Beyond Angelina Jolie: Diagnosis and Management of Hereditary Breast and Ovarian Cancer
Disclosures

No conflicts of interest
<table>
<thead>
<tr>
<th>Identify</th>
<th>Identify the features of family history and ethnic background that influence hereditary risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describe</td>
<td>Describe the referral recommendations for genetic assessment of hereditary breast and ovarian cancer syndrome including the associated other cancer risks.</td>
</tr>
<tr>
<td>Summarize</td>
<td>Summarize the cancer risks associated with BRCA1 and 2 mutations from women and men as well as that of less common mutations associated with breast cancer risk</td>
</tr>
<tr>
<td>Recommend</td>
<td>Ovarian and breast cancer risk management options</td>
</tr>
<tr>
<td>Cite</td>
<td>Cite the management of other cancer risks associated with BRCA mutations</td>
</tr>
</tbody>
</table>
What is the BRCA gene?

*BRCA1* and *BRCA2* are tumour suppressor genes
They encode proteins involved in the repair of DNA double-strand (dsDNA) breaks via the homologous recombination (HR) pathway.

Functional *BRCA* proteins regulate cell growth and prevent abnormal cell division that might otherwise lead to tumour development.
Role of Inherited Causes in Cancer

**Hereditary**
- Gene mutation is inherited in family
- Significantly increased cancer risk

**Familial**
- Multiple genes & environmental factors may be involved
- Some increase in cancer risk

**Sporadic**
- Cancer occurs by chance or related to environmental factors
- General population cancer risk
Cancer Genetics is Evolving

- Family History is always a key component of oncologic care
- Technology testing changing
- Approaches to testing are changing
- Value of genetic information for patients is expanding i.e. parp inhibitor
- Different pathways to patient access
- Prevention in family members is highly effective
- Many new genes to consider
Family History Factors to Consider

- Limited paternal history
- Few women in the family
- Adopted
- Ashkenazi Jewish Ancestry 1/40

Actual population rates are higher than previously thought: 1.64% in large studies*

*Couch NEJM CARRIERS Study 2021
The proportion of cancers that are hereditary varies by **type** and **age** at diagnosis.

Which family is at higher risk for HBOC?

A: One Ovarian Cancer at 55y
B: Three Breast Cancers

Br = breast cancer  
HGSC = high-grade serous carcinoma
<table>
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<th>GENE</th>
<th>Breast</th>
<th>Ovarian</th>
<th>CRC</th>
<th>Endometrial</th>
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</tr>
</tbody>
</table>

Multi-gene Panels are the norm.
Specific combinations may differ.
BRCA and Lynch always included.
What do I look for?

Red flags for HBOC

- Earlier age at diagnosis of breast cancer (e.g. <50y)
- “Triple negative” type breast cancer (ER/PR/HER2-)
- High-grade serous ovarian/fallopian tube cancer
- >1 HBOC-related cancer in the same person
- Multiple individuals affected on same side of the family (paternal or maternal)
- Male breast cancer
- Pancreatic, melanoma
- Prostate cancers, eso aggressive, metastatic
Poll

This unaffected patient has private pay genetic testing from Color Genomics. Her report is a negative 30 gene panel

Which of the following is true (more than one):

A. Her mother should cancel her HCP appointment as this is a BRCA negative family

B. The aunt with ovarian cancer should have genetic counselling and testing

C. The negative test in this patient does not explain the family

D. This result is an uninformative negative

E. The mom should still have testing
The rates of pathogenic mutations are higher than we thought

- Family history criteria alone will miss ~50% of carriers
- The future likely will include increasingly broad testing rules
  - public demand increases
  - costs diminish
  - prevention is proven cost effective for health systems

### Table 2. Associations between Pathogenic Variants in Established Breast Cancer-Predisposition Genes and Risk of Breast Cancer

<table>
<thead>
<tr>
<th>Breast Cancer-Predisposition Gene</th>
<th>Case Patients (N=32,247)</th>
<th>Controls (N=32,564)</th>
<th>Odds Ratio (95% CI)†</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>ATM (0.78)</td>
<td>253 (0.78)</td>
<td>134 (0.41)</td>
<td>1.82 (1.46–2.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BARD1 (0.15)</td>
<td>49 (0.15)</td>
<td>35 (0.11)</td>
<td>1.37 (0.87–2.16)</td>
<td>0.18</td>
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<tr>
<td>BRCA1 (0.85)</td>
<td>275 (0.85)</td>
<td>37 (0.11)</td>
<td>7.62 (5.31–11.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BRCA2 (1.29)</td>
<td>417 (1.29)</td>
<td>78 (0.24)</td>
<td>5.23 (4.09–6.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CDH1 (0.05)</td>
<td>17 (0.05)</td>
<td>6 (0.02)</td>
<td>2.50 (1.01–7.07)</td>
<td>0.06</td>
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<tr>
<td>CHEK2 (1.08)</td>
<td>349 (1.08)</td>
<td>138 (0.42)</td>
<td>2.47 (2.01–3.05)</td>
<td>&lt;0.001</td>
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<tr>
<td>NF1 (0.08)</td>
<td>19 (0.08)</td>
<td>11 (0.03)</td>
<td>1.93 (0.91–4.31)</td>
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</tr>
<tr>
<td>PALB2 (0.46)</td>
<td>148 (0.46)</td>
<td>38 (0.12)</td>
<td>3.83 (2.68–5.53)</td>
<td>&lt;0.001</td>
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<tr>
<td>RAD51C (0.13)</td>
<td>41 (0.13)</td>
<td>35 (0.11)</td>
<td>1.20 (0.75–1.93)</td>
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<tr>
<td>RAD51D (0.08)</td>
<td>26 (0.08)</td>
<td>14 (0.04)</td>
<td>1.72 (0.81–3.51)</td>
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<tr>
<td>TP53 (0.08)</td>
<td>19 (0.08)</td>
<td>2 (0.01)</td>
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<td>NA</td>
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<tr>
<td>Total</td>
<td>1621 (5.03)</td>
<td>531 (1.63)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
1. Personal History Criteria - path/test report required if not in

Age-specific:

- breast cancer diagnosed ≤ age 35
- 2 primary breast cancer diagnoses, at least 1 ≤ age 50
- triple negative (ER- PR- HER2-) breast cancer ≤ age 60
- breast cancer OR colorectal cancer ≤ age 50 AND no family history known due to adoption
- colorectal cancer diagnosed ≤ age 40
- 2 or more colorectal adenomas ≤ age 40
- colorectal or endometrial cancer ≤ age 50 AND ≥ 5 adenomas
- 2 Lynch syndrome related diagnoses, at least 1 ≤ age 50
- diffuse gastric cancer age ≤ 40 *additional HDGC criteria on website
- renal cancer ≤ age 45
- biliary tract cancer ≤ age 50 *additional criteria on website

- pathogenic gene variant identified via tissue test (e.g. Oncopan)
At least 1 of the following diagnoses at any age:

- Lynch syndrome related cancer with dMMR (IHC def)
- Male breast cancer
- Non-mucinous epithelial ovarian, fallopian tube or peritoneal cancer (includes STIC)
- Pancreatic ductal adenocarcinoma
- Medullary thyroid cancer
- Paraganglioma or pheochromocytoma
- 2 or more hamartomatous polyps
- 10 or more colorectal adenomas (cumulative)
- Serrated polyps meeting WHO 2019 criteria
- Ashkenazi Jewish heritage & personal or family history of breast, ovary, pancreatic cancer

2. Family History Criteria - on 1 side of the family & may include

- A close relative with personal history as above
- 2 close female relatives with breast cancer, both ≤ age 50
- 2 close relatives with Lynch syndrome cancer, both ≤ age 50
- 3 breast cancers in close female relatives, at least 1 ≤ age 50
- 3 or more Lynch syndrome cancers, at least 1 ≤ age 50
- 3 melanomas in close relatives at any age

NEW!!!
Female first degree relative of ovarian cancer eligible for testing in BC
## Interpreting genetic test results

<table>
<thead>
<tr>
<th>Positive</th>
<th>Maybe (VUS)</th>
<th>Negative</th>
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</thead>
<tbody>
<tr>
<td>• Deleterious mutation identified</td>
<td>• Typically a missense variant</td>
<td>• No mutation identified</td>
</tr>
<tr>
<td>• Mutation affects gene function</td>
<td>• Unclear if variant affects gene function</td>
<td>• Cause of cancer in patient/family remains unexplained</td>
</tr>
<tr>
<td>• Gene is associated with phenotype</td>
<td>• May be present in population databases</td>
<td>• Multifactorial etiology vs. other causative gene(s)</td>
</tr>
<tr>
<td>• Can test other relatives</td>
<td>• Not clear if variant associated with disease</td>
<td>• Limited value to testing other relatives</td>
</tr>
<tr>
<td>• Presence of mutation impacts medical management</td>
<td>• Testing relatives may be unhelpful</td>
<td>• Management based on family hx</td>
</tr>
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</table>
Private Testing

- Patients are increasingly interested
- “Buyer Beware”
- Reputable companies will include genetic counselling with the test.
- Do not allow a patient to act on Variant Uncertain Significance
- We are here to help
In 2021 Genetic Testing  ➔  Prevention

You only find what you look for.

You only diagnose what you know.
Lifetime Breast Cancer Risk in Women

- **High Risk Genes** (BRCA1/2)
  - BRCA1 72%
  - BRCA2 69%

- General Population 12%

- Contralateral Cancer Risk
  - BRCA1 40%
  - BRCA2 26%

Kuchenbaecker et al JAMA 2017 317(23): 2402-2416
Breast Cancer Risk non BRCA

High Risk Genes

• TP53 79%
• PTEN 67-85%
• STK11 40-60%

Moderate Risk Genes

PALB2,CHEK2,ATM, CDH1,NF
• 15-60% life time risk

NCCN guidelines 2021
## BRCA1 Breast Cancer Risk

<table>
<thead>
<tr>
<th>Current age (yrs)</th>
<th>Approximate remaining lifetime risk to 80 yrs</th>
<th>Approximate 5 yr risk</th>
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<tbody>
<tr>
<td>20-25</td>
<td>70%</td>
<td>5%</td>
</tr>
<tr>
<td>26-30</td>
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<td>31-35</td>
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<td>36-40</td>
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<td>66-70</td>
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# BRCA2 Breast Cancer Risk

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<td>20-25</td>
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<tr>
<td>66-70</td>
<td>35%</td>
<td>15%</td>
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</table>
Risk Management: Hereditary High Risk Clinic

- Referral via the genetic counsellor for women with confirmed mutations or 50% risk and as yet untested
- Telephone or in-person (Vancouver) consultation
- Wait time currently 3-5 months (depending on mutation)
Risk Management: Hereditary High Risk Clinic

- Complete history and breast exam
- Review of risks for given mutation
- Discussion of risk management options
- Written information as needed
- Referrals for surgery
- Imaging (mammo and MRI)
- Annual follow-up
Polling Question

True or False?

Women who carry a BRCA1 or BRCA2 mutation should have prophylactic mastectomies.

1. True
2. False
Management of Known Carriers: Surgical Prevention

- Prophylactic mastectomy +/- reconstruction
- Can be nipple sparing
- >90% reduction in breast cancer risk

- No screening imaging after surgery
- Annual clinical exam with GP
- Investigate any new masses
- Small survival benefit (2-5%) function of age
  - Kurian et al, J Clin Oncol 2010 (28):222-31
Nipple-Sparing Mastectomy with Implant Reconstruction

Colwell et al. Plastic and Recon Surg. 2017
Management of Known Carriers: Increased Surveillance

- Annual mammography age 30 to 75 (+)
- Annual breast MRI from age 25 to 70
- Annual clinical breast exam
- Breast awareness
- Note preventative task force recommendations to not do CBE or self exam do not apply to this population
MRI vs Mammography for Screening

- Contrast enhanced (gadolinium) (preferably with CAD) is more sensitive
  - 80-90% vs 36.8-37.5%
    (ASCO 2015)
    (Ontario Review 2007/2018)
- Specificity 93% vs 97.5 % (MRI vs Mammo)
- Concurrent imaging for diagnostic workup
- No evidence for alternating protocol
- No added value with the addition of US
Breast Cancer on MRI with GAD
Polling Question:

Chemopreventative medication reduces breast cancer risk by what percentage?

1. less than 20%
2. 20-45%
3. 46-65%
4. 66-80%
5. more than 80%
Management of Carriers: Medical Prevention

• Chemoprevention
• No trial specific for mutation carriers
• Only for patients at risk of ER+ tumours
• Options
  • Tamoxifen
  • Raloxifene
  • Aromatase inhibitors
Tamoxifen for Risk Reduction

• 49% reduction in invasive and non-invasive breast (prevented 4 of 10 cancers)
• Premenopausal or post menopausal
• Endometrial Cancer- 2.5 X RR (higher if >50yo)- 4 in 1000 women
  • Not in premenopausal women
• Thromboembolism
  • 1.6 X for DVT
  • 1.59 for stroke, 3.01 for PE
  • Increased risk in smokers
• Cataracts
Tamoxifen – Side Effects

• Generally well tolerated
• 1% discontinue rate in trials
• Hot flashes
• Vaginal dryness
• Basically “menopausal” symptoms

• Can’t take if on OCP or HRT
• Some medications interfere (antidepressants CYP2D6 inhibitors)
Raloxifene for Risk Reduction

- Almost as effective as tamoxifen for invasive cancer (prevented 3 of 10 cancers vs 4 of 10 for tam)
- Postmenopausal only
- No increase in endometrial cancer
- Lower risk of thromboembolism
- Not if on HRT
Aromatase Inhibitors for Risk Reduction

- More effective than tamoxifen or raloxifene
- Prevented 5-6 of 10 cancers
- Only for post-menopausal women
- No increase in endometrial ca or DVT
- Increased risk osteoporosis
  - Need baseline bone density
  - Ca and vit D supplementation
British Columbia’s GCI Gynecologic Cancer Initiative

Motivated by the goal of decreasing death and suffering from gynecologic cancers by 50%.

Funded by UBC Cluster grant

The University of British Columbia

Led by Dr. Gavin Stuart

BC Cancer Coastal Health

BC Women’s Hospital+ Health Centre

VGH UBC Hospital Foundation

BC Cancer Foundation

BC Women’s Hospital+ Health Centre Foundation
Over 2800 Canadian women are diagnosed with ovarian cancer every year. 1800 succumb to disease annually. Second most common gynecologic malignancy. Most lethal gynecologic malignancy, and the 5th ranking cause of cancer death for women.
What is the real risk of ovarian cancer in BRCA carriers?

<table>
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<tr>
<th>Ovarian Cancer</th>
<th>BRCA 1</th>
<th>BRCA 2</th>
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<tr>
<td>Antoniou</td>
<td>40%</td>
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</tr>
<tr>
<td>Chen</td>
<td>59%</td>
<td>16%</td>
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<tr>
<td>Rebbeck</td>
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</tr>
<tr>
<td>Mavaddat</td>
<td>35%</td>
<td>11%</td>
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</table>


How to manage that risk?
Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial


Summary
Background Ovarian cancer has a poor prognosis, with just 40% of patients surviving 5 years. We designed this trial to establish the effect of early detection by screening on ovarian cancer mortality.

Methods In this randomised controlled trial, we recruited postmenopausal women aged 50–74 years from 13 centres in England, Wales, and Northern Ireland. Inclusion criteria were previous bilateral oophorectomy or ovarian malignancy, increased risk of familial ovarian cancer and active non-ovarian malignancy. The trial management system confirmed eligibility and randomly allocated participants in blocks of 32 using compu-

<table>
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<th>Intervention</th>
<th>Patients</th>
<th>Deaths</th>
<th>False positive surgery/case detected</th>
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<tr>
<td>USS</td>
<td>50 624</td>
<td>148</td>
<td>2</td>
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<td>Yearly Ca125</td>
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</tr>
<tr>
<td>USS</td>
<td>50 623</td>
<td>154</td>
<td>10</td>
</tr>
<tr>
<td>No screening</td>
<td>101 299</td>
<td>347</td>
<td>NA</td>
</tr>
</tbody>
</table>
Screening in high-risk women

• UK Familial Ovarian Cancer Screening Study (UK FOCSS)
  • 8000 women
  • U/S and ca125 4 monthly
  • High risk by family history or mutation
  • Completed recruitment 2013

• National Ovarian Cancer Screening Prevention (GOG0199)
  • ROCA (risk of ovarian cancer)
  • Completed recruitment 2011
  • Quality of life analysis
  • Prophylactic surgery data

• CHARM Study
  • cDNA screening via blood test is open in BC

• Stay Tuned!
Chemoprevention

Meta-analysis of OCP in BRCA carriers

- 2855 breast cancer cases
- 1503 ovarian cancer cases
- RR 0.50 (0.33-0.75)
- 36% reduction in ovarian cancer with each additional 10 years of use
- Breast cancer 1.13 (0.88-1.45)

Eur Jour Cancer 2010;46:2275-2284
RRSO is associated with a 70% reduction in all cause mortality

- BRCA 1 HR 0.30 (0.24-0.38 p<0.001)
- BRCA 2 HR 0.33 (0.22-0.50 p<0.001)
• 10 cohort studies
• 8087 participants (2936 surgery and 5151 control participants)
• BRCA1 and BRCA2
• RRSO versus no RRSO
• Follow-up period ranged from 0.5 to 27.4 years.

• Overall survival was longer with RRSO (HR 0.32, 95% CI 0.19 to 0.54; P < 0.001)
• HGSC cancer mortality (HR 0.06, 95% CI 0.02 to 0.17; I² = 69%; P < 0.0001)
• Breast cancer mortality (HR 0.58, 95% CI 0.39 to 0.88; I² = 65%; P = 0.009)
• None of the studies reported bone fracture incidence.
• Ovarian cancer risk perception quality of life (MD 15.40, 95% CI 8.76 to 22.04; P < 0.00001)
<table>
<thead>
<tr>
<th>BRCA 1 carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>27/1196 on screening died of ovarian/fallopian tube cancer</td>
</tr>
<tr>
<td>2/658 deaths after risk reducing salpingo-oophorectomy</td>
</tr>
<tr>
<td>The hazard ratio for oophorectomy versus ultrasound 0.23 (95% CI: 0.05 to 0.97; p = 0.05)</td>
</tr>
</tbody>
</table>

*Gynecol Oncol. 2019 Sep 6, 2019*
RRSO Recommended in BRCA Carriers
35-40y BRCA 1
40-45y BRCA 2
Pathologic Review of Fallopian Tubes

SEE FIM Protocol
Should hysterectomy be done at the time of RRSO?

<table>
<thead>
<tr>
<th>Disadvantages</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR time</td>
<td>Simplifies post surgery HRT</td>
</tr>
<tr>
<td>Recovery time</td>
<td>? Risk of serous endometrial cancer *</td>
</tr>
<tr>
<td>Complication Rate</td>
<td>Eliminates endometrial cancer risk if on tamoxifen</td>
</tr>
</tbody>
</table>

* Prophylactic specimens 1083 BRCA 1 carriers
Incidental uterine cancer in 8 patients

- Cardiovascular Disease
  - Metabolic syndrome 2x
- Bone Health
  - 30-40% more osteopenia
- Cognition
  - Word finding, memory
  - Dementia HR 1.9
  - Parkinson’s HR 1.8
- Quality of Life
  - Vasomotor symptoms
  - Significant Sleep Disruptive
- Sexual Health
  - Libido
  - Desire
  - Lubrication
<table>
<thead>
<tr>
<th>Study</th>
<th>BRCA1/2 Carriers</th>
<th>HRT Duration</th>
<th>OR for Breast Cancer for HRT</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebbeck 2005 (PROSE study)</td>
<td>462</td>
<td>RRSO</td>
<td>0.37</td>
<td>0.14 to 0.96</td>
<td>.03</td>
</tr>
<tr>
<td>Kotsopoulos 2016</td>
<td>432</td>
<td>4+ years</td>
<td>0.80</td>
<td>0.55 to 1.16</td>
<td>.24</td>
</tr>
<tr>
<td>Eisen 2008</td>
<td>472</td>
<td>Ever use of HT</td>
<td>0.58</td>
<td>0.35 to 0.96</td>
<td>.03</td>
</tr>
</tbody>
</table>
IS HORMONE THERAPY SAFE?

- Kotsopoulos 2018
  - 872 BRCA1 mutation carriers
  - mean follow-up 7.6 years (range, 0.4-22.1)
  - HRT use after BSO not associated with an increased risk of breast cancer (HR 0.97 (95% CI, 0.62-1.52; P = .89))
  - Higher breast cancer incidence in E+P users (consistent with literature)
Salpingectomy first?

- Biologically plausible
- Quality of life gains
- Extent of risk reduction is unknown
- RRS and RRO Trials
  - Tubectomy (Netherlands)
  - France
  - UK
  - US GOG 019-9

Not a recommendation at present
Personalized care is essential

Ongoing clinical relationships are essential

Alternatives to oophorectomy need research
Practical Approach to RRSO

Timing
- BRCA 1 or 2
- Work around
  - breast cancer recovery
  - mastectomy/reconstruction
  - Personal considerations

Pathologic processing of specimens

Unexpected findings at OR
- occult pre-invasive findings
- overt cancer

Role of hysterectomy
BRCA2  c. 6065 C > G
BRCA Cancer Risks Other than Female Breast and Ovary
Polling Question

Which of the following statements are false?

1. Pancreatic cancer occurs more frequently in BRCA2 carriers
2. Prostate cancer in BRCA2 carriers is more aggressive than in the general population
3. Colorectal Cancer is more common in BRCA mutation carriers
4. Melanoma is more common in BRCA2 mutation carriers
Pancreatic Cancer

• BRCA2
  • lifetime risk 5-10% (3-8 times)
• BRCA1
  • lifetime risk 2-3% (2-4 times)
• General Population
  • 1%

• Genetic testing:
  • anyone with pancreatic cancer should be considered
  • Anyone with a FH of pancreatic cancer or other syndrome associated cancers
Pancreatic Cancer Risk Management

- Screening- no evidence of improved survival overall
- Research
  - alternating MRI and endoscopic US for carriers with first degree relative with pancreatic cancer.
  - Age 50 or 10 years younger than affected family member
- Investigation on upper abdominal symptoms or new diabetes
- Avoid smoking (known risk factor)

Prostate Cancer

- BRCA 2 – 3-8.5 X increased risk (15-25%)
  - Typically younger age of onset
  - Higher grade
  - Poorer prognosis

- BRCA1 – 3.8 times increased risk (8.6%)
- General population risk 5.9%
Prostate Cancer Risk Management

- Genetic testing recommended (in development in BC)
  - Metastatic prostate cancer
  - High grade (Gleason 7+)/ Intraductal or cribiform histology
    - Family history – breast, ovarian, pancreatic, prostate
    - Ashkenazi Jewish heritage
    - African descent

- BRCA2 – PSA and DRE from age 40
- BRCA1 – Consider screening

Melanoma

• BRCA2 only

• Possible 3-5% (2.7X increase) including uveal

• Not confirmed in all studies

• Patient awareness and consideration of annual skin examinations


Male Breast Cancer

- BRCA 1  1-5%
- BRCA 2  5-10%
- General population  0.1%

Clinical breast examinations beginning at the age of 35 years

Consideration of baseline mammography at the age of 40 years
Other Cancers:

- Many possibly increased cancer risks reported in the literature
- Data is very variable
- Statistical significance inconsistent
- Bone, pharynx, buccal cavity, larynx esophageal, gallbladder and bile duct, stomach, uterine, colorectal, cervix, etc
- No enhanced screening
- Index of suspicion
Beyond Angelina Jolie: Diagnosis and Management of Hereditary Breast and Ovarian Cancer

THANK YOU!

Lesa Dawson
Rona Cheifetz
Extra slides for discussion
No. 366-Gynaecologic Management of Hereditary Breast and Ovarian Cancer

This Committee Opinion has been prepared by the Hereditary Ovarian Cancer Prevention Program, reviewed by the Society of Obstetricians and Gynaecologists of Canada (SOGC)’s Gynaecology Committee and the Society of Gynaecologic Oncology of Canada (SGOC) Guidelines Committee, and approved by the Board of the SOGC.

Michelle Jacobsen, MD, Toronto, ON
Marcus Bernardini, MD, Toronto, ON
Mays, L. Sukhi, MD, Toronto, ON
Raymond H. Kim, MD, PhD, Toronto, ON

Bottom line: Breast cancer is relatively common in the general population (12% lifetime risk) and the majority of cases occur sporadically. About 5-10% of breast cancer is due to an inherited gene change. Mutations in the genes BRCA1 or BRCA2 are the most common cause of hereditary breast and ovarian cancer (HBOC) and BRCA1 and BRCA2...
Emerging counselling issues

• Distributive justice- how do we determine fair, equitable access to genetic testing?

• Management of couples when one partner carries a heterozygous mutation in a gene associated with AR disease
  • ATM- Ataxia Telangiectasia
  • BRCA2, BRIP1, PALB2- Fanconi Anemia

• Insurance discrimination and genetic privacy
  • Bill S-201 (Genetic Non-Discrimination Act)

• Variants of uncertain significance (VUS)
  • More genes analyzed = more VUSs!
  • Follow-up / ressources / over-surveillance and worry for patient when we know about 90% of VUS will be reclassified as polymorphisms

• Prenatal diagnosis and pre-implantation genetic diagnosis (PGD) for cancer survivors or young previvors
THANK YOU!

Lesa Dawson
Rona Cheifetz

Beyond Angelina Jolie: Diagnosis and Management of Hereditary Breast and Ovarian Cancer
Hereditary Ovarian Cancer is more than BRCA 1 & 2

M. Suszynska et al. / Gynecologic Oncology 153 (2019) 452–462
RAD51C, RAD51D, BRIP1
Important Contributors to Ovarian Cancer Risk

<table>
<thead>
<tr>
<th>BRIP1 Ovarian Cancer Risks</th>
<th>RAD51C</th>
<th>RAD51D</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.62 (1.72-3.98) Kurian 2017</td>
<td>RR 3-10 (counsel 4)</td>
<td>RR 4-12 (counsel 8)</td>
</tr>
<tr>
<td>11.22 (3.22-34.1) Ramus 2015 case-control</td>
<td>All breast cancer increased</td>
<td>modestly elevated</td>
</tr>
<tr>
<td>3.41 (2.12-5.54) Ramus 2015 segregation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.4 (3.8-10.6) Norquist 2015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.99 (3.79-6.45) Lilyquist 2017</td>
<td>TN Breast Cancer (stay tuned) RR 1-6</td>
<td>RR 4 - 30</td>
</tr>
<tr>
<td>19.17 (11.13-33) Webber-Lasalle 2018</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.98 (3.73-6.38) Suszynska 2019 meta-analysis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Recommendations NCCN
Risk Reducing Salpingo-oophorectomy 45-50y

Gynecologic Oncology Survivorship Clinic

Personalized Gynecologic Cancer Prevention & Survivorship

The Division of Gynecologic Oncology is launching a new clinic to serve patients in BC with high hereditary risk for gynecologic cancer. The mission of this clinic is to improve the quality of peri-operative care, education and hormone therapy support for patients embarking on preventative gynecologic surgery.
What does this clinic offer?

**Menopause management**
Patients who have had risk-reducing oophorectomy require ongoing expert advice about management of menopause. Our specialty service offers evidence-based guidance about hormone use and post-operative care.

**Preventative Surgical Decision Support**
Many families have inconclusive or negative genetic testing but may still be at high risk for ovarian or endometrial cancer. We can assess patients with a worrisome family history of ovarian cancer and assist with decisions about surgery or prevention.

**Access to Research**
Patients at high hereditary risk benefit from access to research about prevention and risk reduction. Our team will ensure that patients and families in BC have access to research studies and clinical trials.
Who to refer?

- Patients having risk reducing gynecologic surgery due to a known mutation in BRCA1&2, BRIP1, RAD51C, RAD51D, PALB2 or Lynch Syndrome.

- Patients requiring complex post-surgical menopause care.

- Patients with uninformative genetic testing (no mutation OR variant of uncertain significance) and concerns about family cancer history.

- Patients requesting individualized assessment and advice regarding hereditary risk and prophylactic surgery options.

Referrals  Lisa.Andres@vch.ca  605 875 4260