Cancer survivors and cardiovascular disease

Project ideas for the survivorship cohort

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Cancer and cardiovascular disease
# Shared risk factors

<table>
<thead>
<tr>
<th>Cardiovascular disease</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Smoking</td>
</tr>
<tr>
<td>Body mass index</td>
<td>Obesity</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Physical activity</td>
</tr>
<tr>
<td>Diet</td>
<td>Diet</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Radiation</td>
</tr>
<tr>
<td>Glucose</td>
<td>Infection</td>
</tr>
</tbody>
</table>

http://www.cancer.gov/cancer_topics/pdq/prevention/overview/patient/page3
http://mylifecheck.heart.org/multitab.aspx?navid=3&culturecode=en-us
## The Simple 7

### Poor Health

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Yes</th>
<th>Ideal Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>≥30 kg/m²</td>
<td>&lt;25 kg/m²</td>
</tr>
<tr>
<td>Physical activity</td>
<td>No minutes/week of</td>
<td>≥150 min mod, ≥75 min vig, or ≥150 min mod + vig</td>
</tr>
<tr>
<td></td>
<td>moderate or vigorous</td>
<td></td>
</tr>
<tr>
<td>Healthy diet score</td>
<td>0 – 1 components</td>
<td>4 – 5 components</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>≥240 mg/dL</td>
<td>&lt;200 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>SBP ≥140 mmHg or DBP ≥90 mmHg</td>
<td>SBP &lt;120 mmHg and DBP &lt;80 mmHg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥126 mg/dL</td>
<td>&lt;100 mg/dL</td>
</tr>
</tbody>
</table>

### Ideal Health

<table>
<thead>
<tr>
<th>Former ≤ 12 months</th>
<th>≥25 - 29.9 kg/m²</th>
<th>≥150 min mod, ≥75 min vig, or ≥150 min mod + vig</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-149 min mod, 1-74 min vig, or 1-149 min mod + vig</td>
<td>≥25 - 29.9 kg/m²</td>
<td>≥150 min mod, ≥75 min vig, or ≥150 min mod + vig</td>
</tr>
<tr>
<td>2 - 3 components</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 - 5 components</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200-239 mg/dL or treated to goal</td>
<td>≤25 kg/m²</td>
<td>≥150 min mod, ≥75 min vig, or ≥150 min mod + vig</td>
</tr>
</tbody>
</table>

### Ideal Health

http://mylifeccheck.heart.org/multtab.aspx?navid=3&culturecode=en-us
The Simple 7: healthy diet score

1) \( \geq 4.5 \) cups per day of **fruits and vegetables**

2) \( \geq 2 \) servings of **fish** weekly

3) \( \geq 3.5 \) ounces of **whole grains** daily

4) \(< 36 \) ounces of beverages with **added sugar** weekly

5) \( \leq 1,500 \) mg of **sodium** daily
The Simple 7 and cardiovascular disease

- Number of factors at “ideal” levels (0-7)
  - Most commonly used (examples follow) since “intermediate” data may be missing
- Continuous score (0 for poor, 1 for intermediate, 2 for ideal; range 0-14)
  - Stroke Prevention in Healthcare Delivery Environments (SPHERE)
- Categorical score [inadequate (0-4), average (5-9), or optimum (10-14) cardiovascular health]
  - Lower score predicts higher risk of incident stroke in the REGARDS study

Shared risk factors (Simple 7) and incident disease: WHI data

Additionally controlling for age, race/ethnicity, education, marital status, and family history of CVD.
The Simple 7 and incident cancer

 Ideal Cardiovascular Health Is Inversely Associated With Incident Cancer: The Atherosclerosis Risk in Communities Study
Laura J. Rasmussen-Torvik, Christina M. Shay, Judith G. Abramson, Christopher A. Friedrich, Jennifer A. Nettleton, Anna E. Prizment and Aaron R. Folsom

*Circulation. 2013;127:1270-1275; originally published online March 18, 2013; doi: 10.1161/CIRCULATIONAHA.112.001183

Figure 1. Survival curves for combined cancer incidence by total number of ideal health metrics, Atherosclerosis Risk in Communities Study (ARIC), 1987 to 2006.
Shared *lifestyle* factors

**Ideal Cardiovascular Health Is Inversely Associated With Incident Cancer: The Atherosclerosis Risk in Communities Study**
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**Figure 2.** Hazard ratios* of combined cancer according to the number of ideal health behaviors and ideal health factors. Atherosclerosis Risk in Communities Study (ARIC), 1987 to 2006. *All hazard ratios are adjusted for age, sex, race, and ARIC study center. The referent category (farthest left) is participants having 0 ideal health factors (blood pressure, blood sugar, and total cholesterol) and 0 ideal health behaviors (diet, smoking, physical activity, and body mass index) at baseline. Across all categories of ideal health factors, the hazard ratio for combined cancer incidence in individuals with 3 to 4 ideal health behaviors compared with those with 0 ideal health behaviors was significantly <1.*
Shared risk factors: FOCUS data (4-14 year survivors)

Cardiovascular risk factors among long-term survivors of breast, prostate, colorectal, and gynecologic cancers: a gap in survivorship care?

Kathryn E. Weaver · Randi E. Foraker · Catherine M. Alfano · Julia H. Rowland · Neeraj K. Arora · Keith M. Bellizzi · Ann S. Hamilton · Ingrid Oakley-Girvan · Gretchen Keel · Noreen M. Aziz

![Graph showing cardiovascular risk factors among long-term survivors of breast, prostate, colorectal, and gynecologic cancers](image-url)
Effect of cardio-toxic treatments on the risk of cardiovascular disease among breast cancer survivors
Figure 1  The “Multiple-Hit” Hypothesis

A schematic representation describing the “multiple-hit” hypothesis. At diagnosis, a significant proportion of early breast cancer patients present with pre-existing or heightened cardiovascular disease (CVD) risk factors, which increase the risk of adjuvant therapy-associated cardiovascular injury. Independently, many adjuvant therapies used in breast cancer are associated with unique and varying degrees of direct adverse effects on the cardiovascular system. These direct effects occur in the context of concomitant lifestyle perturbations (indirect effects) that combine to reduce cardiovascular reserve. Collectively, these changes may leave the patient more susceptible to further cardiovascular insults and at higher risk of premature death due to cardiovascular mortality.
Cardio-toxic breast cancer treatments

- Anthracyclines
- Alkylating agents (Cisplatin, Cyclophosphamide)
- Microtubule-targeting drugs (Taxanes)
- Antimetabolites (Fluorouracil, Capecitabine, Methotrexate)
- Radiotherapy
- Endocrine therapy (Tamoxifen, Aromatase inhibitors)
- Angiogenesis inhibitors (Bevacizumab)
## Study design elements

<table>
<thead>
<tr>
<th>Cohort study</th>
<th>Nested case-control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women free of CVD at the time of breast cancer diagnosis</td>
<td>Women with breast cancer</td>
</tr>
<tr>
<td>Time-to-CVD data by receipt of cardio-toxic treatment (Y/N)</td>
<td>Cases with CVD, controls without CVD</td>
</tr>
<tr>
<td>Important covariates: age, race, family history of CVD</td>
<td>Assess odds of receipt of cardio-toxic treatment (Y/N)</td>
</tr>
<tr>
<td>Simple 7 as an effect measure modifier (EMM)*</td>
<td></td>
</tr>
</tbody>
</table>

*EMM: Effect Measure Modifier
*Simple 7 as an EMM

- Elements of the Simple 7 may be on the causal path from cardio-toxic treatments to CVD (Table 1)
- Cardio-toxic treatments may have distinct effects on CVD risk among those with pre-existing risk factors

**Table 1**

<table>
<thead>
<tr>
<th>Adjuvant Therapy Polychemotherapy</th>
<th>Short-Term Effects</th>
<th>Long-Term Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Atrial and ventricular arrhythmias</td>
<td>Progressive decrease in left ventricular function, often leading to overt heart failure</td>
</tr>
<tr>
<td></td>
<td>Pericarditis/myocarditis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduced ejection fraction, cardiomyopathy, death</td>
<td></td>
</tr>
</tbody>
</table>

- Alkylating agents
  - Cisplatin
    - Myocardial ischemia/infarction
    - Hypertension
    - Heart failure
    - Arrhythmias
    - Heart block
    - Endocardial fibrosis
  - Cyclophosphamide
    - Pericarditis/myocarditis
    - Heart failure
    - Atrial ectopy
    - Bradycardia

**Reference**

Questions

- What effect size is to be expected? (How many breast cancer survivors develop CVD in the WHI?)
- Will detailed treatment data be available (see slide #12)? Should we consider additional treatments?
- How should we treat the Simple 7 (high/low risk; high/med/low risk)?
Effect of physical activity on the risk of all-cause mortality among cancer survivors
For each 1-unit ↑ in METs, there is a 17% ↓ risk of death from all causes

Gulati, M et al. NEJM 2005;353:468-75
Few women meet physical activity guidelines

- Only 16% of women met physical activity guidelines in 2008
  - 19% of white women
  - 11% of black women
- Up to 90% of breast cancer survivors post-treatment do not exercise regularly

Source: National Health Interview Survey, 2010
Study design elements

- Cohort study

- Time-to-death data by level of physical activity at the time of cancer diagnosis

<table>
<thead>
<tr>
<th>Physical activity</th>
<th>Poor Health</th>
<th>Intermediate Health</th>
<th>Ideal Health</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No minutes/week of moderate or vigorous</td>
<td>1-149 min mod, 1-74 min vig, or 1-149 min mod + vig</td>
<td>≥150 min mod, ≥75 min vig, or ≥150 min mod + vig</td>
</tr>
</tbody>
</table>

- Important covariates: age, race, medical history, family history of CVD, self-rated health

- Simple 7 as an effect measure modifier (EMM)*
Questions? Suggestions?
Project ideas for the survivorship cohort

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