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
- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

Somatic mutations
- Occur in nongermline tissues
- Are nonheritable

Parent
Mutation in egg or sperm
- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

Child
All cells affected in offspring

Somatic mutation (eg, 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.
**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

**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

**Risk for cancer**
- AVERAGE
- MODERATE
- HIGH
BRCA1/2 Mutations
BRCA1 and BRCA2

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

BRCA1 - cloned 1994
- Discovered in 1990
- Isolated in 1994
- 40% to 50% of HBC
- Breast and breast-ovary HBC
- No male breast cancer members

BRCA2 - cloned 1995
- Discovered in 1994
- Isolated in 1995
- 33% to 50% of HBC
- HBC with male breast cancer members
- Less ovarian cancer than with BRCA1

Mutations in different genes can cause the same disease.
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>

Tung et al JCO 2016
Prevalence of BRCA1/2 mutation amongst Breast Cancer patients

<table>
<thead>
<tr>
<th>Genes</th>
<th>Patients ≤ 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></td>
<td>No.</td>
<td>% (95% CI)</td>
<td>No.</td>
</tr>
<tr>
<td>Any deleterious mutation*</td>
<td>30</td>
<td>16.7 (11.5 to 22.9)</td>
<td>15</td>
</tr>
<tr>
<td>Genes related to breast cancer*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1 or BRCA2</td>
<td>29</td>
<td>16.1 (11.1 to 22.3)</td>
<td>14</td>
</tr>
<tr>
<td>BRCA1*</td>
<td>22</td>
<td>12.2 (7.8 to 17.9)</td>
<td>6</td>
</tr>
<tr>
<td>BRCA2*</td>
<td>15</td>
<td>8.3 (4.7 to 13.4)</td>
<td>2</td>
</tr>
<tr>
<td>Other genes related to breast cancer*</td>
<td>7</td>
<td>3.9 (1.6 to 7.9)</td>
<td>4</td>
</tr>
<tr>
<td>ATM*</td>
<td>8</td>
<td>4.4 (1.9 to 8.6)</td>
<td>8</td>
</tr>
<tr>
<td>BRIP1</td>
<td>3</td>
<td>1.7 (0.4 to 4.8)</td>
<td>1</td>
</tr>
<tr>
<td>CHEK2*</td>
<td>4</td>
<td>2.2 (0.6 to 5.6)</td>
<td>2</td>
</tr>
<tr>
<td>NBN</td>
<td>0</td>
<td>0.0 (0.0 to 2.0)</td>
<td>1</td>
</tr>
<tr>
<td>PALB2</td>
<td>0</td>
<td>0.0 (0.0 to 2.0)</td>
<td>1</td>
</tr>
<tr>
<td>PTEN</td>
<td>0</td>
<td>0.0 (0.0 to 2.0)</td>
<td>1</td>
</tr>
<tr>
<td>Genes not clearly related to breast cancer*</td>
<td>2</td>
<td>1.1 (0.1 to 4.0)</td>
<td>1</td>
</tr>
<tr>
<td>MSH6</td>
<td>0</td>
<td>0.0 (0.0 to 2.0)</td>
<td>1</td>
</tr>
<tr>
<td>PMS2*</td>
<td>1</td>
<td>0.6 (0.01 to 3.1)</td>
<td>0</td>
</tr>
<tr>
<td>RAD51C</td>
<td>0</td>
<td>0.0 (0.0 to 2.0)</td>
<td>0</td>
</tr>
<tr>
<td>RAD51D</td>
<td>1</td>
<td>0.6 (0.01 to 3.1)</td>
<td>0</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; or
        - 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.

Independent of degree of relatedness.

Invasive 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 to clinical evidence of Lynch syndrome (see NCCN Guidelines for Genitourinary, 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/CO-V).

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

For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.
BRCA1/2 TESTING CRITERIAa,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 testingb.
- Personal history of breast cancerc + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed 46-50 y with:
    - An additional breast cancer primary at any age
d
  - ≥3 close blood relative with breast cancer at any age
e
  - ≥3 close blood relative with high-grade (Gleason score ≥7) prostate cancer
  - An unknown or limited family historya

- Diagnosed ≤60 y with:
  - Triple-negative breast cancer
  - Diagnosed at any age with:
    - ≥2 close blood relative with breast cancer diagnosed ≤50 y; or
    - Ovarian carcinoma, or male breast cancer; or
    - Metastatic prostate cancer; or

- ≥2 additional diagnoses of breast cancer at any age in patient and/or in close blood relatives
- Ashkenazi Jewish ancestryb
- Personal history of ovarian carcinomaf

bFor further details regarding the nuances of genetic counseling and testing, see BRCA-OVA.

cIrrespective of degree of relatedness.

dFor the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

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

fClose blood relatives include first-, second-, and third-degree relatives on same side of family (See BRCA-OVA).

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

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.

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 relative meeting any of the above criteria. The significant limitations of interpreting test results for an unaffected individual should be discussed.

BRCA testing criteria not met, consider testing for other hereditary syndromes

If BRCA testing criteria not met, then cancer screening as per NCCN Screening Guidelines.
NICE Guidelines (UK) June 2013

• 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 for inherited cancer predisposition

Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease*

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>Uptake</td>
<td>70% (1058/1520)</td>
<td>100% (110/110)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BRCA1/BRCA2 positive</td>
<td>20% (209/1058)</td>
<td>33% (36/110)</td>
<td>.003</td>
</tr>
<tr>
<td>RRM in BRCA positive</td>
<td>4.7% (10/209)</td>
<td>42% (15/36)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Contralateral disease by pathology @ RRM</td>
<td>20% (2/10)</td>
<td>27% (4/15)</td>
<td>NS</td>
</tr>
<tr>
<td>Psychological support usage post RRM (voluntary)</td>
<td>50% (5/10)</td>
<td>53% (8/15)</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

• Dutch RCT – 26 women who had rapid testing (Wevers et al Patient Education and Counseling 89 (2012) 89–95).

• 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..
NCCN Guidelines Version 2.2019
BRCA-Related Breast and/or Ovarian Cancer Syndrome

BRCA-RELATED FOLLOW-UP

FAMILY STATUS

GENETIC TESTING

TEST OUTCOME

SCREENING RECOMMENDATION

For further details regarding the nuances of genetic counseling and testing, see BRCA1/2.

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 other hereditary breast/ovarian cancer syndromes such as Li-Fraumeni (LIFR-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 indicated, 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)?
BRCA1/2-associated cancers: lifetime risk

Significant variability in penetrance

Breast cancer: 50%-70%
Second primary breast cancer: 40%-50%
Ovarian cancer: 15-45%  \textit{BRCA1} > \textit{BRCA2}

Increased risk of other cancers:
- Male breast cancer: \textit{BRCA2} > \textit{BRCA1}
- Pancreatic cancer: \textit{BRCA2}
- Prostate cancer: \textit{BRCA2}
- Melanoma: \textit{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>BRCA1 mutation carriers</th>
<th>BRCA2 mutation carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Women Contributing In Age Category</td>
<td>No. of Person-Years</td>
</tr>
<tr>
<td>21-30</td>
<td>53</td>
<td>2222.5</td>
</tr>
<tr>
<td>31-40</td>
<td>1048</td>
<td>3831.6</td>
</tr>
<tr>
<td>41-50</td>
<td>870</td>
<td>3317.8</td>
</tr>
<tr>
<td>51-60</td>
<td>479</td>
<td>1905.9</td>
</tr>
<tr>
<td>61-70</td>
<td>201</td>
<td>761.3</td>
</tr>
<tr>
<td>71-80</td>
<td>55</td>
<td>243.0</td>
</tr>
<tr>
<td>Total</td>
<td>2276</td>
<td>12356.1</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>44.0</td>
</tr>
<tr>
<td></td>
<td>625</td>
<td>2136.1</td>
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<td></td>
<td>669</td>
<td>2365.0</td>
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<tr>
<td></td>
<td>384</td>
<td>1437.2</td>
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<tr>
<td></td>
<td>174</td>
<td>610.2</td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>274.6</td>
</tr>
<tr>
<td>Total</td>
<td>1610</td>
<td>7913.1</td>
</tr>
</tbody>
</table>
Cumulative Risks of Breast and Ovarian Cancer in $BRCA1\backslash2$ Carriers
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%(^{10})</td>
</tr>
<tr>
<td>BRCA2</td>
<td>45-47%(^{13})</td>
</tr>
<tr>
<td>TP53</td>
<td>49-60%(^{36})</td>
</tr>
<tr>
<td>PTEN</td>
<td>25-50%(^{61,62})</td>
</tr>
<tr>
<td>PALB2</td>
<td>33-58%(^{56})</td>
</tr>
<tr>
<td>STK11</td>
<td>30-50%(^{58,63,64})</td>
</tr>
<tr>
<td>CDH1</td>
<td>39-52%(^{65,66})</td>
</tr>
<tr>
<td>ATM</td>
<td>15-52%(^{67-70})</td>
</tr>
<tr>
<td>CHEK2</td>
<td>20-44%(^{71-74})</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>Age</td>
<td>5 year risk</td>
<td>Cumulative</td>
<td>5 year</td>
<td>Cumulative</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>
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<td>35-39</td>
<td>0.30%</td>
<td>0.5%</td>
<td>0.84%</td>
<td>1.4%</td>
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<td>40-44</td>
<td>0.61%</td>
<td>1.1%</td>
<td>1.70%</td>
<td>3.0%</td>
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<tr>
<td>45-49</td>
<td>0.94%</td>
<td>2.0%</td>
<td>2.64%</td>
<td>5.6%</td>
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<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>
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<tr>
<td>60-64</td>
<td>1.72%</td>
<td>6.0%</td>
<td>4.81%</td>
<td>16.0%</td>
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<tr>
<td>65-69</td>
<td>2.11%</td>
<td>8.0%</td>
<td>5.92%</td>
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<td>70-75</td>
<td>2.20%</td>
<td>10.0%</td>
<td>6.17%</td>
<td>25.5%</td>
</tr>
<tr>
<td>CLTR (80)</td>
<td>2.24%</td>
<td>12.0%</td>
<td>30.0%</td>
<td>31.8%</td>
</tr>
</tbody>
</table>

*Data from 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

<table>
<thead>
<tr>
<th>Reproductive considerations in <em>BRCA</em> mutation carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>BRCA1/2</em> carriers can be reassured that there is no convincing evidence that mutation carriers have reduced ovarian reserve or fertility</td>
</tr>
<tr>
<td>All women harbouring a <em>BRCA1/2</em> mutation should be encouraged to complete child-bearing prior to planned RRSO</td>
</tr>
<tr>
<td>For women who wish to undergo RRSO and have not yet completed child-bearing fertility preservation options should be discussed</td>
</tr>
<tr>
<td><em>BRCA1/2</em> 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</td>
</tr>
<tr>
<td>Women harbouring a <em>BRCA1/2</em> mutation who have been diagnosed with a malignancy should be counselled about options for fertility preservation prior to the commencement of oncology treatment</td>
</tr>
<tr>
<td>Appropriate counselling should be available and vaginal moisturisers and lubricants should be prescribed to all women following RRS</td>
</tr>
<tr>
<td>Short term use of HRT to alleviate menopausal symptoms following RRSO is safe amongst healthy <em>BRCA1/2</em> mutation carriers</td>
</tr>
<tr>
<td>No safety data are available about the use of HRT amongst <em>BRCA1/2</em> 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</td>
</tr>
<tr>
<td>Topical oestrogens to alleviate vaginal dryness may be used with caution</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

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:
- 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 BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening

S. Paluch-Shimon¹, F. Cardoso², C. Sessa³, J. Balmana⁴, M. J. Cardoso², F. Gilbert⁵ & E. Senkus⁶, on behalf of the ESMO Guidelines Committee

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Thank you
"I already diagnosed myself on the Internet.
I’m only here for a second opinion."