Management of Breast Cancer Risk in BRCA Mutation Carriers

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Objectives

At the end of this presentation, participants will be able to:

1) Outline the risk of developing malignancy BRCA carriers

2) Provide an overview of modalities used to reduce breast cancer risk such as:
   ◦ Surveillance
   ◦ Risk reducing salpingo-oophorectomy
   ◦ Chemoprevention
   ◦ Lifestyle modification
   ◦ Prophylactic mastectomy +/- breast reconstruction
Disclosure of Potential for Conflict of Interest

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Case

35 year old patient in your practice with a strong family history of breast cancer.

- Mother died age 52 with a triple negative breast cancer (negative for ER, PR and HER2)
- One maternal aunt with post menopausal breast cancer
- One maternal aunt with ovarian cancer age 43

- PMHx: Negative

- GyneHx: Premenopausal, G2P2 and has completed childbearing

- Patient’s mother was found to be a BRCA 1 mutation carrier and subsequently the patient underwent testing. She is also a carrier.

She comes to your office asking you about this result and looking for more information.
What proportion of women with breast cancer have a genetic mutation?

- Most are sporadic
- 10% of women with breast cancer in an unselected population will have a hereditary form of the disease
- 20% of women with a family history will have a mutation
- BRCA mutations are the most common
Breast cancer risk

Ascertainment basis

Varies based on population studied and modified by environmental and genetic effects

<table>
<thead>
<tr>
<th></th>
<th>Breast cancer*</th>
<th>Ovarian Cancer*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA 1</td>
<td>57%</td>
<td>40%</td>
</tr>
<tr>
<td>BRCA 2</td>
<td>49%</td>
<td>18%</td>
</tr>
</tbody>
</table>

In higher risk cohorts, up to 80% of BRCA carriers could develop breast cancer

Lifetime risk in general population: 12%

* By age 70 years old
Breast cancer risk and age

- Risk varies with age
- Heterogeneous studies
- Goal was to calculate average risk among carriers with a representative mix of mutations in a population
- Studies available of specific subpopulations (i.e. Ashkenazi Jewish, French Canadian)

Clinical characteristics

<table>
<thead>
<tr>
<th>BRCA 1</th>
<th>BRCA 2</th>
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<tbody>
<tr>
<td>Breast cancer risk</td>
<td>55-70%</td>
</tr>
<tr>
<td>Ovarian cancer risk</td>
<td>40%</td>
</tr>
<tr>
<td>Age at onset (BC)</td>
<td>Younger</td>
</tr>
<tr>
<td>Male BC risk</td>
<td>1-2%</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Other cancers</th>
<th>BRCA 1</th>
<th>BRCA 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>1% (RR 2.26)</td>
<td>5% (RR 3.51)</td>
</tr>
<tr>
<td>Prostate</td>
<td>9%*</td>
<td>33%*</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Undefined risk</td>
<td>Positive association</td>
</tr>
</tbody>
</table>

- Other cancers: endometrial, gastric and biliary tree
- Risks low and difficult to quantify

*by age 65 years

Case

Patient is very concerned about risk of cancer. She has read on the internet that she needs to have mastectomies and removal of her ovaries.

She wonders if there are other options to reduce her risk?

Referral to Medical Oncologist is made. Patient has appointment at the Dr. H. Bliss Murphy Cancer Centre.
Risk reducing strategies

1. Surveillance
2. Bilateral salpingo-oophorectomy
3. Chemoprevention
4. Lifestyle modification
5. Prophylactic mastectomy
Surveillance

Malignancy must be detected at an early point

Mammogram alone not an ideal diagnostic test in BRCA carriers
- breast density increased in younger women
- characteristics of some BRCA related tumours result in underdiagnosis (i.e. round, pushing margins or less DCIS)

MRI is a useful tool to increase efficacy surveillance
- no exposure to radiation
- sensitivity 87.4% and specificity 94.2% for mammo and MRI in BRCA carriers
- MRI detects disease at an earlier point (smaller size, less lymph nodes)
- performed annually in most studies
Surveillance

Potential harms of MRI
- Increased risk of false positives with more recalls and biopsies of benign lesions
- In premenopausal women, should be performed during second week of menstrual cycle
- Not 100% sensitivity – women may consider:
  - oophorectomy
  - chemoprevention
  - must accept some risk

Misconception in NL that Family Physicians can not order MRIs – yes they can!
Can repeated imaging increase risk of cancer?

- Exposure to ionizing radiation is a risk factor for breast cancer

- Large European cohort study (GENE-RAD-RISK)
  - n=1993 BRCA carriers
  - any exposure to diagnostic radiation < 30 years increased risk of BC
    - HR 1.9, 95% CI 1.2 to 3.0 (with a dose-response pattern)
    - no association with risk of BC for exposure age 30-39 years
    - mammography < 30 years increased BC risk HR 1.43, 0.85 to 2.40

- Bottom Line: Yes it can. Use non-ionizing radiation imaging in young BRCA carriers.
Surveillance guidelines

NCCN guidelines 2017
- Breast awareness with monthly exam starting age 18 years
- Semiannual clinical breast exam (CBE) starting age 25 years
- Annual MRI age 25-70 years
- Annual mammogram age 30-70 years (may consider mammogram to age 75 years or older)

Other considerations:
- MRI with dedicated breast coil and breast radiologist
- Pregnant and lactating women can undergo CBE alone
- SBE not recommended in all guidelines
- Ultrasound not recommended for screening
CancerCareOntario Guideline – MRI

High risk women
- BRCA carriers
- Untested first degree relative
- FHx consistent with hereditary syndrome with BC risk > 25%

Screen age 30-69 years

Alternating mammogram and MRI annually
Case

Patient decides to undergo surveillance until she can learn more about her options.

You order her first mammogram and MRI. You also perform a clinical breast examination.

Patient has heard that having her ovaries removed may decrease her risk of breast cancer. She asks you more about this. She has already been referred to see a Gyne Oncologist/Gynecologist.
Risk reducing bilateral salpingo-oophorectomy

- RRSO recommended between age 35-40 years on completion of childbearing
- May delay RRSO in BRCA2 carriers until 40-45 years if maximal BC prevention (i.e. mastectomies)
  - ovarian cancer occurs 8-10 years later in BRCA2 than BRCA1
- RRSO has been reported to reduce risk of BC in premenopausal carriers by 50%
- May be an overestimate
Risk reducing bilateral salpingo-oophorectomy

Multiple retrospective and prospective studies have shown reduction in BC risk with RRSO

Uptake of RRSO is high among BRCA carriers (up to 75%)

A 2015 Dutch study examined this by attempting to reduce bias
  ◦ Women with prior BC or OC excluded
  ◦ Allocated person-time before surgery to the group that did not have RRSO
  ◦ HR 1.09; 95% CI, 0.67 to 1.77 (median follow up of 3.2 years)
  ◦ Results show no difference in risk BC with RRSO

Re-analysis of another study accounting for immortal person-time bias still found a protective effect of RRSO (HR 0.59)
Studies have shown a reduction in mortality with RRSO

- PROSE prospective cohort of 2482 BRCA carriers
- Median follow up ≈ 4 years
- Surgical group had lower all cause mortality HR 0.40 95%CI, 0.26-0.61
- Lower BC specific mortality HR 0.44 95% CI, 0.26-0.76 and OC specific mortality HR 0.25 95% CI, 0.08-0.75
- Greater effect on mortality in BRCA1 vs BRCA2

Bottom Line: Multiple studies have shown benefit in reducing risk of BC in BRCA carriers by undergoing RRSO although bias may exist. NB - this is in relation to breast cancer not ovarian cancer risk
Chemoprevention

Selective use of SERMS or AIs in women with high risk of developing BC has shown reduction in risk

Very little randomized data in BRCA carriers

- SERM – Tamoxifen and Raloxifene
- AI – Anastrozole, Letrozole and Exemestane

How do these medications work?

What are the side effects?
Chemoprevention

BRCA carriers – subgroup analysis

288 BC total study population, 19 had BRCA mutation (6.6%)
  ◦ BRCA1 = 8
  ◦ BRCA2 = 11

Conclusion:
  ◦ Tam reduced risk of BC by 61% in BRCA2 carriers
  ◦ Similar rates to entire study population for ER+ tumours

Bottom Line: Tam prophylaxis an option for BRCA2 (not BRCA1) carriers

Table 3. Study Participants Who Developed Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Tamoxifen</th>
<th>Risk Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 mutation</td>
<td>3</td>
<td>5</td>
<td>1.67 (0.32-10.70)</td>
</tr>
<tr>
<td>BRCA2 mutation</td>
<td>8</td>
<td>3</td>
<td>0.38 (0.06-1.56)</td>
</tr>
<tr>
<td>Wild type</td>
<td>162</td>
<td>87</td>
<td>0.46 (0.37-0.61)</td>
</tr>
<tr>
<td>All participants</td>
<td>211</td>
<td>109</td>
<td>0.52 (0.41-0.65)</td>
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</table>

*Includes 288 genotyped cases and 32 cases without DNA available.

Table 4. Estrogen-Receptor (ER) Status of Tumours

<table>
<thead>
<tr>
<th></th>
<th>ER-Positive</th>
<th>ER-Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 mutation</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>BRCA2 mutation</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Wild type</td>
<td>132</td>
<td>41</td>
</tr>
</tbody>
</table>

*ER status unknown for 1 BRCA1 tumor, 2 BRCA2 tumors, and 20 wild-type tumors.
Can lifestyle modifications reduce risk of BC?

Small case-control studies with retrospective collection of lifestyle data
- Null effect of alcohol
- Equivocal effect of increased risk with excess weight and smoking
- Decreased risk with physical activity in adolescence or early adulthood
- Further confirmation required

Recent prospective study of adherence to cancer prevention (physical activity, weight, alcohol) guidelines reduced risk of breast cancer mortality by 61% (HR 0.39 95% CI 0.16-0.97)
Do oral contraceptive pills increase BC risk?

- Conflicting results from meta-analysis but differences may be due to selection/recall bias and older formulations of OCP
- New formulations contain less estrogen
- No association with BC in BRCA2 patients taking OCP
- Very small subset in one study showed increase risk among very young BRCA1 carriers
- Bottom Line: If positive association exists between OCP and BC, effect likely small and benefits of ovarian cancer risk reduction should be considered. Therefore, OCP is recommended.

Case

The patient undergoes BSO. She starts HRT. She does not take Tamoxifen due to the lack of benefit observed in BRCA1 carriers.

She wonders about the role of surgery. She is referred to a General Surgeon/Surgical Oncologist and a Plastic Surgeon to discuss options.
Bilateral prophylactic mastectomy

Multiple retrospective and prospective studies have shown a decrease in risk of BC with RRM by 90%

No change in OS with RRM alone

Important points:
- Should be mentioned as a risk reducing option
- Ensure women’s perception of risk is accurate
- Review potential adverse effects of surgery
- Manage patient as part of a multidisciplinary team
- Consultation regarding reconstruction

Appropriate timing - models
Psychosocial effects of RRM

Retrospective study with long follow up (14 years) found:
- 70% satisfied with decision
- 74% reduction in concern regarding BC
- 80% had favourable or unchanged stress levels

Prospective studies have shown:
- Reduction in perceived risk of BC
- Decreased anxiety
- Some studies have shown change in body image and sexuality post surgery, others not

One study did show that women who chose surgery had a perceived great risk of breast cancer

HATCHER ET AL. (2001) BMJ 322:76
Bilateral prophylactic mastectomy

Only a minority of women with BRCA mutations elect to undergo RRM

Rates vary significantly among studies (range 5-60%)

Canadian literature:
- 246 BRCA carriers enrolled in a MRI-based screening program
- 16% elected to have RRM after enrollment
- Most common reasons cited for RRM:
  - fear of cancer
  - having had previous cancer
  - concern of children
Bilateral prophylactic mastectomy

Risk reduction options for women detected in a clinical genetic program:
- RRM 36%
- RRSO 61%
- Chemoprevention 16%

Large cohort of unselected Jewish women (n=2080) tested for BRCA and 1.1% positive:
- RRM 11%
- RRSO 90%
Surgical options

No mastectomy can remove all breast tissue

Options:
- Simple/standard mastectomy
- Skin-sparing mastectomy
- Nipple-sparing
Surgical Options

Total skin sparing or nipple sparing mastectomy
- preserves overlying skin of the NAC but underlying glandular tissue removed
- one study of BRCA carriers demonstrated no development of new breast cancer with 4 year follow up
- another study of NSM in BRCA carriers showed that breast tissue* was present in 24% of cases on histological exam of NAC
  - BRCA with prophylactic mastectomy – no malignancy noted
  - BRCA with therapeutic mastectomy – 10% had malignant or premalignant lesion
- largest study of nearly 400 NSM in 200 BRCA carriers demonstrates low complication rate or risk of local recurrence

Bottom line:
- probably safe low recurrence rate but understudied and long term outcomes unknown
- careful patient selection if embarking on this procedure

* TDLU – terminal duct lobular unit

Breast reconstruction

Autologous reconstruction
- TRAM Flap
- DIEP Flap
- Latissimus dorsi Flap +/- implant

Alloplastic reconstruction (most common)
- Two stage procedure
  - Tissue expander followed by implant
- Direct to implant reconstruction
  - Using acellular dermal matrix
TRAM Flap

- Breast
- Nipple
- Areola
- Incisions
- Umbilicus
- Abdominal tissue flap
Practical considerations

Timing of surgery

- RRM
  - Depends on pedigree
  - 5-10 years prior to incident case
  - Consider childbearing/lactation
- BSO
  - Once childbearing complete
- Sequential versus concurrent procedures
  - Laparoscopic outpatient procedure
  - Can be done after to autologous reconstruction if using abdominal tissue
  - BSO can be done safely at time of RRM and reconstruction
- Screening
  - No role for mammogram or MRI post mastectomy/reconstruction
Case

Patient is considering bilateral mastectomies with immediate reconstruction. She continues to undergo surveillance.

She has an abnormal mammogram. She undergoes biopsy and is referred to a Surgical Oncologist.

- Bilateral mastectomies reveal a node positive triple negative breast cancer
- Staging for metastatic disease is negative
- Adjuvant (curative intent) chemotherapy x 8 cycles
- Radiation

She wonders if her prognosis is worse because she has a genetic mutation.
Breast cancer in BRCA carriers

Pathological characteristics differ compared with non-carriers

Typical features vary among BRCA1 vs BRCA2 as well

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<tr>
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<th>BRCA 1</th>
<th>BRCA 2</th>
</tr>
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<tbody>
<tr>
<td><strong>Histology</strong>*</td>
<td>Medullary</td>
<td>Lobular</td>
</tr>
<tr>
<td><strong>Estrogen Receptor</strong></td>
<td>Negative (78%)</td>
<td>Positive (23% are negative)</td>
</tr>
<tr>
<td><strong>Age/ER tumours</strong></td>
<td>Age ↑ ER positive ↑</td>
<td>Age ↑ ER positive ↓</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td>Higher</td>
<td>Lower</td>
</tr>
</tbody>
</table>

*majority are ductal
Breast cancer in BRCA carriers

Propensity for TNBC (ER- PR- HER2 -) in BRCA1

TNBC
- 15% of all BC
- More frequent in young women and African Americans
- Worse outcome than other tumour types
- 60-80% of BC from BRCA1 mutation carriers are triple negative
- Only form of therapy in clinical practice is chemotherapy

In patients unselected for family history, around 10% (8-14%) have BRCA mutations (BRCA1= 9% and BRCA2=3%)

BRCA2 = 77% ER positive and 16% TNBC

Do BRCA carriers with BC have worse outcomes?

- Multiple studies have shown that outcomes among BRCA carriers with BC are similar to with sporadic disease.

- One international population based study demonstrated:
  - Similar outcomes for BRCA1 and sporadic disease.
  - Increased distant recurrence for BRCA2 in univariate analysis.
  - Likely reflects adverse tumour characteristics in carriers.
  - This was not seen in multivariate analysis.

### Approach to BC risk management in BRCA

<table>
<thead>
<tr>
<th>Focus and Approach</th>
<th>BRCA1 Carriers</th>
<th>BRCA2 Carriers</th>
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<tbody>
<tr>
<td><strong>Breast cancer in women</strong></td>
<td>NCCN guidelines recommend breast “awareness” starting at age 18 yr; clinical breast examination, every 6–12 mo, starting at age 25 yr; ages 25–29 yr: annual MRI (preferred) or mammography if MRI unavailable; ages 30–75 yr: annual mammography and MRI; &gt;75 yr: individualized care</td>
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</tr>
<tr>
<td><strong>Risk-reducing medication†</strong></td>
<td>Inadequate data to support its use</td>
<td>Option, given anticipated 50% risk reduction in ER-positive breast cancers^63</td>
</tr>
<tr>
<td><strong>Risk-reducing mastectomy</strong></td>
<td>Given the often aggressive high-grade, ER-negative nature of breast cancers and uncertain benefit of chemoprevention, surgical prevention may be given higher priority than surveillance</td>
<td>Option for women who prefer surgical risk reduction rather than surveillance and chemoprevention</td>
</tr>
</tbody>
</table>

HARTMANN ET AL (2016) NEJM 374(5): 454-468
Conclusions:

Breast cancer risk in carriers is dependent on many factors

Types of breast cancer (and treatment) varies between BRCA 1 and 2

Multidisciplinary approach is essential

Options for BRCA carriers include:

- Surveillance
- Risk reducing salpingo-oophorectomy
- Chemoprevention
- Bilateral prophylactic mastectomy +/- reconstruction

Approach should be personalized to each patient
Questions?

Thank you for your attention

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