Cardiovascular Disease Prevention in Cancer Survivors

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Disclosures

• I do not have any conflicts of interest.
Introduction

• Over 10 years, preventive and non-invasive General Cardiology (Madison, WI)

• Joined the Lynn Women’s Institute Preventive Cardiology Program, January 2020
  – Collaboration with Lynn Cancer Institute, Primary Care, Cardiology, Ob/Gyn & Other Specialties
Objectives

1) Describe population trends for incident cardiovascular disease (CVD) among cancer survivors

2) Discuss the prevalence of cardiovascular disease risk factors among cancer survivors

3) Summarize best-practice recommendations for CVD risk assessment and longitudinal risk factor management for cancer survivors

4) Explain the importance of a collaborative healthcare team to decrease CVD events among cancer survivors
Objectives

1) Describe population trends for incident cardiovascular disease (CVD) among cancer survivors

2) Discuss the prevalence of cardiovascular disease risk factors among cancer survivors

3) Summarize best-practice recommendations for CVD risk assessment and longitudinal risk factor management for cancer survivors

4) Explain the importance of a collaborative healthcare team to decrease CVD events among cancer survivors

This talk will NOT focus on management of Cardiotoxicity.
16.9 million cancer survivors

67% of survivors living 5+ years

45% of survivors living 10+ years

10-year relative survival rates:
Invasive breast cancer: 83%
Prostate: 98%

Growing Prevalence of US Cancer Survivors

TOP TWO KILLERS

By AMERICAN HEART ASSOCIATION NEWS

The total number of Americans dying from heart disease rose in recent years following decades in decline. Cancer deaths have nearly tripled since 1950 and continue to climb.

Source: Centers for Disease Control and Prevention
Published Aug. 24, 2016
RAISING AWARENESS

- Ischemic heart disease
- Stroke
- Heart failure
• Retrospective cohort study to describe the magnitude of CVD risk among survivors
  – incidence of late-occurring CVD after therapy completion

• Kaiser Permanente Southern California Surveillance, Epidemiology, and End Results (SEER)-affiliated cancer registry (n=36,232)

• ≥40 years old at cancer diagnosis (2000-2007), with at least 2 years of survival data

• IRR = Incidence Rate Ratios
  – Ischemic heart disease, stroke, cardiomyopathy/heart failure
  – compared to age-, sex-, ZIP code–matched non-cancer controls

## Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study

Saro H. Armenian, Lanfang Xu, Bonnie Ky, Canlan Sun, Leonardo T. Farol, Sumanta Kumar Pal, Pamela S. Douglas, Smita Bhatia, and Chun Chao

### Table 1. Study Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cancer Survivors* (N = 36,232)</th>
<th>Noncancer Controls* (N = 73,545)</th>
<th>P</th>
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<td>Age at diagnosis, years</td>
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<td>Range</td>
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<td>Sex, No. (%)</td>
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<td>19,055 (52.6)</td>
<td>39,225 (63.3)</td>
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<td>Race/ethnicity, No. (%)</td>
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<td>Hispanic</td>
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<td>Other/unknown</td>
<td>72 (0.2)</td>
<td>9,129 (12.4)</td>
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<td>Follow-up time from index date, years</td>
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<td>Yes</td>
<td>15,730 (43.4)</td>
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<td>Smoking, No. (%)†</td>
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<td>Never</td>
<td>24,368 (67.3)</td>
<td>58,045 (78.9)</td>
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<tr>
<td>Ever</td>
<td>11,864 (32.7)</td>
<td>15,500 (21.1)</td>
<td>—</td>
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</table>

• Magnitude of CVD risk varied among cancer survivors
  – Breast cancer: IRR 1.13
  – Multiple myeloma: IRR 1.70
  – Lung/bronchus carcinoma: IRR 1.58
  – Non-Hodgkin lymphoma: IRR 1.41
All p=0.01

• Cancer survivors with ≥2 CVD RFs
  – IRR: 1.83 to 2.59

All-cause Mortality, Cancer Survivors and Non-cancer Cohort by CVD Status

Survival was worse among cancer survivors who developed CVD:
- 5 yr. survival: 75%; 8 yr. survival: 60%

Survivors without CVD (87% and 81%, respectively)

A population-based study of cardiovascular disease mortality risk in US cancer patients

- The Surveillance, Epidemiology, and End Results (SEER), 1973-2015, Penn State Cancer Institute
  - Last cohort entry: 2012, at least 3 years of follow-up
  - “Modern treatment era”: 2000-2015

- 3,234,256 cancer patients among 28 cancer sites

- Incidence of: heart disease, hypertension, cerebrovascular disease, atherosclerosis, and aortic aneurysm/dissection

<table>
<thead>
<tr>
<th></th>
<th>No. of cancer patients</th>
<th>Index-cancer deaths</th>
<th>CVD deaths</th>
<th>Heart disease deaths</th>
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<td>% of cancer patients</td>
<td>No.</td>
<td>% of cancer patients</td>
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<td>576,811</td>
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<td>60–79 years</td>
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<td>20,794</td>
<td>67,404</td>
<td>15.9</td>
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<td>98,579</td>
<td>18,723</td>
<td>7.9</td>
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<td>224,723</td>
<td>91,850</td>
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<td>Stage at presentation</td>
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<td>Localized</td>
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<td>Regional</td>
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<td>282,521</td>
<td>65,304</td>
<td>10.3</td>
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<td>Distant</td>
<td>528,923</td>
<td>389,794</td>
<td>25,220</td>
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<td>Months since diagnosis</td>
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<td></td>
<td></td>
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<tr>
<td>2–11 months</td>
<td>3,234,256</td>
<td>519,279</td>
<td>45,592</td>
<td>1.4</td>
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<td>12–59 months</td>
<td>2,533,198</td>
<td>498,282</td>
<td>105,581</td>
<td>4.2</td>
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<td>60–179 months</td>
<td>1,493,858</td>
<td>176,561</td>
<td>148,842</td>
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<td>180–239 months</td>
<td>490,191</td>
<td>20,554</td>
<td>34,398</td>
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<td>240+ months</td>
<td>257,961</td>
<td>13,652</td>
<td>31,276</td>
<td>12.1</td>
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</tbody>
</table>
• 1 in 10 cancer survivors – fatal CVD event
• Higher than the US average (11.3%):
  – Urinary bladder: 19.4%
  – Larynx: 17.3%
  – Prostate: 16.6%
  – Corpus uteri (endometrial): 15.6%
  – Colorectal: 13.7%
  – Breast: 11.7%

• Standardized mortality ratios (SMRs):
  – observed number of deaths in the study population compared to the expected number of deaths, based on the age- and sex-specific rates in the population
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  – observed number of deaths in the study population compared to the expected number of deaths, based on the age- and sex-specific rates in the population

• <85 years old (all sites) have an increased risk of CVD death compared to men and women in the general population

• The younger a cancer survivor is diagnosed (all sites), the higher their risk of CVD-related death

• Endometrial cancer has the greatest risk of mortality from heart disease at all time points following a diagnosis.

• Breast, melanoma, and prostate cancer – ongoing elevated risk of CVD mortality starting after the first year of diagnosis.
Cancer patients, survivors face increased risk of heart disease deaths


- Identify subgroups of cancer patients at greatest risk of fatal CVD compared to:
  (1) the general population
  (2) other cancer patients during the study time

- n= 7,529,481 cancer patients
CVD death, By Cancer Site

- All sites after diagnosis:
  - SMR at 1–5 years: 1.93 (95% CI: 1.91 - 1.95)
  - SMR at >10 years: 2.73 (95% CI: 2.7 - 2.75)
• <40 yrs. old: breast cancer and lymphoma
• ≥40 yrs. old: prostate, colon/rectum, breast, lung

CVD risk increases with survivorship time

10+ yrs. of follow-up, greater risk of death from CVD than from primary cancer: prostate, colon/rectum, bladder, melanoma, kidney, endometrial, oral cavity/pharynx

Cardiovascular Disease Among Cancer Survivors

- Significant improvements in cancer survivorship are challenged by:
  - an increased prevalence of CVD morbidity & mortality
  - ischemic heart disease, stroke, heart failure, valve

- Cancer survivors have a higher risk of CVD than the general population

- Early identification of individuals at higher risk for CVD is critical for supporting cancer survivorship

Three mechanisms:
1. Inflammatory/oxidative cancer biology
2. Short- and long-term cardiotoxic treatment effects
3. Shared risk factors for CVD and cancer
Mechanisms of CVD Among Cancer Survivors

Three mechanisms:
1. Inflammatory/oxidative cancer biology
2. Short- and long-term cardiotoxic treatment effects
3. Shared risk factors for CVD and cancer
Inflammation, cardiovascular disease, and cancer: a common link with far-reaching implications

Chronic inflammation: shapes the “early tumor microenvironment...promoting cancer initiation and development”.

Mechanisms of CVD Among Cancer Survivors

Three mechanisms:

1. Inflammatory/oxidative cancer biology
2. Short- and long-term cardiotoxic treatment effects
3. Shared risk factors for CVD and cancer
   - Genetic, metabolic, and inflammatory
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1. Inflammatory/oxidative cancer biology
2. Short- and long-term cardiotoxic treatment effects
3. Shared risk factors for CVD and cancer
   - Genetic, metabolic, and inflammatory
Cancer and CVD: Shared Modifiable Risk Factors

Inflammation & oxidative stress

Multiplicative Risk:
Cancer +
Each Additional Shared Risk Factor

Bidirectional Risk

Cancer
Cardiovascular Disease

Shared Modifiable Risk Factors
- Tobacco
- Obesity
- Physical Inactivity
- Poor Nutrition
- Alcohol
- Diabetes Mellitus
- Hypertension*
- Hyperlipidemia*
## Shared Modifiable CVD and Cancer Risk Factors

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<th>Risk Factor</th>
<th>Breast</th>
<th>Prostate</th>
<th>Lung</th>
<th>Colorectal (colon)</th>
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<td>Physical activity</td>
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<td>Unhealthy diet</td>
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<tr>
<td>Obesity</td>
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<td></td>
<td>▲</td>
<td>▲ (w) ▲▲ ▲ (m)</td>
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<td>Diabetes</td>
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<td>Hypertension</td>
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<tr>
<td>Tobacco smoking</td>
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<td>▲▼</td>
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</tr>
</tbody>
</table>

w = women; m = men. Hazard ratios (HR): ▼▼ HR 0.6–0.79, ▼ HR 0.80–0.99, ▲ HR 1.01–1.19, ▲▲ HR 1.20–1.39, ▲▲▲ HR ≥1.40,
AHA SCIENTIFIC STATEMENT

Cardiovascular Disease and Breast Cancer: Where These Entities Intersect
A Scientific Statement From the American Heart Association

Cancer Survivors: Hypertension

• Most common cardiovascular comorbidity among cancer survivors: 37%

• Several cancers and cancer-related treatments directly cause hypertension
  – high risk of developing new or worsening HTN
  – home blood pressure monitoring

• Increase in blood pressure has been shown to predict efficacy of cancer treatment

• n=2,943 patients with non-metastatic breast cancer without prior CVD

• Stage I to III invasive breast cancer with abdominal CT at diagnosis

• Outcomes:
  – acute myocardial infarction, ischemic stroke, heart failure
  – composite end point (any above +/- coronary revascularization +/- CVD-related deaths)

Incident CVD Events: The Decade after a Non-metastatic Breast Cancer Diagnosis

A. 15% by year 10

B. Visceral

C. Subcutaneous

D. Intramuscular

Models are accounting for competing risks, adjusted for: age, race/ethnicity, cancer stage, estrogen receptor/progesterone receptor, human epidermal growth factor receptor 2 status, type of chemotherapy (none, anthracycline containing, or other), smoking history, diabetes, hypertension, and dyslipidemia.
• Significant others of cancer survivors:
  – Have persistent psychological stress
  – Also at increased risk for CVD

• n=1,026 survivor-spouse dyads
  – Survivors ≥18 years old, self-reported cancer

• 2010-2015 (MEPS) Medical Expenditure Panel Survey
A Prevalence of the CVD and CVD risk factors

- Other heart disease: 18.95% (Survivor), 15.59% (Spouse)
- Coronary heart disease: 11.65% (Survivor), 9.14% (Spouse)
- Heart attack: 9.46% (Survivor), 6.07% (Spouse)
- Stroke: 8.71% (Survivor), 6.16% (Spouse)
- Angina: 4.83% (Survivor), 3.34% (Spouse)
- High blood pressure: 55.04% (Survivor), 50.76% (Spouse)
- High cholesterol: 54.32% (Survivor), 49.61% (Spouse)
- Diabetes: 18.45% (Survivor), 16.00% (Spouse)

B Prevalence of health behaviors

- Currently non-smoking: 88.66% (Survivor), 90.01% (Spouse)
- Active physical activity: 46.21% (Survivor), 50.68% (Spouse)
- Normal weight (18.5 <= BMI < 25): 30.27% (Survivor), 28.42% (Spouse)
- Overweight (25 <= BMI < 30): 39.05% (Survivor), 38.01% (Spouse)
- Obese (BMI >= 30): 29.44% (Survivor), 32.30% (Spouse)
CVD Prevention Among Cancer Survivors

Longitudinal Multidisciplinary Focus

A. (Healthy heart patient or patient with CV risk factors)

B. (Patient with heart disease (eg., CAD, HF stage B-D, valvular disease))

- CV risk factor management (Primary CVD prevention)
- Precancer-treatment CV risk stratification, decision about CV risk and management with respect to chosen cancer therapy
- On treatment CV monitoring, preventive CV interventions for high-risk patients
- Long-term CV monitoring, preventive CV interventions for high-risk patients

Evidence-based treatment of CV disease and CV risk factors (Primary and secondary CVD prevention)

Multidisciplinary decision about cancer therapy choice with respect to CV risk stratification and treatment plan

Parallel CV and cancer treatment cardiotoxicity monitoring

Heart disease management and CV monitoring, interventions to reduce long-term CV effects

Ellahham SH. Amer Coll of Card. Expert Analysis. October 2019
### Assessment of cardiovascular risk

- Baseline data
- Medical and family history
- Symptoms of CVD
- Physical examination including blood pressure, waist circumference, weight, and cardiovascular and pulmonary assessment
- Laboratory tests including lipids, Lp(a), hs-CRP, fasting serum insulin level, and glucose
- 10-year risk of atherosclerosis and CVD
- Depression screening
- Menopausal status
- EKG and evaluation of LV function by echocardiography or cardiac magnetic resonance
- Baseline biomarkers (NT-proBNP and BNP)

### Management goals

- Referral to cardiology
  - For known CVD
  - For decreased LV function
  - For monitoring and treatment with carvedilol and/or ACE inhibitors
- Lifestyle behaviors
- Lipid management
  - LDL < 100 mg/dL (< 70 mg/dL for high-risk patients)
  - Total cholesterol < 200 mg/dL
  - HDL > 40 mg/dL for men, > 50 mg/dL for women
  - Triglycerides < 150 mg/dL
  - hs-CRP < 1 mg/dL
- Blood pressure management
  - Normal < 120/80 mmHg
  - < 35 inches for women
  - < 40 inches for men
- Maintain glucose < 100 mg/dL
- Insulin < 15 mg/dL or HgA1c < 5.7 mg/dL

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### Long-term surveillance following cardiotoxic cancer treatment

- Annual cardiology assessment to determine LV function either by echocardiography or cardiac magnetic resonance
- Lipid profile
- Glucose
- Insulin or HgA1c
- Waist circumference
- Weight
- Blood pressure
- Assessment of lifestyle behavior
Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography

Summary

• Increased prevalence of cancer survivors in the US

• The gain in life expectancy for cancer survivors is compromised by higher rates of CVD morbidity and mortality

• Ongoing research on the overlap of inflammatory mechanisms for cancer and CVD
Summary

• Known overlap of risk factors for CVD and cancer

• Risk of CVD morbidity and fatal CVD is higher among survivors than the general population

• Most effective strategy for primary prevention of CVD among survivors is:
  – Optimizing and monitoring CVD risk factors
  – Surveillance and management of subclinical and advanced CVD
Preventive Cardiology in Cancer Survivorship

• Long-term cancer survivorship care
  – Advancing preventive area within Cardio-Oncology
  – Growing recommendations for CVD surveillance and prevention
  – Additional research is needed

• Requires multidisciplinary, longitudinal survivorship care
THANK YOU!

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Time-Varying Analysis (1973 - 2012)

Influenced by:
- Cancer screening
- Cancer incidence

Patients diagnosed with this cancer this year

Influenced by:
- Cancer prevalence

Cancer patients alive from previous calendar year(s)

Calendar year

Influenced by:
- All other factors
- Success of treatment(s)

Patients living to next calendar year

Patient death from:
-- Index cancer
-- Non-index cancer
  -- Cardiovascular causes*
  -- Non-cardiovascular medical causes

Influenced by:
- Cancer aggressiveness and follow-up time
- Treatment aggressiveness and follow-up time
- How death is coded (e.g. from cancer or treatment for cancer)
- Common risk factors among cancers and comorbidities (e.g. tobacco)
- Patient age (i.e. higher chance of death with higher age)