no known familial pathogenic/likely pathogenic variants, comprehensive genetic testing is the approach, if done.

If no pathogenic/likely pathogenic variant is found, consider testing another family member with next highest likelihood of having a pathogenic/likely pathogenic variant and/or other hereditary breast/ovarian cancer syndromes such as Li-Fraumeni (LiF-1) and/or Cowden syndrome (COWD-1) or multi-gene testing (GENE-1). For additional information on other genetic pathogenic/likely pathogenic variants associated with breast/ovarian cancer risk for which genetic testing is clinically available, see GENE-2.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Results from Genetic Testing

• **Positive**
  – Deleterious mutation identified

• **Negative**
  – Interpretation differs if a mutation has previously been identified in the family
    • Mutation known – true negative
    • Mutation unknown – uninformative

• **Variant of unknown significance**
  – Significance will depend on how variant tracks through family - i.e. is variant present in people with disease?
  – Can use databases to check previous reports
Why do this?

- If it’s clinically indicated!
- More cost effective (for the testing) to do multigene rather than serial testing
- Patients (and providers!) can get testing fatigue
- The same cancer can be seen in different hereditary syndromes
  - Ovarian cancer in both BRCA1/2 and Lynch
  - Uterine cancer in Lynch and Cowden
  - Breast in Li-Fraumeni and BRCA1/2
NGS Panels- Breast

• 800 families with negative BRCA1/2 testing
  – 206 tested positive with NGS BROCA panel (26%)

• Of the 26% with a new positive results
  – 39% (80/206) had BRCA1/2 mutations
  – 37% carried mutations in CHEK2, PALB2, or TP53
  – 20% carried mutations in 10 less characterized genes

Walsh et. al. 2013
This has become very complicated....
What is the risk (penetrance)?
Increased risk of other cancers:
- Male breast cancer: BRCA2 > BRCA1
- Pancreatic cancer: BRCA2
- Prostate cancer: BRCA2
- Melanoma: BRCA2

Breast cancer: 50%-70%
Second primary breast cancer: 40%-50%
Ovarian cancer: 15-45% \(BRCA1 > BRCA2\)

Increased risk of other cancers:
- Male breast cancer: \(BRCA2 > BRCA1\)
- Pancreatic cancer: \(BRCA2\)
- Prostate cancer: \(BRCA2\)
- Melanoma: \(BRCA2\)

Different definitions of “lifetime” yield different outcomes

“Remaining lifetime risk” higher for younger patients
# Breast Cancer Risk

## Table 2. Breast and Ovarian Cancer Incidence Rates Per 1000 Person-Years, Kaplan-Meier Estimates of the Cumulative Risks, and Standardized Incidence Rates by 10-Year Age Groups

<table>
<thead>
<tr>
<th>Age During Follow-up, y</th>
<th>No. of Women Contributing in Age Category</th>
<th>No. of Person-Years</th>
<th>No. of Events</th>
<th>Incidence per 1000 Person-Years (95% CI)</th>
<th>Cumulative Risk, % (95% CI)</th>
<th>Standardized Incidence Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>53</td>
<td>74.0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>605</td>
<td>2222.5</td>
<td>13</td>
<td>5.9 (4.4-10.1)</td>
<td>4 (2-7)</td>
<td>73.7 (42.9-126.8)</td>
</tr>
<tr>
<td>31-40</td>
<td><strong>1048</strong></td>
<td><strong>3831.6</strong></td>
<td><strong>90</strong></td>
<td><strong>23.5 (19.1-28.9)</strong></td>
<td><strong>24 (21-26)</strong></td>
<td><strong>46.2 (37.3-57.1)</strong></td>
</tr>
<tr>
<td>41-50</td>
<td>870</td>
<td>3317.8</td>
<td>94</td>
<td>28.3 (23.1-34.7)</td>
<td>43 (39-48)</td>
<td>17.2 (14.0-21.2)</td>
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<tr>
<td>51-60</td>
<td>479</td>
<td>1905.9</td>
<td>49</td>
<td>25.7 (19.4-34.0)</td>
<td>56 (51-61)</td>
<td>9.7 (7.2-12.9)</td>
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<td>61-70</td>
<td>201</td>
<td>761.3</td>
<td>19</td>
<td>25.0 (15.9-39.1)</td>
<td>66 (61-72)</td>
<td>7.0 (4.5-11.0)</td>
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<td>71-80</td>
<td><strong>55</strong></td>
<td><strong>243.0</strong></td>
<td><strong>4</strong></td>
<td><strong>16.5 (6.2-43.9)</strong></td>
<td><strong>72 (65-79)</strong></td>
<td><strong>4.8 (1.8-12.8)</strong></td>
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<tr>
<td>Total</td>
<td><strong>2276</strong></td>
<td><strong>12356.1</strong></td>
<td><strong>269</strong></td>
<td><strong>21.8 (19.3-24.5)</strong></td>
<td></td>
<td><strong>16.6 (14.7-18.7)</strong></td>
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<td><strong>BRCA1 mutation carriers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>30</td>
<td>44.0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>329</td>
<td>1046.0</td>
<td>5</td>
<td>4.8 (2.0-11.5)</td>
<td>4 (2-9)</td>
<td>60.8 (25.5-144.9)</td>
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<td>31-40</td>
<td><strong>625</strong></td>
<td><strong>2136.1</strong></td>
<td><strong>23</strong></td>
<td><strong>10.8 (7.2-16.2)</strong></td>
<td><strong>13 (9-19)</strong></td>
<td><strong>20.3 (13.5-30.5)</strong></td>
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<tr>
<td>41-50</td>
<td>669</td>
<td>2365.0</td>
<td>65</td>
<td>27.5 (21.6-35.1)</td>
<td>35 (29-41)</td>
<td>16.4 (12.9-20.9)</td>
</tr>
<tr>
<td>51-60</td>
<td>384</td>
<td>1437.2</td>
<td>44</td>
<td>30.6 (22.8-41.1)</td>
<td>53 (46-59)</td>
<td>11.4 (8.4-15.5)</td>
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<tr>
<td>61-70</td>
<td>174</td>
<td>610.2</td>
<td>14</td>
<td>22.9 (13.6-38.7)</td>
<td>61 (55-68)</td>
<td>5.4 (3.8-10.7)</td>
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<tr>
<td>71-80</td>
<td><strong>68</strong></td>
<td><strong>274.6</strong></td>
<td><strong>6</strong></td>
<td><strong>21.9 (9.8-48.6)</strong></td>
<td><strong>69 (61-77)</strong></td>
<td><strong>5.6 (3.0-14.7)</strong></td>
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<tr>
<td>Total</td>
<td><strong>1610</strong></td>
<td><strong>7913.1</strong></td>
<td><strong>157</strong></td>
<td><strong>19.8 (17.0-23.2)</strong></td>
<td></td>
<td><strong>12.9 (11.1-15.1)</strong></td>
</tr>
</tbody>
</table>

Kuchenbacker, JAMA 2017
Cumulative Risks of Breast and Ovarian Cancer in BRCA1\2 Carriers

Figure 2. Estimated Cumulative Risks of Breast and Ovarian Cancer in Mutation Carriers

A  Cumulative risk of first breast cancer among BRCA1 and BRCA2 mutation carriers
B  Cumulative risk of ovarian cancer among BRCA1 and BRCA2 mutation carriers

Kuchenbacker, JAMA 2017
Lifetime risk of breast cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Estimated lifetime risk of breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>55-65%&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>BRCA2</td>
<td>45-47%&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>TP53</td>
<td>49-60%&lt;sup&gt;36&lt;/sup&gt;</td>
</tr>
<tr>
<td>PTEN</td>
<td>25-50%&lt;sup&gt;61,62&lt;/sup&gt;</td>
</tr>
<tr>
<td>PALB2</td>
<td>33-58%&lt;sup&gt;56&lt;/sup&gt;</td>
</tr>
<tr>
<td>STK11</td>
<td>30-50%&lt;sup&gt;58,63,64&lt;/sup&gt;</td>
</tr>
<tr>
<td>CDH1</td>
<td>39-52%&lt;sup&gt;65,66&lt;/sup&gt;</td>
</tr>
<tr>
<td>ATM</td>
<td>15-52%&lt;sup&gt;67-70&lt;/sup&gt;</td>
</tr>
<tr>
<td>CHEK2</td>
<td>20-44%&lt;sup&gt;71-74&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
## Average estimated cumulative 5-year and lifetime breast cancer risks

<table>
<thead>
<tr>
<th>Population</th>
<th>ATM/NBN (RR 2.7-2.8)*</th>
<th>CHEK2 (1100delC) (RR 3.0)‡</th>
<th>CHEK2 (I157T) (RR 1.58)</th>
<th>PALB2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td><strong>5 year risk</strong></td>
<td><strong>Cumulative</strong></td>
<td><strong>5 year</strong></td>
<td><strong>Cumulative</strong></td>
</tr>
<tr>
<td>25-29</td>
<td>0.04%</td>
<td>0.1%</td>
<td>0.12%</td>
<td>0.1%</td>
</tr>
<tr>
<td>30-34</td>
<td>0.14%</td>
<td>0.2%</td>
<td>0.38%</td>
<td>0.5%</td>
</tr>
<tr>
<td>35-39</td>
<td>0.30%</td>
<td>0.5%</td>
<td>0.84%</td>
<td>1.4%</td>
</tr>
<tr>
<td>40-44</td>
<td>0.61%</td>
<td>1.1%</td>
<td>1.70%</td>
<td>3.0%</td>
</tr>
<tr>
<td>45-49</td>
<td>0.94%</td>
<td>2.0%</td>
<td>2.64%</td>
<td>5.6%</td>
</tr>
<tr>
<td>50-54</td>
<td>1.12%</td>
<td>3.1%</td>
<td>3.14%</td>
<td>8.5%</td>
</tr>
<tr>
<td>55-59</td>
<td>1.33%</td>
<td>4.4%</td>
<td>3.71%</td>
<td>11.8%</td>
</tr>
<tr>
<td>60-64</td>
<td>1.72%</td>
<td>6.0%</td>
<td>4.81%</td>
<td>16.0%</td>
</tr>
<tr>
<td>65-69</td>
<td>2.11%</td>
<td>8.0%</td>
<td>5.92%</td>
<td>20.8%</td>
</tr>
<tr>
<td>70-75</td>
<td>2.20%</td>
<td>10.0%</td>
<td>6.17%</td>
<td>25.5%</td>
</tr>
<tr>
<td><strong>CLTR (80)</strong></td>
<td>2.24%</td>
<td>12.0%</td>
<td>30.0%</td>
<td>31.8%</td>
</tr>
</tbody>
</table>

TUNG, NATURE REVIEWS CLINICAL ONCOLOGY, 2016
Considerations in the healthy BRCA carrier
Risk reduction & screening

• Risk reducing surgery
  - Bilateral RRM
  - RRSO
• Chemoprevention
• Lifestyle intervention
• Screening for early detection:
  ✓ Breast & Ovarian cancer
  ?? Pancreatic cancer, prostate cancer
REPRODUCTIVE ISSUES
Reproductive considerations in carriers

### Reproductive considerations in BRCA mutation carriers

**BRCA1/2** carriers can be reassured that there is no convincing evidence that mutation carriers have reduced ovarian reserve or fertility.

All women harbouring a **BRCA1/2** mutation should be encouraged to complete child-bearing prior to planned RRSO.

For women who wish to undergo RRSO and have not yet completed child-bearing fertility preservation options should be discussed.

**BRCA1/2** mutation carriers (male and female) planning to conceive should be made aware of the options of pre-natal diagnosis (via chorio-villous or amniotic fluid sampling in week 11-20 of gestation) and PGD.

Women harbouring a **BRCA1/2** mutation who have been diagnosed with a malignancy should be counselled about options for fertility preservation prior to the commencement of oncology treatment.

Appropriate counselling should be available and vaginal moisturisers and lubricants should be prescribed to all women following RRS.

Short term use of HRT to alleviate menopausal symptoms following RRSO is safe amongst healthy **BRCA1/2** mutation carriers.

No safety data are available about the use of HRT amongst **BRCA1/2** carriers with a previous diagnosis of breast cancer. The relationship between hormonal influences and the development of different breast cancer subtypes, including triple negative breast cancers, has not been fully elucidated thus HRT in the setting of a past breast cancer diagnosis should be strongly discouraged – irrespective of endocrine status of the initial tumour.

Topical oestrogens to alleviate vaginal dryness may be used with caution.

As a result of premature menopause, bone health needs to be routinely monitored, preventive measures taken and any reduction in bone density treated as clinically indicated.

---

Reproductive issues

• Timing of RRSO (risk reducing oophorectomy)
  - For BRCA1 – between 35-40
  - For BRCA2 – 40-45
• Fertility preservation
• Understanding the clinical significance of reduced ovarian reserve in $BRCA$ carriers
• PGD – pre-implantation genetic diagnosis
• Premature menopause – impact on sexual health, bone health, quality of life
• Understanding the hormonal axis & breast cancer in $BRCA$ carriers:
  - Role of oophorectomy in ↓ BC risk & mortality
  - HRT in healthy & affected $BRCA$ carriers
Management of Mutation Carriers

Consider...

- **Psychosocial support to assist with:**
  - Adjusting to new information
    - most adjust within 3-6 months
    - subset remain psychologically distressed (16-25% anxiety and/or depression)
  - Making decisions regarding management
    “to inflict surgery is a hard decision to make... when I don’t have the disease and feel healthy”
  - Addressing family issues, self concept, body image
  - Dealing with future concerns i.e. child bearing, surgical menopause after oophorectomy

- **Referral to support groups**
Precision medicine in risk reduction

Risk Reduction measures

• Prevention studies: BRCA-P Collaborative academic study by ABCSG Principles and Practices of Cancer Trials Group

• Salpingectomy - 1st step risk-reducing procedure?? Under study!

• Fine tuning timing of RRSO (*tailored to family history):
  - For BRCA1 – between 35-40
  - For BRCA2 – 40-45

Risk assessment tools

• Clinical utility/validity of genetic modifiers → tailoring risk and risk-reducing measures

RRSO= risk reducing salpingoophorectomy
In summary:
Unique challenges in BRCA1/2 associated BC

• Multitude of therapeutic & reproductive decisions
• Knowledge of BRCA1/2 status may arrive at a time of great distress
• Risk reducing measures are often an assault on self-image, “womanhood”
• Far reaching implications for family planning and for the extended family
• Multiple psychosocial issues - support is imperative
• Multi-disciplinary care – is a MUST
Prevention and screening in \textit{BRCA} mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening\textsuperscript{†}

S. Paluch-Shimon\textsuperscript{1}, F. Cardoso\textsuperscript{2}, C. Sessa\textsuperscript{3}, J. Balmana\textsuperscript{4}, M. J. Cardoso\textsuperscript{2}, F. Gilbert\textsuperscript{5} & E. Senkus\textsuperscript{6}, on behalf of the ESMO Guidelines Committee\textsuperscript{*}

\textsuperscript{1}Division of Oncology and the Dr Pinchas Borenstein Talpiot Medical Leadership Program, Sheba Medical Center, Ramat Gan, Israel; \textsuperscript{2}Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal; \textsuperscript{3}Oncology Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland; \textsuperscript{4}Vall d’Hebron University Hospital Institut d’Oncòlogia, Barcelona, Spain; \textsuperscript{5}School of Clinical Medicine, University of Cambridge, Cambridge, UK; \textsuperscript{6}Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland
Thank you
Advanced Breast Cancer

Fifth ESO-ESMO International Consensus Conference

14-16 November 2019 | Lisbon, Portugal

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Co-Chairs: G. Curigliano, IT - S.A. Mertz, US
Scientific Committee Members: K. Gelmon, CA - F. Penault-Llorca, FR - E. Senkus, PL
C. Thomassen, DE

The ABC5 guidelines will be developed by ESO and ESMO
The ABC5 conference and guidelines are endorsed by

The ABC5 conference is held under the auspices of with official representatives of and is endorsed by

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