Minimizing Cardiovascular Complications in Patients with High Cancer Risk Genetic Syndromes

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September 2018
Disclosures

• I previously owned Merck and Pfizer stock

• My husband is a co-inventor of technology licensed by Mayo Clinic to AliveCor (MountainView, CA), which makes a smartphone-enabled remote ECG monitoring system
Learning objectives

• Describe cardiovascular risks associated with:
  • prophylactic salpingoophorectomy and endocrine-based cancer prevention strategies
  • chemotherapy, chest radiotherapy, and HER2 directed therapies

• Explain potential management strategies
Li Faumeni Syndrome

- Rare autosomal dominant germline mutation of p53
- Predisposition to early onset:
  - breast cancer (occurs in >50% of female carriers by age 60)
  - Sarcoma
  - Brain tumors
  - Adrenocortical carcinoma
  - Leukemia
  - Other tumors?
Implications of Li Fraumeni Syndrome

• Preventative option:
  • Bilateral mastectomy in women
• Multiple sequential cancers are common
• Multiple courses of oncologic treatment may lead to compounded toxicity
Lifetime risk of cancers most commonly associated with *BRCA1/2*

<table>
<thead>
<tr>
<th>Cancer</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>~70%</td>
<td>~70%</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>~45%</td>
<td>~15-20%</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>~15%</td>
<td>~25%</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td></td>
<td>~5%</td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td>~5%</td>
</tr>
</tbody>
</table>
Prophylactic bilateral salpingoophorectomy (BSO)

- Guideline-recommended at 35-40 with \textit{BRCA1} and at 35-45 with \textit{BRCA2} (to prevent ovarian cancer)
- Also reduces risk of breast cancer pre-bilateral mastectomies
- BSO before age 50 may increase hyperlipidemia, cardiac arrhythmias, and coronary artery disease, though data are mixed

## BSO data from Nurses’ Health Study (NHS)

### Table: Number of Deaths

| Type                  | Ovarian Conservation | Bilateral Oophorectomy | HR (95% CI)^a | P-value
|-----------------------|----------------------|------------------------|---------------|--------
| **ALL-CAUSE DEATHS**  |                      |                        |               |        
| < 50 y                | 1388                 | 2045                   | 1.13 (1.05-1.22) | 0.46   
| 50-59 y               | 227                  | 655                    | 1.10 (0.93-1.31) | 0.05   
| ≥ 60 y                | 134                  | 149                    | 1.31 (0.98-1.75) |        
| **ALL**               | 1749                 | 2850                   | 1.13 (1.06-1.21) |        
| **BREAST CANCER**     |                      |                        |               |        
| < 50 y                | 110                  | 114                    | 0.82 (0.60-1.11) |        
| 50-59 y               | 22                   | 50                     | 1.19 (0.66-2.14) |        
| ≥ 60 y                | 1                    | 9                      | NA            |        
| **ALL**               | 133                  | 173                    | 0.89 (0.69-1.55) |        
| **LUNG CANCER**       |                      |                        |               |        
| < 50 y                | 139                  | 199                    | 1.20 (0.94-1.53) | 0.16   
| 50-59 y               | 13                   | 61                     | 1.58 (0.78-3.18) |        
| ≥ 60 y                | 19                   | 9                      | NA            |        
| **ALL**               | 162                  | 269                    | 1.29 (1.04-1.61) |        
| **COLORECTAL CANCER** |                      |                        |               |        
| < 50 y                | 39                   | 77                     | 1.63 (1.05-2.53) | 0.30   
| 50-59 y               | 5                    | 23                     | 2.52 (0.64-9.88) |        
| ≥ 60 y                | 5                    | 1                      | NA            |        
| **ALL**               | 49                   | 101                    | 1.49 (1.02-2.18) |        
| **TOTAL CANCERS**     |                      |                        |               |        
| < 50 y                | 574                  | 791                    | 1.13 (1.00-1.27) | 0.22   
| 50-59 y               | 78                   | 246                    | 1.29 (0.97-1.70) |        
| ≥ 60 y                | 38                   | 45                     | 1.63 (0.91-2.97) |        
| **ALL**               | 690                  | 1081                   | 1.16 (1.05-1.29) |        
| **CHD**               |                      |                        |               |        
| < 50 y                | 136                  | 225                    | 1.29 (1.01-1.64) | 0.33   
| 50-59 y               | 23                   | 51                     | 0.78 (0.42-1.46) |        
| ≥ 60 y                | 19                   | 13                     | NA            |        
| **ALL**               | 169                  | 289                    | 1.23 (1.00-1.52) |        
| **STROKE**            |                      |                        |               |        
| < 50 y                | 83                   | 133                    | 1.15 (0.85-1.56) | 0.54   
| 50-59 y               | 21                   | 50                     | 0.82 (0.54-1.24) |        
| ≥ 60 y                | 8                    | 9                      | NA            |        
| **ALL**               | 112                  | 192                    | 1.10 (0.85-1.42) |        
| **CVD**               |                      |                        |               |        
| < 50 y                | 219                  | 358                    | 1.24 (1.03-1.50) | 0.18   
| 50-59 y               | 44                   | 101                    | 0.82 (0.54-1.24) |        
| ≥ 60 y                | 18                   | 22                     | 1.13 (0.42-3.05) |        
| **ALL**               | 281                  | 481                    | 1.19 (1.01-1.39) |        

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**Parker et al. Obstet Gynecol. 2013, 21(4): 709-16**

©2017 MFMER | 3603814-8
Estrogen (ET) may mitigate cardiac risks

Hormone replacement therapy (HRT)

- NCCN recommends caution in BRCA1/2 carriers due to concerns about safety, but in 872 BRCA1 carriers s/p BSO but not bilateral mastectomy:

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Progesterone-containing regimens do appear to increase breast cancer risk.
Chemoprophylaxis

- Tamoxifen or aromatase inhibitor (AI) reduces risk of breast cancer (without bilateral mastectomies)
- AI would be ineffective in a premenopausal patient or a patient on HRT
- Hypercholesterolemia and cardiac events are more common with AIs than tamoxifen
  - Possibly because tamoxifen is protective
  - A recent meta-analysis found 19% more cardiovascular events with AI than tamoxifen, but no increased risk compared to placebo

Despite prophylactic measures, cancers are common
Estimated U.S. cancer survivors by site

As of January 1, 2016

**MALE**
- Prostate: 3,306,760 (45%)
- Colon & rectum: 724,690 (10%)
- Melanoma: 614,460 (8%)
- Urinary bladder: 574,250 (8%)
- Non-Hodgkin lymphoma: 361,480 (5%)
- Kidney: 305,340 (4%)
- Testis: 266,550 (4%)
- Lung & bronchus: 238,300 (3%)
- Leukemia: 230,920 (3%)
- Oral cavity & pharynx: 223,880 (3%)

**FEMALE**
- Breast: 3,560,570 (43%)
- Uterine corpus: 757,190 (9%)
- Colon & rectum: 727,350 (9%)
- Thyroid: 630,660 (8%)
- Melanoma: 612,790 (8%)
- Non-Hodgkin lymphoma: 324,890 (4%)
- Lung & bronchus: 288,210 (4%)
- Uterine cervix: 282,780 (3%)
- Ovary: 235,200 (3%)
- Kidney: 204,040 (3%)

**ALL SITES**
- 7,377,100

As of January 1, 2026

**MALE**
- Prostate: 4,521,910 (45%)
- Colon & rectum: 910,190 (9%)
- Melanoma: 848,020 (8%)
- Urinary bladder: 754,280 (8%)
- Non-Hodgkin lymphoma: 488,780 (5%)
- Kidney: 429,010 (4%)
- Testis: 335,790 (3%)
- Leukemia: 318,430 (3%)
- Lung & bronchus: 303,380 (3%)
- Oral cavity & pharynx: 293,290 (3%)

**FEMALE**
- Breast: 4,571,210 (44%)
- Uterine corpus: 942,670 (9%)
- Colon & rectum: 885,940 (9%)
- Thyroid: 885,590 (9%)
- Melanoma: 811,490 (8%)
- Non-Hodgkin lymphoma: 436,370 (4%)
- Lung & bronchus: 369,990 (4%)
- Uterine cervix: 286,300 (3%)
- Kidney: 284,380 (3%)
- Ovary: 280,940 (3%)

**ALL SITES**
- 9,983,900

There will be a projected 21% increase in the number of female survivors and 26% increase in male survivors between 2016-2026

Surveillance Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD, 2016
Long-term/late effects of cancer treatments

Related to local therapy
- Secondary malignancy
- Lymphedema

Related to systemic therapy
- Secondary malignancy
- Neuropathy
- Osteoporosis
- Premature menopause, infertility
- Myalgias, arthralgias

Related to both
- Cardiac dysfunction
- Thromboembolic events
- Chronic pain
- Sexual dysfunction
- Psychosocial distress
- Weight gain
- Fatigue
Common treatments for BRCA-associated tumors

- **Chemotherapies:** anthracyclines for breast cancer; taxanes for breast, ovarian, and prostate cancers; platinums for breast, ovarian, and pancreatic cancers; capecitabine for breast and pancreatic cancers

- **Chest radiation:** for breast cancer

- **Trastuzumab:** for Her2/neu+ breast and gastric cancer

- **PARP inhibitors:** for metastatic breast cancer and ovarian cancer

- **PD-1 and PD-L1 inhibitors:** for melanoma
What’s unique about tumors in BRCA carriers?

• **More** likely to be sensitive to:
  - PARP inhibitors, which block poly(ADP-ribose) polymerase, resulting in double-strand DNA breaks that are more difficult to repair in the setting of a deleterious BRCA mutation
  - Platinums, which result in crosslinking of DNA

• **Less** likely to need chest radiation for breast cancer
  - Because usually recommended to have bilateral mastectomies (after which only large or node-positive tumors require radiation)

## Cardiac consequences of chemotherapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Potential Cardiovascular Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>CHF, asymptomatic decline in LVEF, arrhythmias</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Arrhythmias</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Variant angina, acute coronary syndrome, cardiomyopathy, arrhythmias</td>
</tr>
<tr>
<td>Platinums</td>
<td>ECG abnormalities, arrhythmias, angina, acute myocardial infarction, hypertension, cardiomyopathy, CHF</td>
</tr>
</tbody>
</table>
Cardiac consequences of other types of cancer therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Potential Cardiovascular Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
<td>Coronary artery disease, chronic pericarditis, valvular heart disease, HF with preserved ejection fraction</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>CHF</td>
</tr>
<tr>
<td>PARP inhibitors</td>
<td>Increased blood cholesterol, hypertension, palpitations</td>
</tr>
<tr>
<td>PD-1/PD-L1 inhibitors</td>
<td>Myocarditis</td>
</tr>
</tbody>
</table>

How are *BRCA1* and *BRCA2*-associated breast cancers different?

- *BRCA1*-associated tumors are more often estrogen receptor-negative, requiring chemotherapy

- *BRCA2*-associated tumors are usually estrogen receptor-positive, requiring adjuvant endocrine therapy (but sometimes not chemotherapy)
Unique features of breast cancers in patients with Li Fraumeni Syndrome

• May be more often estrogen-sensitive (requiring adjuvant endocrine therapy, possibly with ovarian function suppression if premenopausal)
• May be more often HER2+ (requiring trastuzumab-based therapy)
• Bilateral mastectomy usually recommended
• Threshold for radiation is higher due to concern that radiation might increase the likelihood of future sarcoma
## Survivorship Assessment (Patient version)

Please answer the following questions:

<table>
<thead>
<tr>
<th>Survivorship Concerns</th>
<th>Survivorship Care Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Toxicity</td>
<td>1. Did you receive anthracycline therapy (e.g., doxorubicin, epirubicin, daunorubicin, AC [doxorubicin + cyclophosphamide])? Yes/No</td>
</tr>
<tr>
<td></td>
<td>2. Do you have shortness of breath or chest pain after daily activities (e.g., walking up stairs) or exercise? Yes/No</td>
</tr>
<tr>
<td></td>
<td>3. Do you have shortness of breath when lying flat, wake up at night needing to get air, or have persistent leg swelling? Yes/No</td>
</tr>
<tr>
<td>Anxiety, Depression, and Distress</td>
<td>4. Have you been bothered more than half the days by little interest or pleasure in doing things? Yes/No</td>
</tr>
<tr>
<td></td>
<td>5. Have you been bothered more than half the days by feeling down, depressed, or hopeless? Yes/No</td>
</tr>
<tr>
<td></td>
<td>6. Have you been bothered more than half the days by not being able to stop or control worrying, or have you felt nervous or on edge? Yes/No</td>
</tr>
<tr>
<td>Cognitive Function</td>
<td>7. Do you have difficulties with multitasking or paying attention? Yes/No</td>
</tr>
<tr>
<td></td>
<td>8. Do you have difficulties with remembering things? Yes/No</td>
</tr>
<tr>
<td></td>
<td>9. Does your thinking seem slow? Yes/No</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10. Do you feel persistent fatigue despite a good night's sleep? Yes/No</td>
</tr>
<tr>
<td></td>
<td>11. Does fatigue interfere with your usual activities? Yes/No</td>
</tr>
<tr>
<td></td>
<td>12. How would you rate your fatigue on a scale of 0 (none) to 10 (extreme) over the past month? 0–10</td>
</tr>
<tr>
<td>Menopause</td>
<td>13. Have you been bothered by hot flashes/night sweats? Yes/No</td>
</tr>
<tr>
<td></td>
<td>14. Have you been bothered by other menopause-related symptoms (e.g., vaginal dryness, incontinence)? Yes/No</td>
</tr>
<tr>
<td>Pain</td>
<td>15. Are you having any pain? Yes/No</td>
</tr>
<tr>
<td></td>
<td>16. How would you rate your pain on a scale of 0 (none) to 10 (extreme) over the past month? 0–10</td>
</tr>
<tr>
<td>Sexual Function</td>
<td>17. Do you have any concerns regarding your sexual function, sexual activity, sexual relationships, or sex life? Yes/No</td>
</tr>
<tr>
<td></td>
<td>18. Are these concerns causing you distress? Yes/No</td>
</tr>
<tr>
<td>Sleep Disorder</td>
<td>19. Are you having problems falling asleep, staying asleep, or waking up too early? Yes/No</td>
</tr>
<tr>
<td></td>
<td>20. Are you experiencing excessive sleepiness (i.e., sleepiness or falling asleep in inappropriate situations or sleeping more during a 24-hour period than in the past)? Yes/No</td>
</tr>
<tr>
<td></td>
<td>21. Have you been told that you snore frequently or that you stop breathing during sleep? Yes/No</td>
</tr>
<tr>
<td>Healthy Lifestyle</td>
<td>22. Do you engage in regular physical activity or exercise, such as brisk walking, jogging, weight/resistance training, bicycling, swimming, etc.? Yes/No</td>
</tr>
<tr>
<td></td>
<td>22a. If you answered &quot;Yes,&quot; how often?</td>
</tr>
<tr>
<td></td>
<td>23. Excluding white potatoes, do you eat at least 2½ cups of fruits and/or vegetables each day? Yes/No</td>
</tr>
<tr>
<td></td>
<td>24. Do you have concerns about your weight? Yes/No</td>
</tr>
<tr>
<td></td>
<td>25. Do you take vitamins or supplements? Yes/No</td>
</tr>
<tr>
<td>Immunizations and Infections</td>
<td>26. Have you received your flu vaccine this flu season? Yes/No</td>
</tr>
<tr>
<td></td>
<td>27. Are you up to date on your vaccines? Yes/No/Don't know</td>
</tr>
</tbody>
</table>

**Notes:** 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.
In 2015, NCCN started to recommend consideration of post-anthracycline echocardiograms for some patients.

Which of the following does NCCN not consider to be a reason to consider a post-anthracycline echocardiogram?

- A. >200mg/m^2 doxorubicin
- B. Age >65
- C. EF 50-54% at baseline
- D. Underlying cardiovascular disease or other cardiovascular risk factors
INITIAL CLINICAL ASSESSMENT FOR PATIENTS WHO HAVE RECEIVED PREVIOUS ANTHRACYCLINE THERAPY

- History and physical
  - Assess for signs and symptoms of heart failure\textsuperscript{a,d}
  - Assess patient's ability to perform routine and desired activities of daily living
  - Look for signs of volume overload
- Evaluate for presence of heart failure risk factors
  - Hypertension
  - Dyslipidemia
  - Diabetes mellitus
  - Family history of cardiomyopathy
  - Age >65 years
  - High cumulative anthracycline dose (ie, cumulative doxorubicin dose at or higher than 250 mg/m\textsuperscript{2} or equivalent)
  - Low-normal LVEF (50%-54%) at baseline
  - History of other cardiovascular comorbidities (ie, atrial fibrillation, known coronary artery disease [CAD], baseline evidence of structural heart disease)
  - Smoking
  - Obesity
- Review medications, alcohol use, and other substance use
- Review oncologic history
  - Review total cumulative dose of anthracycline
  - Other systemic therapy\textsuperscript{b} and/or chest radiation therapy

- Workup for other causes of symptoms
- Referral to other specialties (eg, pulmonology or cardiology)

- Cardiovascular risk factor management\textsuperscript{c}
- Consider two-dimensional echocardiogram (ECHO) with doppler flow study for survivors with one or more risk factors within 1 year after completion of anthracycline therapy\textsuperscript{d,e}

- No evidence of structural heart disease, but symptomatic\textsuperscript{a}

- No evidence of structural heart disease and asymptomatic
  - See Stage A (SCARDIO-3)

- Evidence of structural heart disease (asymptomatic or symptomatic\textsuperscript{a}):
  - Left ventricular (LV) dysfunction
  - LV hypertrophy
  - Valvular disease
  - LV dilatation and/or wall thinning

- Determine stage of cardiomyopathy (heart failure)
  - (See SCARDIO-3)
Are BRCA carriers at higher risk of anthracycline-related cardiotoxicity?

• Survey open to 13,000 cancer survivors with BRCA mutations who were members of the FORCE and/or ICARE registry

• 232 women with BRCA1, 159 with BRCA2, and 10 with both genes mutated participated

• Rates of CHF and arrhythmia were high (9.2% and 8.3%, respectively), but anthracycline receipt was not a risk factor
  • May reflect more interest in cardiac-focused studies among patients with cardiac problems, not more risk of cardiotoxicity for BRCA carriers

Sajjad et al. Genes (Basel). 2017 Feb 2;8(2)
Side effects of androgen deprivation therapy (ADT) for prostate cancer

- Insulin resistance, diabetes, and metabolic syndrome
- Increased cardiovascular morbidity and mortality
- There may be an increased risk of sudden cardiac death related to prolonged QTc
- ADT drugs may vary in associated cardiac risks

What might improve cardiac outcomes for men and women who carry deleterious BRCA mutations?

- Exercise
- Diet/weight control
- Smoking cessation
- Antihypertensive medications
- Statin
- Aspirin
- Biomarker assessment and/or echocardiographic monitoring in patients at high risk of cardiovascular compromise
Ongoing BWEL Study

Goal N=3136
Key Eligibility:
• Stage II-III breast cancer
• HER-2 -
• BMI ≥ 27 kg/m2

Randomize

2-year telephone-based weight loss intervention + Health education

Health Education Alone

PI: Jennifer Ligibel

Activation date: August 29, 2016
BWEL study objectives

- **Primary:** Assess the impact of a weight loss intervention upon Invasive Disease Free Survival (STEEP)

- **Secondary:**
  - Assess the relationship between weight loss and IDFS and OS
  - Assess the impact of the weight loss intervention upon:
    - Overall mortality
    - Distant disease free survival
    - Weight change
    - **Hospitalizations for cardiovascular disease or diabetes**
  - To evaluate the impact of the weight loss intervention upon IDFS in subsets of participants defined by:
    - Hormone receptor status of the tumor
    - Menopausal status
Ongoing INTERVAL-GAP4 trial: metastatic prostate cancer

REGISTRATION
Eligibility: Metastatic castrate-resistant prostate cancer on androgen deprivation therapy (ADT)

RANDOMIZATION

ARM A
Supervised exercise (n=433)

ARM B
Self-directed exercise (n=433)

On trial assessments including cardiopulmonary exercise testing, electrocardiograms, and surveys; primary endpoint is overall survival

2018 ASCO Abstract 6518: Park et al.

- Smart After-Care intervention = mobile application and wearable device
  - General health information
  - Nutritional and medication-related advice
  - Exercise program: aerobic exercise at least 90 minutes every week for 12 weeks
SMART Trial Schema (N=200)

**Men on ADT for prostate cancer**

**Smart After-Care**

**Control group: brief education regarding exercise**

**Endpoints:**
1. **Primary:** physical function measured by 2-minute walk test
2. **Secondary:**
   - improvement in muscle strength (30 second chair stand test, grip strength test)
   - short physical performance battery
   - body composition
   - health-related quality of life (EORTC-QLQ-C30, and PR 25)
SMART After-Care arm superior in:

- 2-minute walk test ($p = 0.042$)
- Right hand grip strength ($p = 0.038$)
- Reduction in body fat percentage ($p = 0.022$)
- Social functioning ($p = 0.016$)

Conclusion: An exercise program that includes a smartphone-linked wearable can help improve fitness in men on ADT
Remaining questions

• Will there be cardiac benefits associated with increased exercise in survivors?
• Is a fitness-focused intervention feasible to continue indefinitely?
• Can we engage friends/family members to encourage persistence with lifestyle changes?
Summary

• Patients with deleterious \textit{BRCA} mutations are at increased risk of various cancers including breast cancer, ovarian cancer, pancreatic cancer, prostate cancer, and melanoma

• Some strategies to prevent cancer (e.g., BSO) may increase cardiac risks

• Those who go on to develop cancer may receive cardiotoxic therapies

• Research is needed to identify optimal cardiac surveillance strategies over time

• Potential interventions to reduce cardiac risks in this population include tobacco cessation, diet, exercise, treatment of hypertension and hyperlipidemia, and aspirin
Thank You