Familial Breast or Ovarian Cancer
Syndromes

Disclaimer

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About familial breast or ovarian cancer syndromes

➢ About 5% of all breast cancer is due to an inherited mutation in a gene such as the BRCA1 or BRCA2 gene. Mutations in these genes also cause about 15% of all high grade serous ovarian cancer. Genetic testing is only useful in limited circumstances for patients. Absence of an identified mutation in these patients does not exclude a familial cause.

➢ BRCA mutations:
  • are more likely if there is a personal or family history of early onset breast or ovarian cancer, bilateral breast cancer, male breast cancer, and/or breast and ovarian cancer.
  • occur in about 1 in every 500 to 800 people (equally in both males and females but more common in people with Ashkenazi Jewish heritage).
  • result in an increased lifetime risk of developing breast and ovarian cancer:
    o In women:
      ▪ lifetime (age > 80 years) breast cancer risk is around 72% for BRCA1 and 69% for BRCA2, compared with 12.5% in the general population.
      ▪ ovarian cancer risk is around 44% for BRCA1 and 17% for BRCA2, compared with 1.2% in the general population.
    o In men:
      ▪ breast cancer risk is around 1.2% for BRCA1 and around 6.8% for BRCA2, compared to < 1% in the general population.
      ▪ prostate cancer risk is around 8.6% for BRCA1 and around 15% for BRCA2, compared to 5.9% in the general population.
    o There is a potentially increased risk of pancreatic cancer in all people with a mutation in the BRCA2 gene.

➢ Each child of a BRCA 1 or 2 mutation carrier has a 1 in 2 chance of inheriting the mutation.

Assessment

1. Clarify whether the patient has any current symptoms. If so, manage these symptoms appropriately before fully assessing the family history.

2. Take a family history and sketch a 3-generation family tree. Understand cultural considerations for Aboriginal and Torres Strait Islander patients.

➢ **Family history** - Note in particular:
  • Type of primary cancers present in the family
  • Number of relatives affected
  • Age of onset in the family members
  • Multiple primary cancers
  • Any known mutation carrier
  • Ancestral background (particularly of Jewish decent)
3-generation family tree

- Genetic pedigrees are drawn using standardised symbols:

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Sex Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual</td>
<td>![male symbol]</td>
<td>![female symbol]</td>
<td>![unknown symbol]</td>
</tr>
<tr>
<td>Affected individual (symbol coloured in)</td>
<td>![affected symbol]</td>
<td>![affected symbol]</td>
<td>![affected symbol]</td>
</tr>
<tr>
<td>Multiple individuals</td>
<td>![multiple symbol]</td>
<td>![multiple symbol]</td>
<td>![multiple symbol]</td>
</tr>
<tr>
<td>Deceased</td>
<td>![deceased symbol]</td>
<td>![deceased symbol]</td>
<td>![deceased symbol]</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>![pregnancy symbol]</td>
<td>![pregnancy symbol]</td>
<td>![pregnancy symbol]</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>![miscarriage symbol]</td>
<td>![miscarriage symbol]</td>
<td>![miscarriage symbol]</td>
</tr>
<tr>
<td>Person providing pedigree info</td>
<td>![person symbol]</td>
<td>![person symbol]</td>
<td>![person symbol]</td>
</tr>
</tbody>
</table>

- Marriage/partnership
- Divorce/separation
- Where the partners are blood relatives (consanguineous relationship)
- Children/siblings
- Identical twins (monozygotic)
- Non-identical twins (dizygotic)

Reproduced with permission from Health Education England’s Genomics Education Programme – Taking and Drawing a Family History

- See the following example of a family tree:

Reproduced with permission from Health Education England’s Genomics Education Programme – Taking and Drawing a Family History

- Start with the patient in the centre (note the arrow)
- Include first degree relatives (children, siblings, parents), and second-degree relatives (aunts, uncles, grandparents) on both sides of the family.
- Include age at diagnosis, other conditions as well as presenting condition, miscarriages, stillbirths, infertility and birth defects.
➢ **Cultural Considerations**
- The concept of family is broader than being genetically related for many Aboriginal and Torres Strait Islander patients.
- Be sensitive when talking about cultural taboos such as Sorry Business (people who have died), Men’s Business, and Women’s Business, and references to members of the Stolen Generation.

3. Determine the specific risk category for breast and/or ovarian cancer based on family history alone, using either:
   ➢ an online calculator e.g., FRA-BOC (familial history assessment), or
   ➢ **Risk factors based on family history**
     ➢ **Category 1 – at or slightly above average risk:**
       - More than 95% of the female population.
       - No family history of breast cancer, or family history of breast cancer occurring in:
         ▪ one first-degree relative aged ≥ 50 years.
         ▪ one second-degree relative at any age.
         ▪ two first or second-degree relatives aged ≥ 50 years, on different sides of the family.
         ▪ two second-degree relatives on the same side of the family, both with breast cancer aged ≥ 50 years.
       - As a group, the risk of breast cancer up to age 75 years is between 1 in 8 and 1 in 11. This risk is no more than 1.5 times the population average.

     ➢ **Category 2 – moderately increased risk:**
       - Less than 4% of the female population.
       - Family history of breast cancer occurring in any of:
         ▪ one first-degree relative aged < 50 years.
         ▪ two first-degree relatives on the same side of the family.
         ▪ two second-degree relatives on the same side of the family with at least one diagnosed aged < 50 years.
         ▪ without the additional features of the potentially high-risk group.
       - As a group, the risk of breast cancer up to age 75 years is between 1 in 4 and 1 in 8. This risk is 1.5 to 3 times the population average.

     ➢ **Category 3 – potentially high-risk:**
       - Less than 1% of the female population.
       - Family history of breast or ovarian cancer occurring in two first- or second-degree relatives on the same side of the family, and one or more of the following:
         ▪ Additional relatives with breast cancer or ovarian cancer
         ▪ A relative with both breast and ovarian cancer
         ▪ Breast cancer diagnosed before age 40 years
         ▪ Breast cancer affecting both breasts
         ▪ Ashkenazi Jewish ancestry
         ▪ Breast cancer in a male relative
         ▪ A relative who has tested positive for a high-risk gene mutation e.g., in genes such as BRCA1 or BRCA2. Genetic testing of BRCA1 and BRCA2 will be fully funded for high-risk patients.
       - As a group, the risk of breast cancer up to age 75 years is between 1 in 2 and 1 in 4. This risk may be more than 3 times the population average. Individual risk may be higher or lower if genetic test results are known.
Management

1. If a patient is found to be potentially high-risk or a blood relative of a high-risk breast and/or ovarian cancer predisposition gene mutation carrier (BRCA1, BRCA2, TP53, PLAB2, PTEN, STK11), refer to the Familial Genetic Counselling Service for further assessment and advice.

➢ Potential high-risk factors for breast cancer. Category 3 – potentially high-risk:

- Less than 1% of the female population.
- Family history of breast or ovarian cancer occurring in two first- or second-degree relatives on the same side of the family, and one or more of the following:
  - Additional relatives with breast cancer or ovarian cancer
  - A relative with both breast and ovarian cancer
  - Breast cancer diagnosed before age 40 years
  - Breast cancer affecting both breasts
  - Ashkenazi Jewish ancestry
  - Breast cancer in a male relative
  - A relative who has tested positive for a high-risk gene mutation e.g., in genes such as BRCA1 or BRCA2. Genetic testing of BRCA1 and BRCA2 will be fully funded for high-risk patients.

- As a group, the risk of breast cancer up to age 75 years is between 1 in 2 and 1 in 4. This risk may be more than 3 times the population average. Individual risk may be higher or lower if genetic test results are known.

2. Genetic testing can only be ordered by the treating specialist. Genetic testing is best ordered by a genetic specialist. It is covered by Medicare, but only for women affected by breast or ovarian cancer who meet specific criteria.

➢ Genetic testing, there are 2 types of genetic testing:

- Mutation search:
  - In the first instance this involves testing a blood sample from an affected family member.
  - Determines whether a gene mutation that causes the increased risk of cancer for that family can be identified.
- Predictive test:
  - Only available to family members when a mutation has already been found in a mutation search.
  - Determines whether or not the patient actually has the familial gene mutation.

3. If a patient has had breast or ovarian cancer, request assessment at the Familial Genetic Counselling Service if:

➢ personal history of breast cancer.
  - Breast cancer diagnosed aged < 40 years, especially if histology is triple negative (oestrogen, progesterone, and HER2 receptor negative)
  - Bilateral breast cancer if:
    - first diagnosis aged < 50 years, or
    - family history of breast or ovarian cancer.
  - Ashkenazi Jewish ancestry e.g., from Central and Eastern Europe
  - Male breast cancer
  - Epithelial or high grade serous ovarian, fallopian tube, or primary peritoneal cancer
  - Both ovarian and breast cancer in the same woman

- Significant family history
  - First-degree female relative diagnosed with breast cancer age < 50 years
  - 2 first-degree female relatives on the same side of the family diagnosed with breast cancer
  - 2 second-degree female relatives diagnosed with breast cancer, at least age < 50 years
  - A female relative with ovarian cancer, and a family history of breast or ovarian cancer
  - A female relative with bilateral breast cancer, and a family history of breast or ovarian cancer
  - A relative with ovarian cancer age < 70 years
  - A male relative with breast cancer
  - Ashkenazi Jewish ancestry e.g., from Central and Eastern Europe
  - Blood relative of known cancer predisposition gene mutation carrier
    - BRCA1 or BRCA2 mutation
    - Li-Fraumeni syndrome – TP53 mutation
    - Peutz-Jeghers syndrome – STK11 mutation
    - Cowden syndrome – PTEN mutation
    - Ataxia telangiectasia syndrome – homozygous ataxia telangiectasia mutations (ATM), heterozygous mutation carriers have increased risk of breast cancer
    - PALB2 mutation
    - Hereditary diffuse gastric cancer and lobular breast cancer – CDH1 mutation

4. If at moderate risk, or not meeting the criteria for referral to the Familial Genetic Counselling Service:

- Moderate risk factors - Category 2 – moderately increased risk:
  - Less than 4% of the female population.
  - Family history of breast cancer occurring in any of:
    - one first-degree relative aged < 50 years.
    - two first-degree relatives on the same side of the family.
    - two second-degree relatives on the same side of the family with at least one diagnosed aged < 50 years.
    - without the additional features of the potentially high-risk group.
  - As a group, the risk of breast cancer up to age 75 years is between 1 in 4 and 1 in 8. This risk is 1.5 to 3 times the population average.

- see eviQ – Risk Management for Women at Moderately Increased Risk of Breast Cancer, and discuss breast cancer screening and general preventative strategies e.g., healthy diet, healthy lifestyle, medications to reduce the risk of breast cancer.

5. If at average risk, discuss breast cancer screening and general preventative strategies.

- Average risk factors - Category 1 – at or slightly above average risk:
  - More than 95% of the female population.
  - No family history of breast cancer, or family history of breast cancer occurring in:
    - one first-degree relative aged ≥ 50 years.
    - one second-degree relative at any age.
    - two first or second-degree relatives aged ≥ 50 years, on different sides of the family.
    - two second-degree relatives on the same side of the family, both with breast cancer aged ≥ 50 years.
  - As a group, the risk of breast cancer up to age 75 years is between 1 in 8 and 1 in 11. This risk is no more than 1.5 times the population average.
Referral

Refer to the Familial Genetic Counselling Service if the patient meets eviQ criteria for:

- Breast Cancer Risk Assessment and Consideration of Genetic Testing
- Ovarian Cancer Risk Assessment and Consideration of Genetic Testing

Information

For health professionals

- Cancer Australia:
  - Advice About Familial Aspects of Breast Cancer and Epithelial Ovarian Cancer
  - Risk-reducing Medication for Women at Increased Risk of Breast Cancer due to Family History
- Cancer Institute NSW – EviQ – Referral Guidelines for Breast Cancer Risk Assessment and Consideration of Genetic Testing
- NSW Government Health Centre for Genetics Education – Breast and Ovarian Cancer and Inherited Predisposition

For patients

- Breast Cancer Network Australia
- Breast Cancer Trials – iPrevent Breast Cancer Risk Assessment Tool
- Cancer Council – Checking for Cancer: What to Expect
- Cancer Council Victoria – Aboriginal Communities: Information
- eviQ - Consumer Information Sheets
- Genetic Alliance Australia
- National Indigenous Cancer Network – About Cancer
- NSW Government Health Centre for Genetics Education:
  - Breast and Ovarian Cancer and Inherited Predisposition
  - Individuals and Families: Cancer Resources
  - What if I have a Family History of Cancer?

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