Cancer Risks and Management for Men with Mutations

Rachel Shapira, ScM, LCGC
October 19, 2018
Disclosures

- No conflicts to disclose
Outline

• HBOC-Associated Cancers
  • Prostate
  • Pancreas
  • Breast
  • Melanoma
  • Colon

• Reproductive Risks
Show of hands

Thank you!
BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

WOMEN
• Breast awareness\(^1\) starting at age 18 y.
• Clinical breast exam, every 6–12 mo,\(^2\) starting at age 25 y.
• Breast screening\(^3,4\)
  • Age 25–29 y, annual breast MRI\(^5\) screening with contrast\(^6\) (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present.
  • Age 30–75 y, annual mammogram with consideration of tomosynthesis and breast MRI\(^5\) screening with contrast.
  • Age >75 y, management should be considered on an individual basis.
• For women with a BRCA pathogenic/likely pathogenic variant who are treated for breast cancer and have not had a bilateral mastectomy, screening with annual mammogram and breast MRI should continue as described above.
• Discuss option of risk-reducing mastectomy
  • Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.
• Recommend risk-reducing salpingo-oophorectomy (RRSO),\(^7\) typically between 35 and 40 y, and upon completion of child bearing. Because ovarian cancer onset in patients with BRCA2 pathogenic/likely pathogenic variants is an average of 8–10 years later than in patients with BRCA1 pathogenic/likely pathogenic variants, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40–45 y in patients with BRCA2 pathogenic/likely pathogenic variants unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery. See Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol in NCCN Guidelines for Ovarian Cancer - Principles of Surgery.
• Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term hormone replacement therapy, and related medical issues.
  • Salpingectomy alone is not the standard of care for risk reduction, although clinical trials of interval salpingectomy and delayed oophorectomy are ongoing. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy likely reduces the risk of developing breast cancer but the magnitude is uncertain and may be gene-specific.
• Limited data suggest that there may be a slightly increased risk of serous uterine cancer among women with a BRCA1 pathogenic/likely pathogenic variant. The clinical significance of these findings is unclear. Further evaluation of the risk of serous uterine cancer in the BRCA population needs to be undertaken. The provider and patient should discuss the risks and benefits of concurrent hysterectomy at the time of RRSO for women with a BRCA1 pathogenic/likely pathogenic variant prior to surgery.
• Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or salpingo-oophorectomy.
• For those patients who have not elected RRSO, transvaginal ultrasound combined with serum CA-125 for ovarian cancer screening, although of uncertain benefit, may be considered at the clinician's discretion starting at age 30–35 y.
• Consider risk reduction agents as options for breast and ovarian cancer, including discussing risks and benefits (See Discussion for details).
  (See NCCN Guidelines for Breast Cancer Risk Reduction).
• Consider investigational imaging and screening studies, when available (eg, novel imaging technologies, more frequent screening intervals) in the context of a clinical trial.

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

BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

MEN
• Breast self-exam training and education starting at age 35 y
• Clinical breast exam, every 12 mo, starting at age 35 y
• Starting at age 45 y: (See Guidelines for Prostate Cancer Early Detection)
  > Recommend prostate cancer screening for BRCA2 carriers
  > Consider prostate cancer screening for BRCA1 carriers

MEN AND WOMEN
• Education regarding signs and symptoms of cancer(s), especially those associated with BRCA gene pathogenic/likely pathogenic variants.
• No specific screening guidelines exist for pancreatic cancer and melanoma, but screening may be individualized based on cancers observed in the family.9

RISK TO RELATIVES
• Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
• Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

1Women should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent breast self exam (BSE) may facilitate breast self awareness.
2Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending clinical breast exam every 6–12 mo is the concern for interval breast cancers.
5The criteria for high-quality breast MRI include a dedicated breast coil, the ability to perform biopsy under MRI guidance, radiologists experienced in breast MRI, and regional availability.
6Breast MRI is preferably performed on days 7–15 of a menstrual cycle for premenopausal women.
7Breast MRI is preferred due to the theoretical risk of radiation exposure in pathogenic/likely pathogenic variant carriers.
8Given the high rate of occult neoplasms, special attention should be given to sampling and pathologic review of the ovaries and fallopian tubes. (See Discussion for details.) See the College of American Pathologists, Protocol for the Examination of Specimens from Patients with Carcinoma of the Ovary. See NCCN Guidelines for Ovarian Cancer for treatment of findings.
9There are limited data to support breast imaging in men.
10Consider full-body skin and eye exam for melanoma and investigational protocols for pancreatic cancer. See International Cancer of the Pancreas Screening Consortium recommendations.

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Genes associated with hereditary cancer

- BRCA1
- BRCA2
- Moderate Risk HBOC Genes
  - ATM, BRIP1, CHEK2, NBN, PALB2
- Other hereditary cancer syndromes
  - Lynch syndrome – MLH1, MSH2, MSH6, PMS2, EPCAM
  - Li-Fraumeni syndrome – TP53
  - Cowden syndrome – PTEN
  - Peutz-Jeghers – STK11
- Plus many many many more
Prostate Cancer
Prostate Cancer Risks: General Population

<table>
<thead>
<tr>
<th>Common Types of Cancer</th>
<th>Estimated New Cases 2018</th>
<th>Estimated Deaths 2018</th>
</tr>
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<tbody>
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Prostate cancer represents 9.5% of all new cancer cases in the U.S.

Prostate Cancer Risks: Average vs. Hereditary

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<thead>
<tr>
<th>General Population</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>ATM</th>
<th>CHEK2</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.2%</td>
<td>Elevated</td>
<td>20%</td>
<td>Elevated</td>
<td>Elevated</td>
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</tbody>
</table>

- 692 men with metastatic prostate cancer
- 82 had mutations in 16 DNA-repair genes

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. NEJM 2016
Prostate Cancer
Average vs. Hereditary

- Quantitative vs. qualitative differences
  - Risk magnitude
  - Age of onset
  - Likelihood of aggressive and metastatic cancers
  - Reflected in new NCCN Guidelines BRCA testing criteria
    - Personal history of metastatic prostate cancer
    - Personal history of high-grade prostate cancer with family history
Prostate Cancer Screening Tools

• Prostate specific antigen (PSA) blood test
  • Protein produced by the prostate gland
  • Measures level of protein in the blood
  • High levels:
    • MAY indicate prostate cancer that requires treatment
    • Benign conditions e.g. inflammation or enlargement of prostate.
    • Potential for overtreatment

• Digital rectal exam (DRE)
  • Clinical exam to feel for abnormalities
Prostate Cancer Screening Guidelines for Men at Average Risk

• ACS
  • Discussion about screening at age 50
  • Repeat every 1-2 years depending on PSA

• NCCN
  • Discussion about screening at age 45
  • Repeat every 1-4 years depending on PSA and DRE
  • No routine screening after age 75

• USPSTF
  • Discussion about screening at age 55
  • No routine screening after age 69
Prostate Cancer Screening Guidelines for Mutation Carriers

• BRCA1
  • Consider screening starting at age 45
• BRCA2
  • Recommend screening starting at age 45
• HBOC moderate risk genes
  • No recommendations (yet)
Pancreatic Cancer
Pancreatic Cancer Risks: Average vs. Hereditary

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<th>PALB2</th>
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<tbody>
<tr>
<td>1.5%</td>
<td>3-4%</td>
<td>7-8%</td>
<td>Increased</td>
<td>Increased</td>
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Common Types of Cancer

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<tr>
<td>11. Pancreatic Cancer</td>
<td>55,440</td>
<td>44,330</td>
</tr>
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Pancreatic cancer represents 3.2% of all new cancer cases in the U.S.

Pancreatic Cancer Screening Tools

- Endoscopic Ultrasound (EUS)
  - Upper endoscopy with US
  - May include fine needle aspiration

- MRI/ Magnetic resonance cholangiopancreatography (MRCP)
Pancreatic Cancer Screening Guidelines: Average Risk

• None

• Why?
  • Lack of evidence that it’s effective
  • Screening is invasive and/or expensive
  • Relatively rare cancer
Pancreatic Cancer Screening Guidelines: Mutation Carriers

• No specific guidelines
  • “Screening may be individualized based on cancers observed in the family” (NCCN Guidelines)

• Why?
  • Same reasons as in the general population

• International Cancer of the Pancreas Screening (CAPS) Consortium
  • Candidates for screening
  • Screening schedule
  • Screening modalities
    Consensus = 75% of 49-expert panel (37)
CAPS Recommendations

- **Candidates for screening**
  - First-degree relatives of patients from a family with 2+ affected FDRs
  - Peutz–Jeghers syndrome (STK11)
  - CDKN2A, BRCA2 and Lynch with ≥1 affected FDR

- **Screening schedule**
  - No consensus for age to initiate screening or stop surveillance, but half recommended starting at 50
  - Disagreement on optimal intervals for follow-up imaging, but majority suggested annual

- **Screening modality**
  - Disagreement on screening modalities, but generally favor EUS and MRI/MRCP
  - Initial screening should include EUS and/or MRI/MRCP
CAPS Conclusions

• Screening is recommended for high-risk individuals, but more evidence is needed, particularly for how to manage patients with detected lesions.

• Screening and subsequent management should take place at high-volume centres with multidisciplinary teams, preferably within research protocols.

International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut 2013
Male Breast Cancer
### Male Breast Cancer Risk: Average vs. Hereditary

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<th>ATM</th>
<th>CHEK2</th>
<th>PALB2</th>
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</thead>
<tbody>
<tr>
<td>0.1%</td>
<td>1-2%</td>
<td>7-8%</td>
<td>Possibly increased</td>
<td>Possibly increased</td>
<td>Increased</td>
</tr>
</tbody>
</table>

**Graphs:**
- **Left:** Comparison of average BRCA1 and BRCA2 risks.
- **Right:** Comparison of average, BRCA1, BRCA2, and female breast cancer risks.
Breast Cancer Screening: General Population

- **Women**
  - Breast self-exam (BSE)
  - Clinic breast exam
  - Mammogram

- **Men**
  - None
Breast Cancer Screening: Men with Mutations

- BSE training and education starting at age 35
- Annual clinical breast exam starting at age 35
Melanoma
Melanoma Risk: 
Average vs. Hereditary

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<tbody>
<tr>
<td>Varies by race/ethnicity</td>
<td>May be increased</td>
<td>Increased</td>
<td>May be increased</td>
</tr>
<tr>
<td>2% - Whites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5% - Hispanics</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0.1% - Blacks</td>
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May be increased

Melanoma Screening Tools

**ABCD**

- **A** - Asymmetry: The two halves of the mole do not match.
- **B** - Borders: The edges are irregular or uneven (scalloped, blurred, or notched).
- **C** - Color: Multiple or changing shades of brown, tan, black, red, blue, or pink are present.
- **D** - Diameter: Usually, but not always, larger than 6mm.
- **E** - Evolution: Changes in appearance, such as size, shape, or color and/or changes in symptoms, such as bleeding, oozing, or itching.
Melanoma Screening Guidelines

• General Population
  • No formal guidelines
  • Skin self-exam
  • Clinical exam
  • Practice sun-protective behavior

• BRCA1/2 Mutations Carriers
  • “Screening may be individualized based on cancers observed in the family” (NCCN Guidelines)
Colon Cancer
### Colon Cancer Risk

**Average vs. Hereditary**

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<tr>
<td>1/20 or 5%</td>
<td>May be increased</td>
<td>No known risk</td>
<td>~10%</td>
<td>May be increased</td>
</tr>
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#### Common Types of Cancer (2018 Data)

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Colorectal cancer represents 8.1% of all new cancer cases in the U.S.

Colon Cancer Screening Tools and Average Risk Frequency

• **Stool-based tests**
  - Highly sensitive fecal immunochemical test (FIT) every year
  - Highly sensitive guaiac-based fecal occult blood test (gFOBT) every year
  - Multi-targeted stool DNA test (MT-sDNA) every 3 years

• **Visual (structural) exams of the colon and rectum**
  - Colonoscopy every 10 years
  - CT colonography (virtual colonoscopy) every 5 years
  - Flexible sigmoidoscopy (FSIG) every 5 years
Colon Cancer Screening for People at Average Risk

• ACS
  • Begin at age 45 (recently updated)
  • Stool-based or visual exam
  • Continue through age 75
  • Individualized through age 85

• NCCN and USPSTF
  • Begin at age 50
  • Stool-based or visual exam
  • Continue through age 75
  • Individualized through age 85
Colon Cancer Screening for Mutation Carriers

- **BRCA1**
  - No official recommendations
  - Consider colonoscopy starting at age 40?

- **CHEK2**
  - Colonoscopy beginning at age 40
  - Repeat every 5 years
  - If FDR diagnosed under age 50, start colonoscopy 10 years earlier than age at diagnosis
Reproductive Risks
Reproductive Risks

• Autosomal dominant inheritance
  • Each child has a 50% chance of inheriting your mutation
  • Not sex-linked!
Reproductive Risks

- **Autosomal recessive inheritance**
  - Carriers with mutations in the same gene
  - 25% risk for each child
Recessive Conditions

- BRCA2 + BRCA2 → Fanconi Anemia
- PALB2 + PALB2 → Fanconi Anemia
- ATM + ATM → Ataxia Telangectasia

- BRCA1 + BRCA1 →
- BRCA1 + BRCA2 → Super BRCA?
Reproductive Technologies

• In vitro fertilization (IVF)
• Preimplantation genetic testing (PGD)
• Prenatal testing
Upcoming Sessions

• Melanoma and Pancreatic Cancer Risks and Prevention
  • Friday 2:00-2:40

• Hereditary Prostate Cancer Treatment
  • Saturday 11:30-12:15

• Cancer Risks for People with Non-BRCA Mutations
  • Saturday 1:55-3:15

• Treating Breast Cancer in Men
  • Saturday 5:15-6:00
Thank you

Rachel Shapira, ScM, LCGC
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