A Case for Onco-Cardiology

Late Cardiac Effects after Treatment for Breast Cancer

Thomas C. Andrews, MD, FACC
Traverse Heart and Vascular
Cancer Survivorship

- 13.7 million cancer survivors in the US
- Treatment-associated mortality in pediatric oncology patients
  - Recurrence
  - Secondary malignancies
  - **Cardiotoxicity**
- Adult survivors self reported post treatment issues
  - Men: “heart problems” #1
  - Women: “heart problems” #2 (behind osteoporosis)
Improved survival has allowed the emergence of late effects of adjuvant therapy
- Breast cancer mortality in steady decline since 1990
- In 2012, 3 million survivors of breast cancer in US

Some subsets of breast cancer survivors are at a higher risk of cardiovascular disease than age and sex matched controls without cancer.

Breast cancer and cardiovascular disease share common risk factors
71 year old with stage 1 triple negative breast cancer

- Stage 1 triple negative left breast cancer
  - Surgical treatment: lumpectomy and sentinel node
  - Planned chemotherapy
    - 4 cycles of adriamycin and cytoxan
    - Weekly taxotere
  - Planned radiation therapy
- Past medical history
  - Systemic hypertension
  - Hypercholesterolemia
Current medications
- Diltiazem
- Lovastatin
- Aspirin
- Maxide prn for edema

Baseline echo: Normal EF. Dilated left atrium. Normal diastolic function.

Referred for increase in palpitations during first 2 cycles of chemotherapy
Dose dependent anthracycline cardiomyopathy first reported in 1971.

Risk factors
- Age (<4 or >65)
- Female gender
- Pre-existent cardiovascular risk factors (hypertension, CAD, valvular disease)
- Co-effects of other chemotherapies
- Radiation therapy
- Cumulative dose /bolus dosing/higher single doses

Damage has traditionally felt to be irreversible
Long-term incidence of cardiotoxicity after anthracycline


N=2625
Chemo-prevention of anthracycline cardiotoxicity

- Dexrazoxane (reduces free radicals)
- Prophylactic beta blockers and/or ACEI
- Atorvastatin
- Agents showing promise in animal models
  - Phosphodiesterase inhibitors
  - Iloprost
Carvedilol prevents Anthracycline Cardiotoxicity

Black bars: baseline
White bars: after ADR (525 mg/m2)

N=25 for both groups
Carvedilol 12.5 bid vs placebo

ACE Inhibitors prevent LV dysfunction after chemotherapy

- 114 patients with positive Troponin I 72 hours after chemotherapy
- Enalapril 20/d vs placebo
- Effect greater in patients with persistent troponin elevation (white boxes)

Treatment of anthracycline cardiotoxicity

Figure 1: Percentage of Responders According to the Time Elapsed From AC Administration and Start of HF Therapy

AC = anthracyclines; HF = heart failure.

Figure 2: Cumulative Cardiac Event Rate During the Study Follow-Up

2-year Kaplan-Meier analysis for major adverse cardiac events in the 3 study groups. p = 0.0003 (log-rank test).

### Risk of Death from CHD in irradiated breast cancers

<table>
<thead>
<tr>
<th>Years since breast cancer diagnosis</th>
<th>No radiotherapy</th>
<th>Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of deaths left/right</td>
<td>Mortality ratio, left-sided vs right-sided (95% CI)</td>
</tr>
<tr>
<td>Death from heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>2164/1972</td>
<td>1.03 (0.97–1.09)</td>
</tr>
<tr>
<td>5–9</td>
<td>1632/1479</td>
<td>1.05 (0.98–1.13)</td>
</tr>
<tr>
<td>10–14</td>
<td>806/758</td>
<td>1.01 (0.91–1.11)</td>
</tr>
<tr>
<td>≥15</td>
<td>568/524</td>
<td>1.02 (0.91–1.15)</td>
</tr>
<tr>
<td>Death from all other known causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>14775/13522</td>
<td>1.04 (1.01–1.06)</td>
</tr>
<tr>
<td>5–9</td>
<td>8009/7863</td>
<td>0.97 (0.94–1.00)</td>
</tr>
<tr>
<td>10–14</td>
<td>3472/3343</td>
<td>0.99 (0.94–1.04)</td>
</tr>
<tr>
<td>≥15</td>
<td>2106/2040</td>
<td>0.98 (0.92–1.04)</td>
</tr>
</tbody>
</table>

Darby et al.  Lancet Oncology 2005; 6:557
Risk of coronary events is related to cardiac radiation dose

Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

Darby et al. NEJM 2013; 368:987-98
Table 3. Percentage Increase in the Rate of Major Coronary Events per Gray, According to Time since Radiotherapy.

<table>
<thead>
<tr>
<th>Time since Radiotherapy*</th>
<th>No. of Case Patients</th>
<th>No. of Controls</th>
<th>Increase in Rate of Major Coronary Events (95% CI)†</th>
<th>% increase/Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 4 yr</td>
<td>206</td>
<td>328</td>
<td>16.3 (3.0 to 64.3)</td>
<td></td>
</tr>
<tr>
<td>5 to 9 yr</td>
<td>216</td>
<td>296</td>
<td>15.5 (2.5 to 63.3)</td>
<td></td>
</tr>
<tr>
<td>10 to 19 yr</td>
<td>323</td>
<td>388</td>
<td>1.2 (−2.2 to 8.5)</td>
<td></td>
</tr>
<tr>
<td>≥20 yr</td>
<td>218</td>
<td>193</td>
<td>8.2 (0.4 to 26.6)</td>
<td></td>
</tr>
<tr>
<td>0 to ≥20 yr</td>
<td>963</td>
<td>1205</td>
<td>7.4 (2.9 to 14.5)</td>
<td></td>
</tr>
</tbody>
</table>

Darby et al. NEJM 2013; 368:987-98
## Cause of death in elderly patients with breast cancer

### Women Age 67-79 Years

<table>
<thead>
<tr>
<th>Mortality</th>
<th>DCIS (n = 4,798)</th>
<th>Stage I (n = 14,765)</th>
<th>Stage II (n = 8,539)</th>
<th>Stage III/IV (n = 2,923)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5-year mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%*</td>
<td>11</td>
<td>13</td>
<td>26</td>
<td>70</td>
</tr>
<tr>
<td>95% CI</td>
<td>10 to 12</td>
<td>13 to 14</td>
<td>25 to 27</td>
<td>69 to 72</td>
</tr>
<tr>
<td>No.</td>
<td>513</td>
<td>1,960</td>
<td>2,227</td>
<td>2,058</td>
</tr>
<tr>
<td><strong>Cause of death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>7</td>
<td>18</td>
<td>47</td>
<td>76</td>
</tr>
<tr>
<td>95% CI</td>
<td>5 to 10</td>
<td>16 to 20</td>
<td>45 to 49</td>
<td>74 to 78</td>
</tr>
<tr>
<td>Other cancers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>25</td>
<td>20</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>95% CI</td>
<td>22 to 29</td>
<td>18 to 22</td>
<td>9 to 12</td>
<td>6 to 8</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>27</td>
<td>26</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>95% CI</td>
<td>23 to 31</td>
<td>24 to 28</td>
<td>16 to 19</td>
<td>7 to 9</td>
</tr>
</tbody>
</table>
Obesity as a risk factor for breast cancer

- Data strongest and most consistent for postmenopausal breast cancers
  - Most cancers are estrogen receptor positive
  - Increased estrogen production due to increased expression of aromatase in adipose tissue
- ? role of inflammation
- ? Role of dysregulated metabolism
  - Elevated insulin, IGF-2, leptin
  - Decreased levels of adiponectin
Breast cancer survival and BMI

Physical activity and breast cancer

- Increasing fitness level is associated with decreased risk of developing breast cancer.
- Most patients decrease physical activity after a diagnosis of breast cancer (2 hrs/week).
- Observational studies have demonstrated a consistent reduction in cancer-specific mortality with exercise.
Fitness and likelihood of dying of breast cancer

- **Mortality Rate per 10,000 woman-years**
  - <8.0: 5
  - 8.0-8.9: 4
  - 9.0-9.9: 3
  - ≥10.0: 2

- **Linear trend** $P = 0.007$

Physical activity after breast cancer diagnosis and mortality

Holmes et al. JAMA 2005:293:2479
## Exercise and cancer-specific mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Cohort/Setting</th>
<th>Risk Reduction</th>
<th>Physical Activity Dose</th>
<th>Dose Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borugian et al, 2004</td>
<td>603</td>
<td>Breast cancer patients after surgery before the start of adjuvant treatment</td>
<td>1.0 (multi-variate adjusted relative risk) Exercise was not associated with breast cancer mortality</td>
<td>&gt;1 time/wk</td>
<td>No</td>
</tr>
<tr>
<td>Holmes et al, 2005</td>
<td>2,987</td>
<td>Stages I-III breast cancer; Nurses' Health Study</td>
<td>0.5 (multi-variate adjusted relative risk)</td>
<td>9–14.9 MET-h/wk</td>
<td>No</td>
</tr>
<tr>
<td>Pierce et al, 2007</td>
<td>1,490</td>
<td>Stages I-IIa breast cancer; Women's Healthy Eating and Living Study</td>
<td>0.58</td>
<td>≥1,320–6,420 MET-min/wk</td>
<td>Yes</td>
</tr>
<tr>
<td>Holick et al, 2008</td>
<td>4,482</td>
<td>Invasive breast cancer free of recurrence &gt;2 yr since diagnosis</td>
<td>0.51 (multi-variate adjusted relative risk) (P &lt; .05)</td>
<td>≥21 MET-h/wk</td>
<td>Yes</td>
</tr>
<tr>
<td>Irwin et al, 2008</td>
<td>933</td>
<td>Breast cancer survivors; Health, Eating, Activity, and Lifestyle Study</td>
<td>0.65 (multi-variate adjusted relative risk)</td>
<td>≥9 MET-h/wk</td>
<td>Yes</td>
</tr>
<tr>
<td>Dal Maso et al, 2008</td>
<td>1,453</td>
<td>Invasive breast cancer survivors</td>
<td>0.85 (multi-variate adjusted relative risk)</td>
<td>≥2 h/wk</td>
<td>NA</td>
</tr>
<tr>
<td>Sternfeld et al, 2009</td>
<td>1,970</td>
<td>Stages I-IIa breast cancer; Life After Cancer Epidemiology</td>
<td>0.69 (multi-variate adjusted relative risk)</td>
<td>3–&lt;6 h/wk moderate activity</td>
<td>No</td>
</tr>
<tr>
<td>Chen et al, 2011</td>
<td>4,826</td>
<td>Stages I-III breast cancer, 6 mo after diagnosis; Shanghai Breast Cancer Survival Study</td>
<td>0.60 (multi-variate adjusted relative risk)</td>
<td>≥2 times/wk (P &lt; .05)</td>
<td>Yes</td>
</tr>
<tr>
<td>Irwin et al, 2011</td>
<td>4,643</td>
<td>Invasive breast cancer survivors; Women's Health Initiative</td>
<td>0.60 (multi-variate adjusted relative risk)</td>
<td>≥9 MET-h/wk (P &lt; .05)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

71 year old with stage 1 triple negative breast cancer

Onco-cardiology recommendations

- **To prevent cardiotoxicity**
  - Change diltiazem to carvedilol
  - Echocardiogram within 3 months of last dose of adriamycin

- **To prevent CAD**
  - Aggressive lipid lowering treatment (LDL <70)
  - Weight loss
  - Exercise
Some cancers that were once uniformly fatal are now cured in nearly all cases. Many of those who get common cancers become long term survivors. Other people may be living with a cancer that is controlled but not cured. All of these individuals can be considered survivors of their disease, and also of their treatment.”