Breast Cancer and the Heart

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- No disclosures

Objectives

- Discuss cardiac complications from cancer treatments
- Strategies to protect the heart during and after cancer treatment
- Ongoing research

Background

- The cardiotoxicity of anticancer agents can lead to significant complications
- As more and more patients are treated and cured of their malignancies, it is critical for cancer survivors to limit comorbid illnesses
- Some studies suggest cancer survivors will actually be at as great a risk from cardiac disease as from recurrent cancer

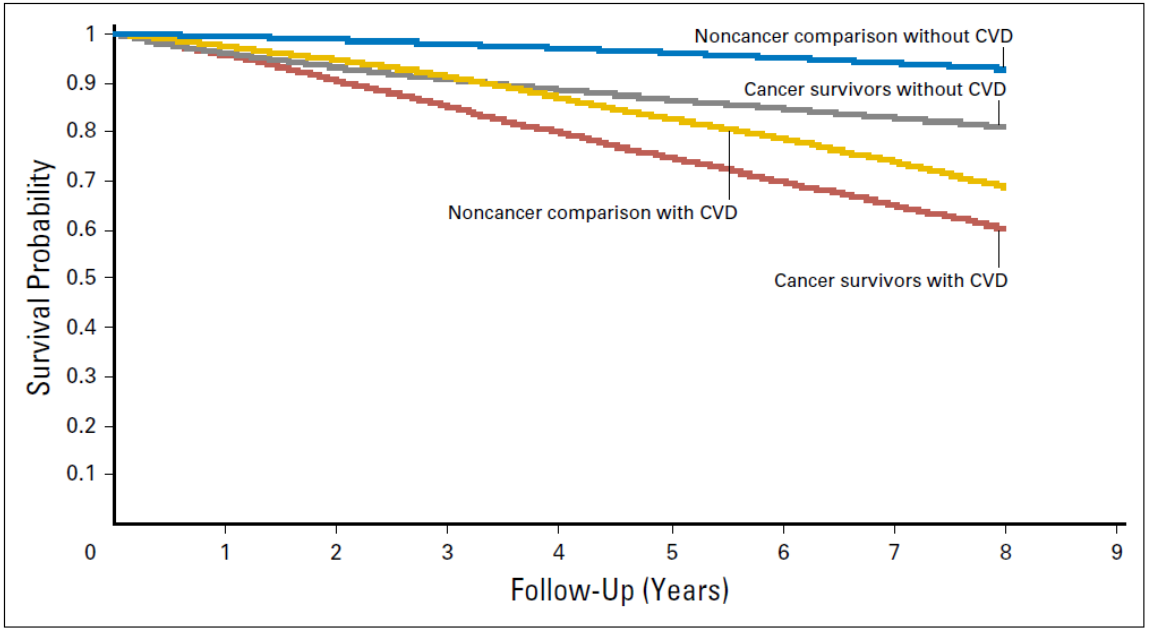


Fig 1. All-cause mortality in cancer survivors and noncancer comparison cohort by cardiovascular disease (CVD) status.

Armenian S, JCO 2017

- Breast cancer (IRR, 1.13; P < .01) had significantly higher CVD risk when compared with noncancer controls
- Cancer survivors with two or more CVRFs had the highest risk of CVD when compared with noncancer controls with less than two CVRFs (IRR, 1.83 to 2.59; P < .01)

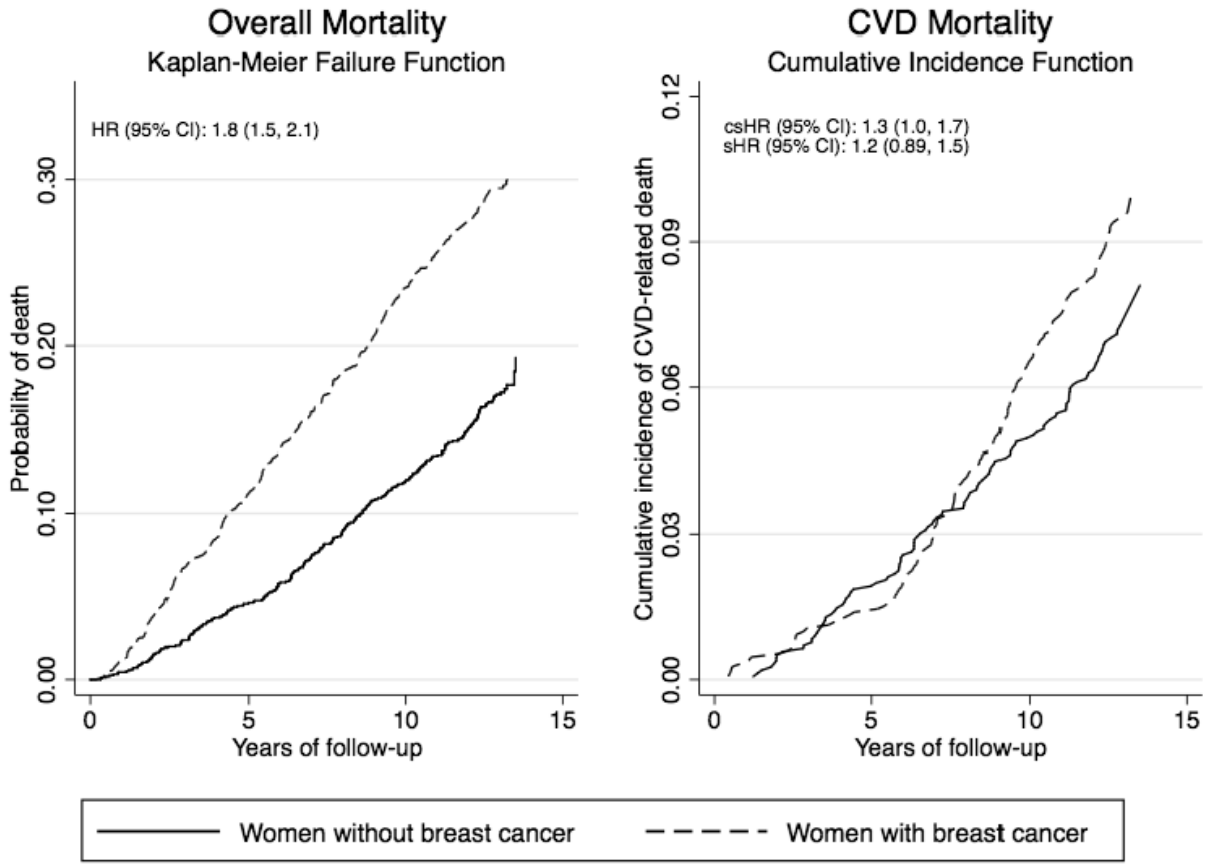


Figure 1.

Unadjusted Kaplan-Meier failure curves and adjusted hazard ratios (HR) for overall mortality (first panel) and cumulative incidence function, cause-specific HR (csHR) and subdistribution HR (sHR) for CVD-related mortality (second panel) among a population-based sample of breast cancer survivors and age-matched women without breast cancer. The Long Island Breast Cancer Study, 1996-2009.

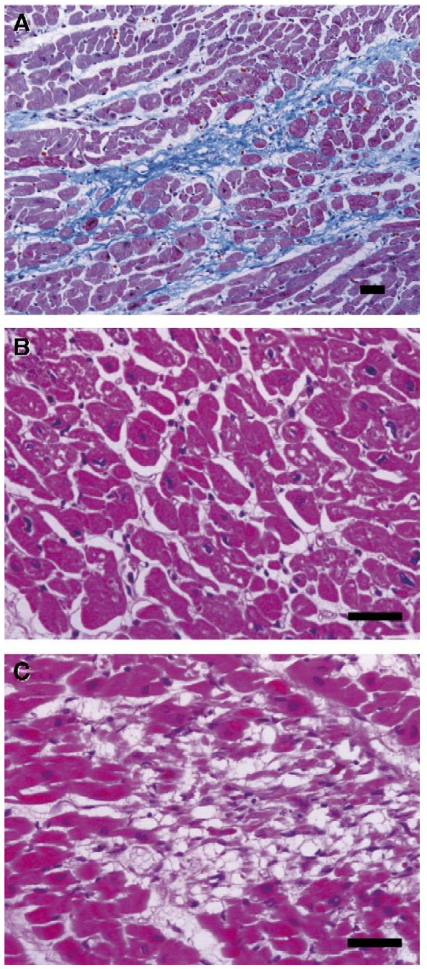
Bradshaw et al, Epidemiology 2016

Cardiac Complications from Chemotherapy

- 1. Anthracycline Induced
- 2. Radiation Effects
- 3. Her2 Directed Therapies
- 4. Vascular Effects (Endothelial Dysfunction)
- 5. Other (hypertension, etc)

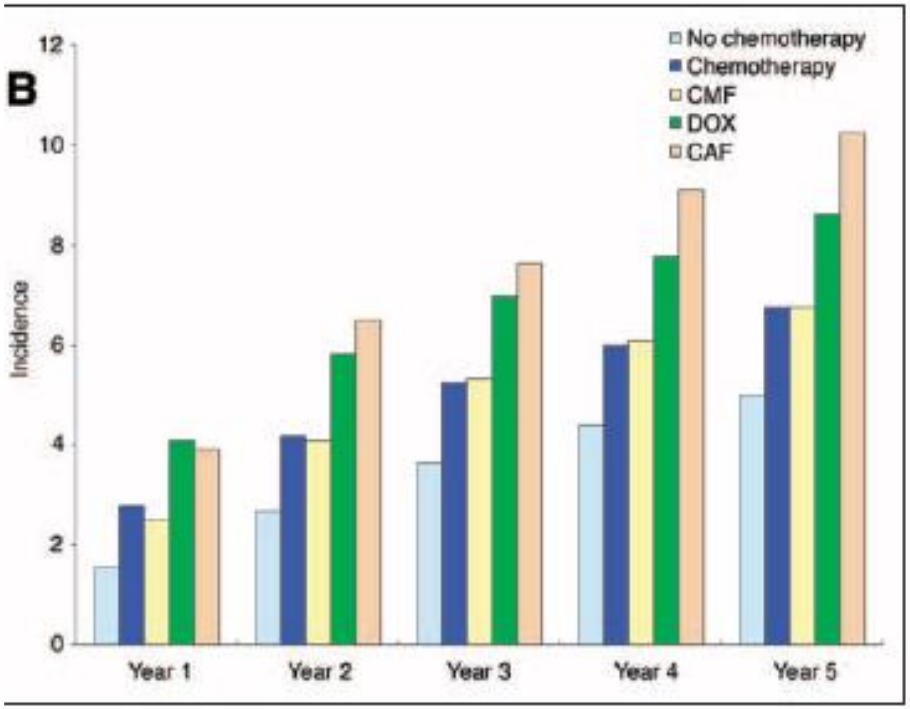
Background - Anthracyclines

- Doxorubicin – “AC” “The Red Devil” anthracycline chemotherapeutic agent
  - First approved in the late 1960s
  - Most commonly, it plays an important role in:
    - Breast cancer – adjuvant, metastatic setting
- LV dysfunction could be symptomatic or asymptomatic
- Clinical manifestations can by acute during therapy or late manifestations after completing therapy



Elderly Breast Cancer Survivors

- Dose related:
  - 3-4% pts with doses 400-500 mg/m2
  - 18% at 550 mg/m2
  - 30+% at >/= 600 mg/m2
- Asymptomatic decrements in EF occur in up to 20-25% of patients treated with moderate doses of doxorubicin (240-400 mg/m2), and up to 30-35% of pts treated at high doses
- Other risk factors: treatment at a young or old age, mediastinal radiation, history of hypertension, female



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Trastuzumab and the Heart

- Incidence of Cardiomyopathy: 1.7-20%
- Trastuzumab: significantly improves survival in her2 positive breast cancer
  - Mech: Inhibits cardiomyocyte epidermal growth factor receptor 2 thereby interfering with normal growth, repair and survival of cardiomyocytes
  - Not dose related
  - Histology: no ultrastructural abnormalities
  - Prognosis: often reversible

- Risk Factors for trastuzumab based cardiomyopathy:
  - Previous or concomitant anthracyclines
  - Age > 65 years
  - BMI > 30 kg/mg2
  - Previous LV dysfunction
  - Arterial hypertension
  - Prior chest radiation

Other trastuzumab based therapies

- At this time, we are not seeing cardiac toxicity with pertuzumab (Perjeta) or trastuzumab emtansine (Kadcyla)
- FDA still recommends cardiac monitoring while on these medications though

Chemotherapy and Ischemia

Table 2 Chemotherapy Associated With Ischemia

Chemotherapy Agents	Incidence (%)	Frequency of Use
Antimetabolites		
Capecitabine (Xeloda) (71,74,83–85)	3–9	+++
Fluorouracil (Adrucil) (8,70,71,73–79)	1–68*	+++
Antimicrotubule agents		
Paclitaxel (Taxol) (90,91)	<1–5	+++
Docetaxel (Taxotere) (10,92)	1.7	++
Monoclonal antibody-based tyrosine kinase inhibitor		
Bevacizumab (Avastin) (10,93,94)	0.6–1.5	++
Small molecule tyrosine kinase inhibitors		
Erlotinib (Tarceva) (10)	2.3	+++
Sorafenib (Nexavar) (10,96)	2.7–3	+++

- Pathophysiology:
  - Coronary artery thrombosis, arteritis, vasospasm
- Risk Factors:
  - High doses > 800 mg/m2; continuous infusions of 5-FU

Chemotherapy and HTN

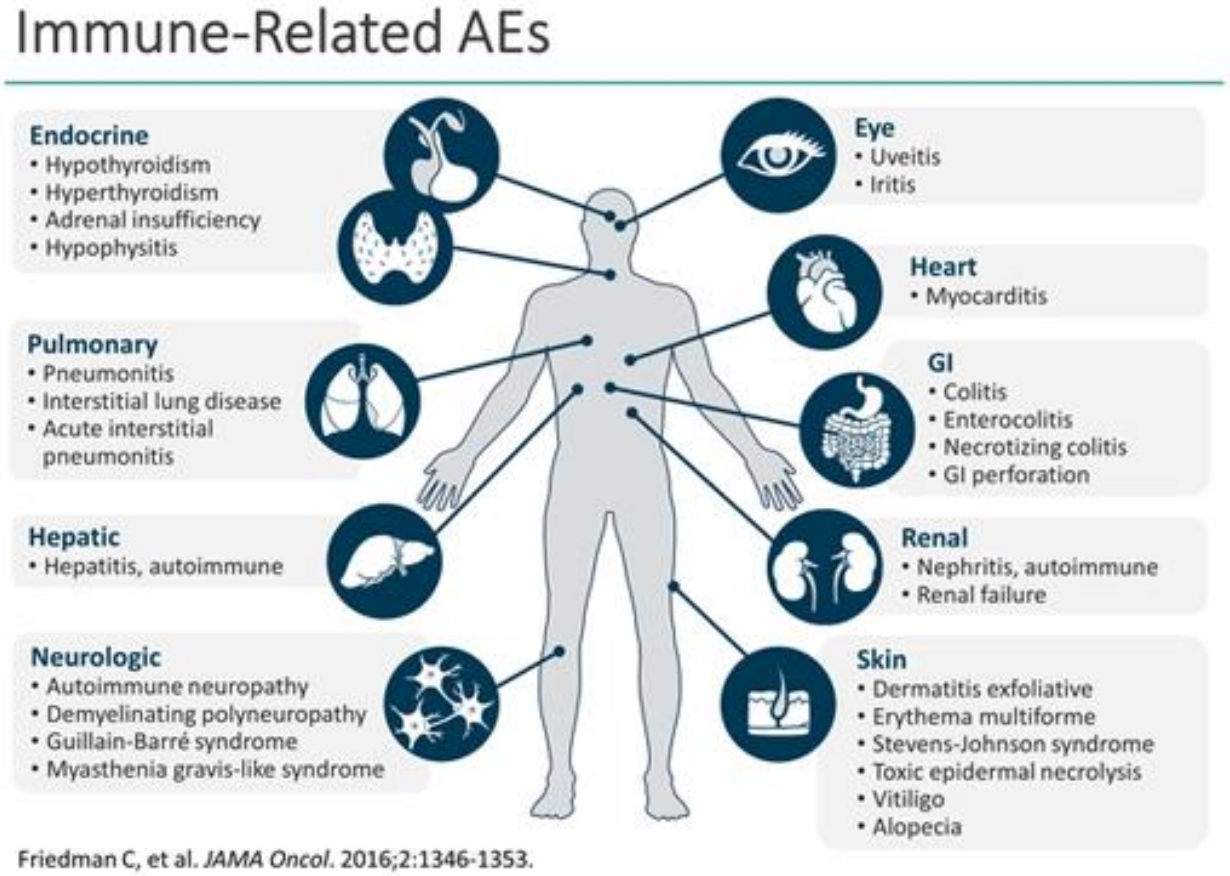
- Typically our newer small molecule agents or those that affect VEGF (Avastin)
- Less used in breast cancer

Table 3 Chemotherapy Associated With Hypertension

Chemotherapy Agents	Incidence	Frequency of Use
Monoclonal antibody-based tyrosine kinase inhibitor		
Bevacizumab (Avastin) (18,19,107–112)	4–35	++
Small molecule tyrosine kinase inhibitors		
Sorafenib (Nexavar) (96,113–116)	17–43	+++
Sunitinib (Sutent) (37,118–122)	5–47	+++

Yeh ETH, et al. JACC 2009; 53

Immunotherapy and the Heart



Friedman C, et al. *JAMA Oncol*. 2016;2:1346-1353.

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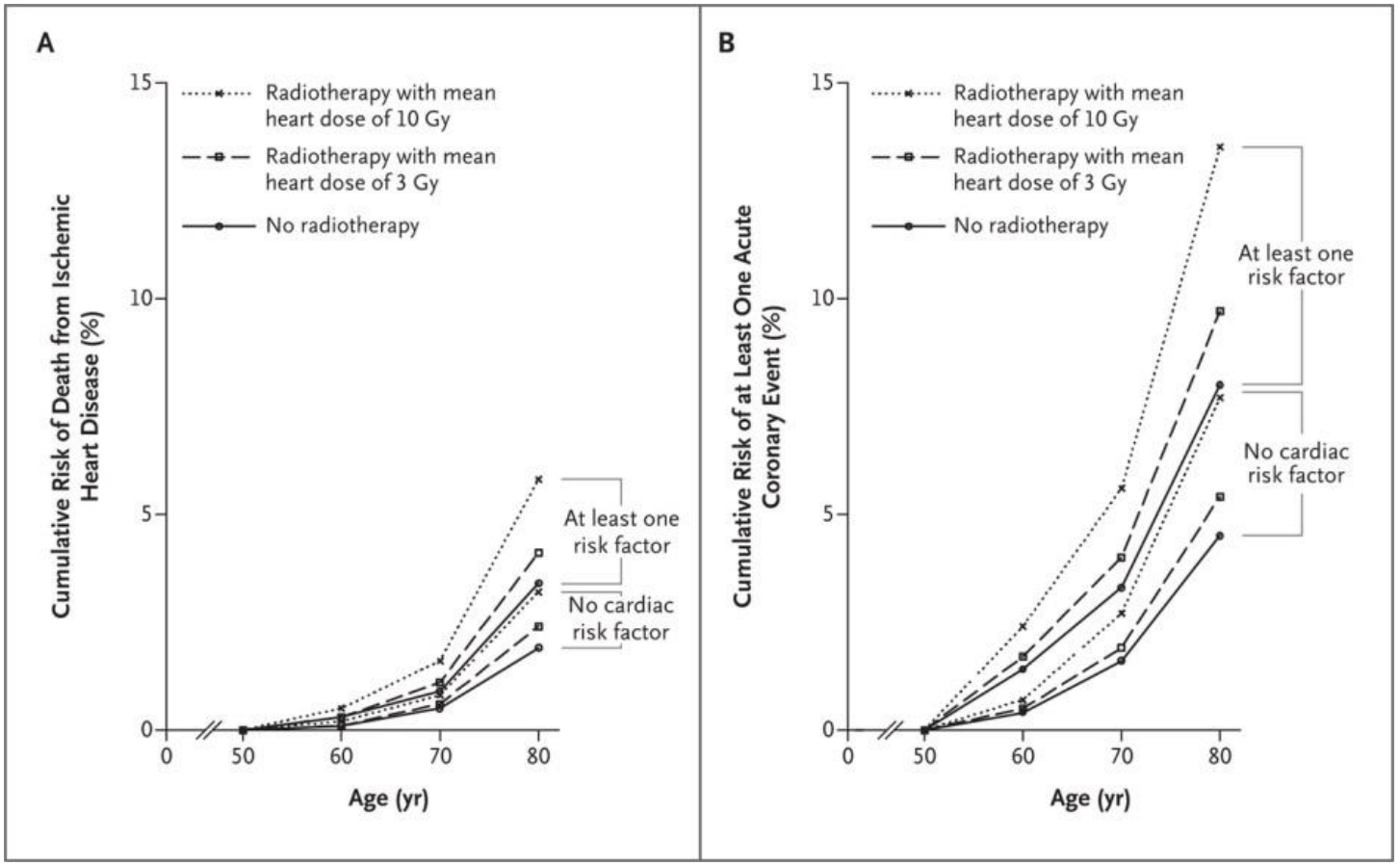
Radiation and the Heart



Left sided breast radiation > right

Hodgkin survivors: significant risk with mantle radiation

Mulrooney D, BMJ 2009
Henson, Circulation 2016
Darby, NEJM 2013

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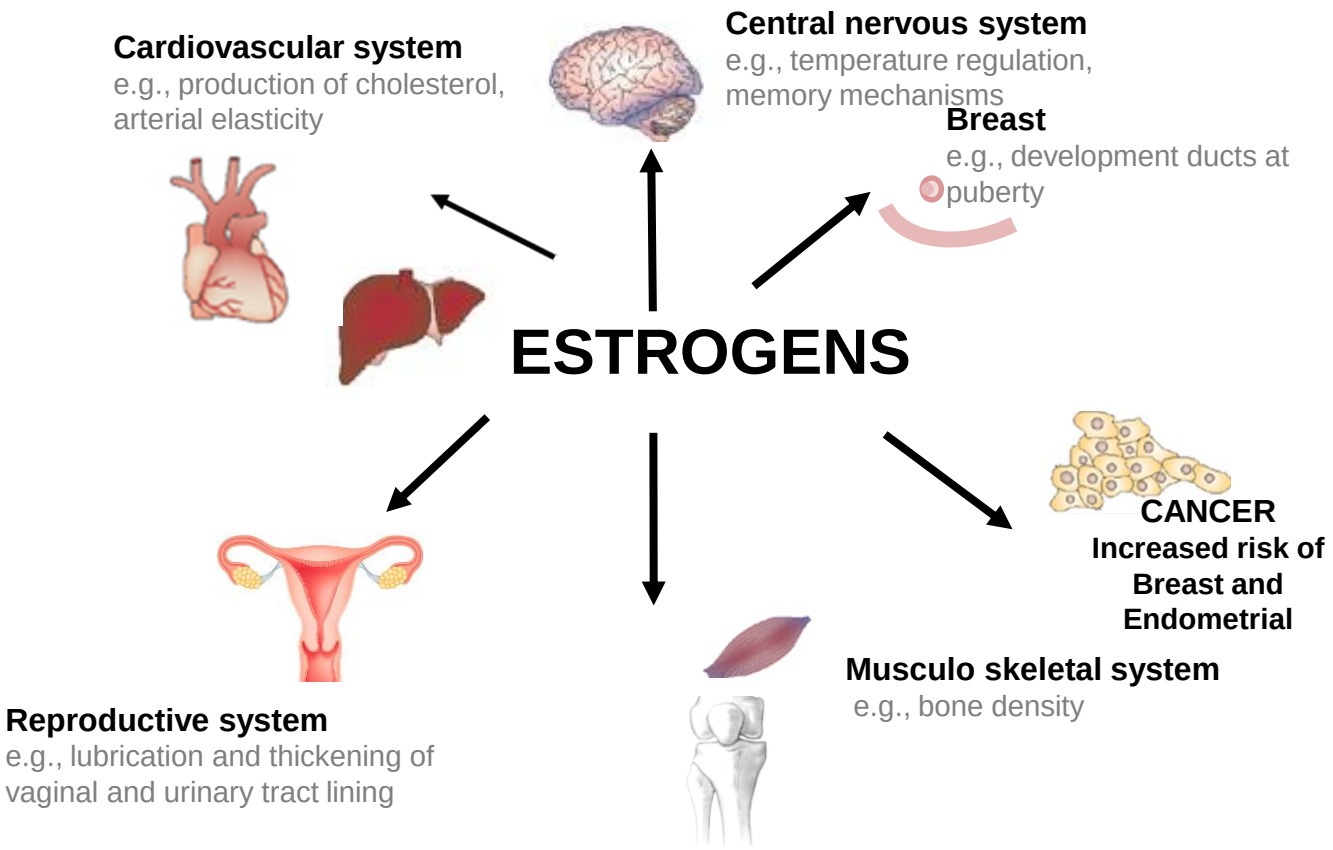
Effects of Estrogens in Women



Adapted from Clemons, NEJM, 2001

Endocrine Therapy in Breast Cancer Survivors

- Block estrogen- Tamoxifen (SERM)
- Lower estrogen-
  - Aromatase inhibitors (steroidal and non-steroidal)
  - Ovarian suppression
    - GnRH
    - Oophorectomy/Ablation
    - Chemotherapy-related amenorrhea (CRA), premature menopause

Estrogen receptor degradation (SERD) fulvestrant

Clinical Trial Results:

- AI trials:
  - When compared to placebo, slight increases in htn, hyperlipidemia but no real measured CV different outcomes
  - In comparison to tamoxifen, elevations in htn, hyperlipidemia, ischemia in those with preexisting CV disease though the trial results are mixed

PA-1 Tamoxifen trials: Fisher et al, JNCI 2005

MA-17, MA-17R, ATAC, IES, BIG 1-98

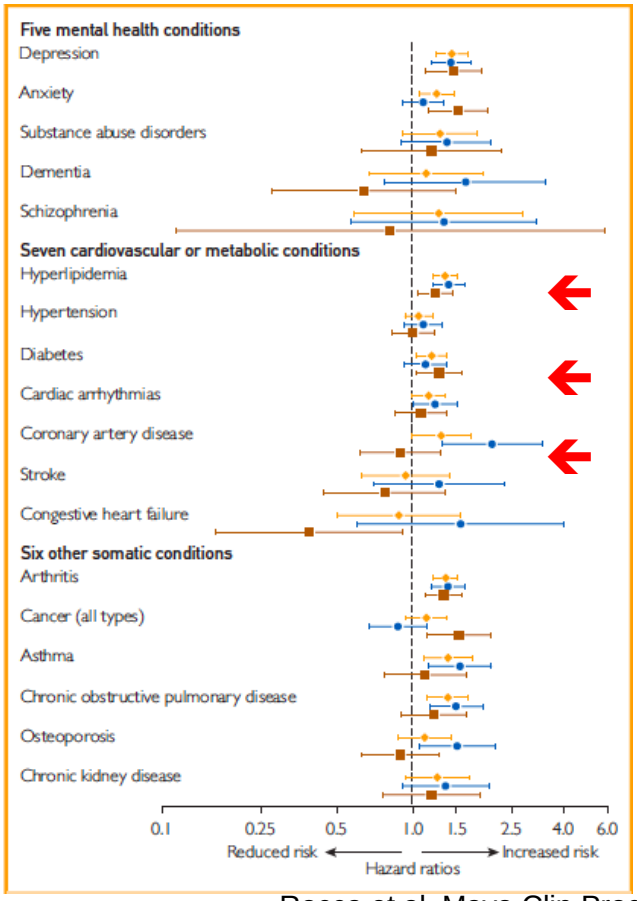
Multimorbidity after Bilateral Oophorectomy

- 1653 Premenopausal women undergoing oophorectomy age <50 from 1988-2007 and 1653 age-matched controls
- Excluded women with ovarian cancer, estrogen sensitive cancer, high risk indication
- Median followup ~14.5 yrs
- Analysis adjusted for baseline morbidity, BMI, smoking etc.

All women with oophorectomy

Women 46-49 at oophorectomy

Women ≤ 45 at oophorectomy



Rocca et al, Mayo Clin Proc, 2016

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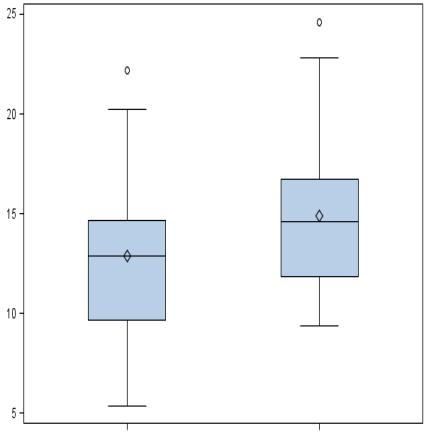
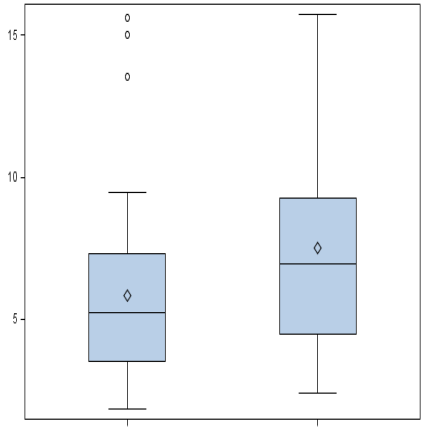
Aromatase inhibitors and Endothelial function

Large artery elasticity p=0.12



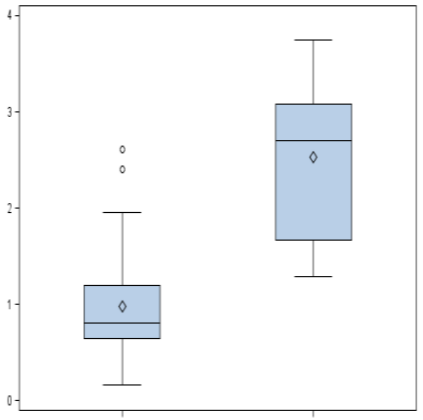
Breast Cancer **Controls**

Small artery elasticity p=0.07



Breast Cancer **Controls**

EndoPat Ratio p<0.0001



Breast Cancer **Controls**

Shared Risk Factors:
Cancer and Cardiovascular Disease

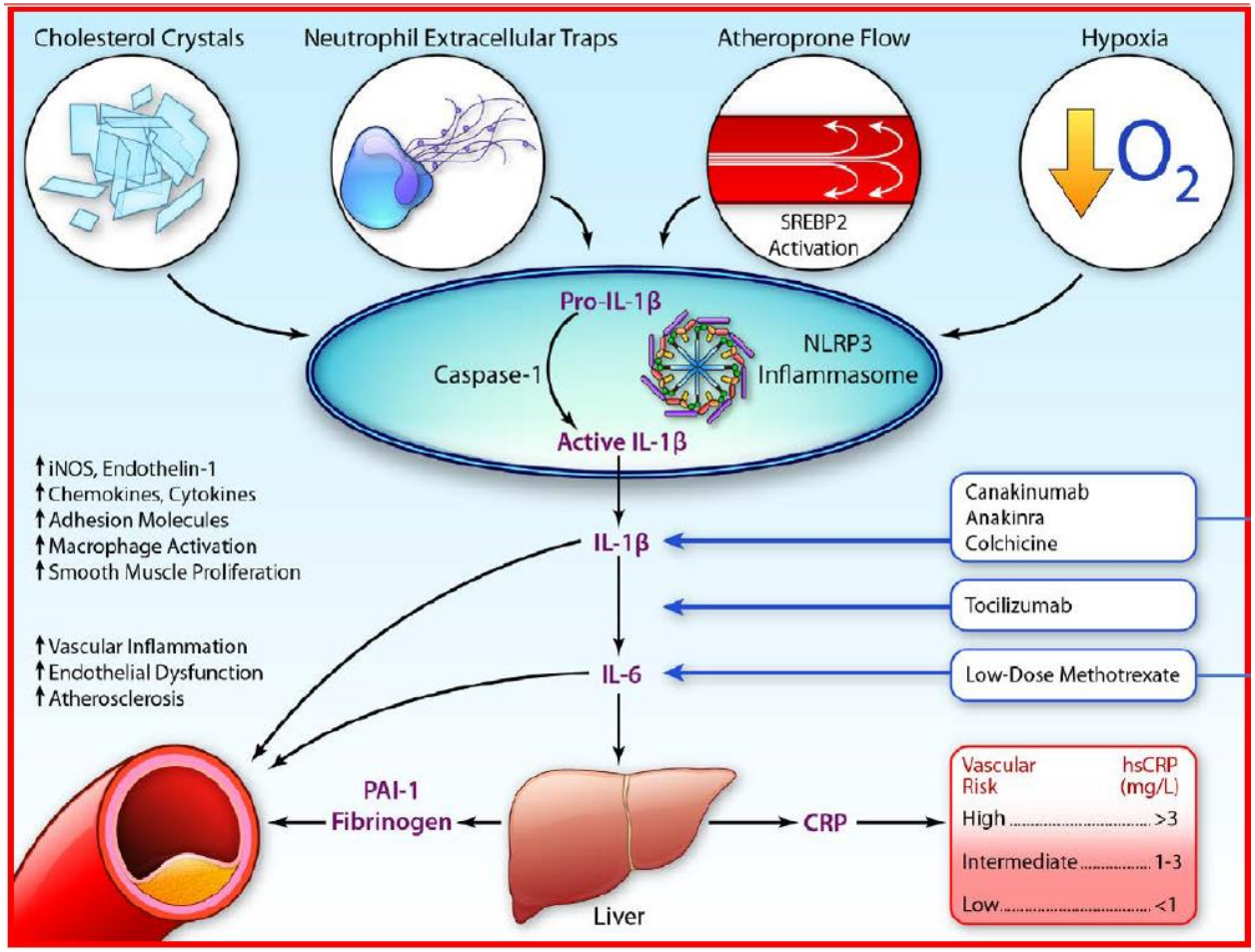
Overlapping Risk Factors:

- Age
- Sex
- Obesity
- Diabetes
- Hypertension
- Hyperlipidemia
- Tobacco Use
- Diet
- Physical Activity
- Advancing Age

- EPIC study
  - N=23,153 individuals ages 35-65 years
  - After f/u 7.8 years, adherence to all 4 vs 0 risk factors:
    - 93% less diabetes
    - 81% less heart attacks
    - 36% less cancer
- ARIC study
  - N=13,253 individuals
  - Adhering to 6 of 7 risk factors → 51% lower incidence of cancer compared to adhering to 0 measures

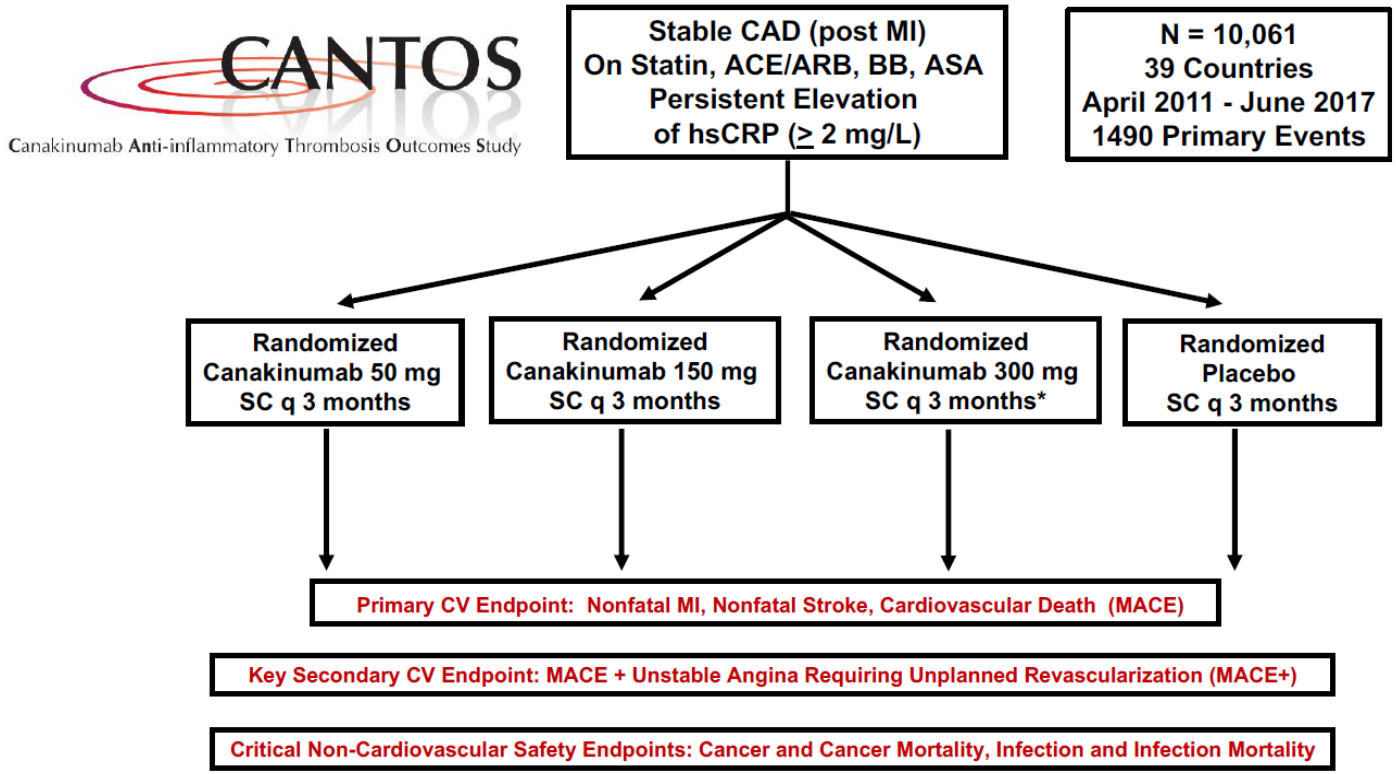
Koene, Prizment, Blaes, Konety. Circulation 2016
Rasmussen-Torvik et al, Circulation 2013
Nothlings U et al, J Diabetes 2010

Novel Inflammatory Targets



Ridker PM.
Circ Res 2016;118:145-156

Canakinumab Anti-Inflammatory Thrombosis Outcomes Study: *CANTOS*



Ridker et. al.
NEJM 2017

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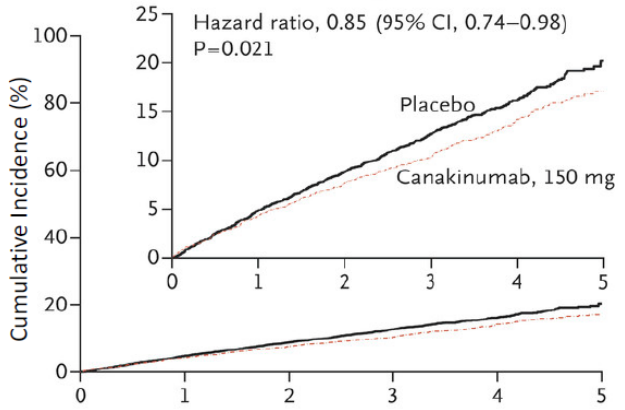
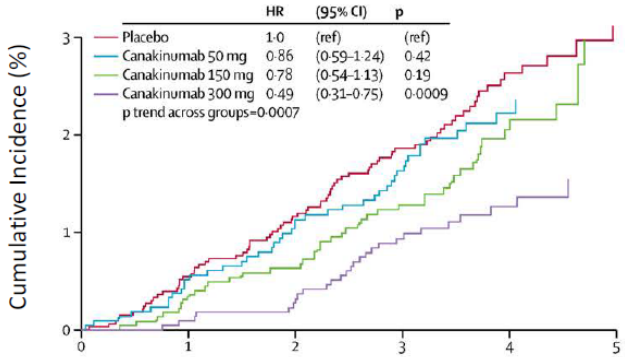
CANTOS: *Primary and Key Secondary Outcomes*

MACE (150mg dose): Non-fatal MI and stroke, and Cardiovascular Death



Fatal Cancer (all doses)



CANTOS: Key Outcomes (all doses pooled)

Endpoint	Hazard Ratio	*P*-value
'MACE' (primary)	**0.88**	**0.02**
Death, all-cause	0.94	0.39
Death, CVD	0.87	0.15
Death, Cancer	**0.71**	**0.02**
	Incident Ratio	
Death, Infection/sepsis	**1.72**	**0.02**

Ridker et. al. NEJM 2017;377:1119
Ridker et. al. LANCET 2017;390:1833

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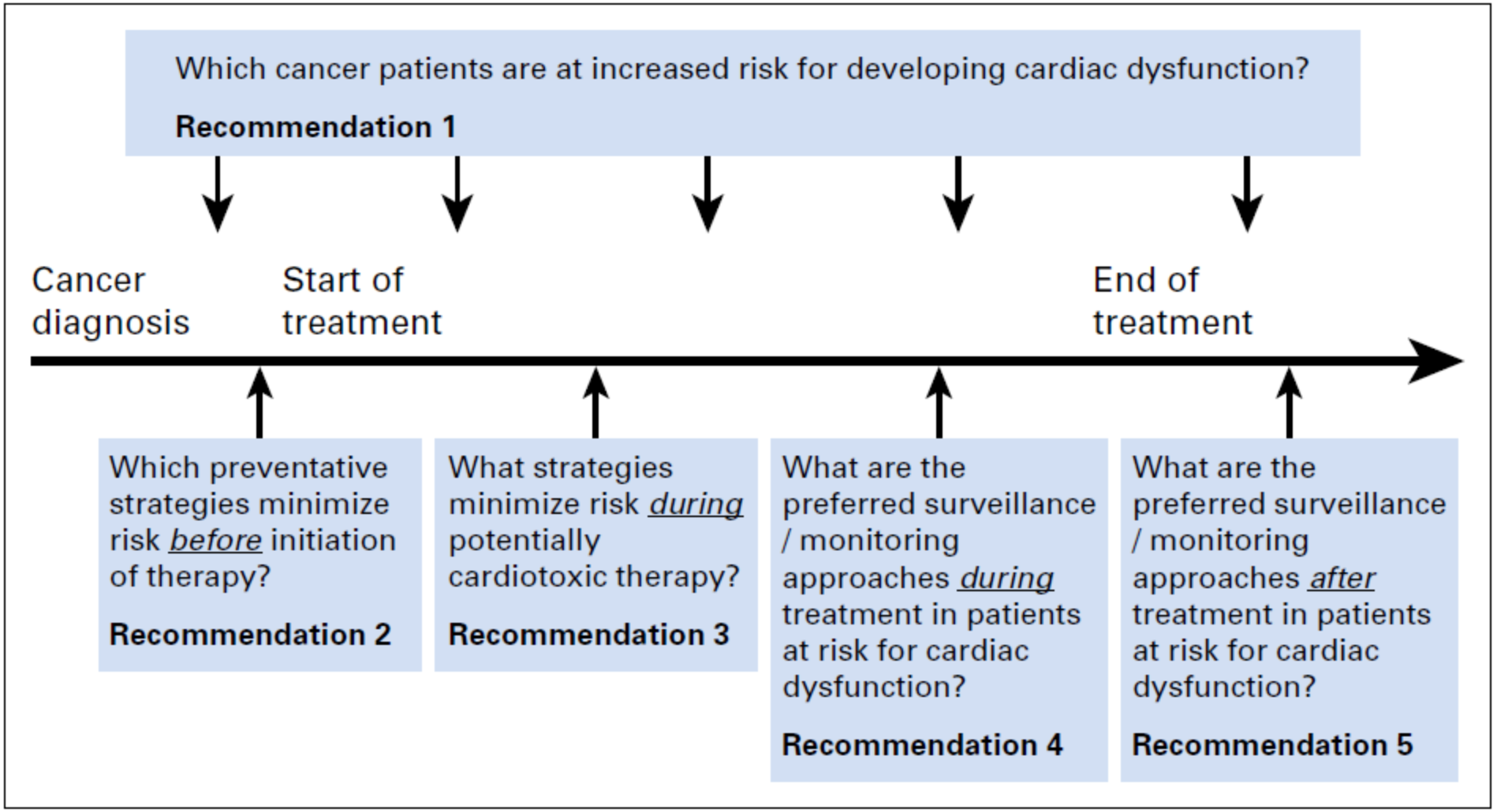
What about in breast cancer survivors?



Barac A et al, Journal of Clinical Oncology 2017

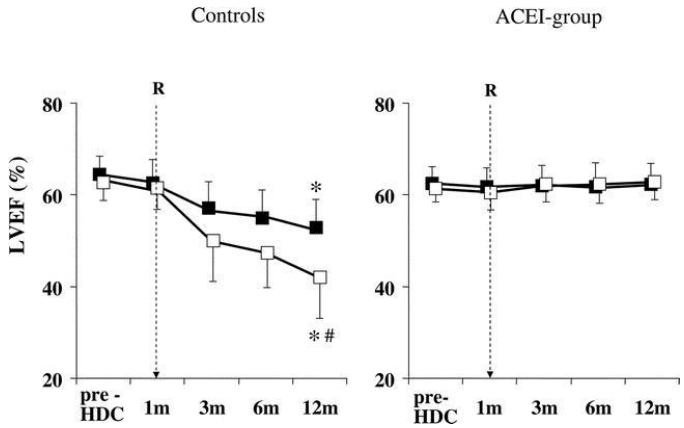
Monitoring and Prevention

- For oncologists:
  - Changes in infusions: liposomal preparations, change in infusion time
  - Alternative therapies?
  - Cardioprotective agents?
    - Dexrazoxane
    - ACE-I
    - B-Blockers
    - Statins?
- For all:
  - Cardio-oncology Clinic and referral
  - Risk stratify
    - Highest risk - > 65 years, underlying hypertension or heart disease, prior chest radiation (not breast cancer radiation), diabetes, tobacco use

Prevention

1. Medications
2. Biomarkers

- ACE-I



- B-blockers

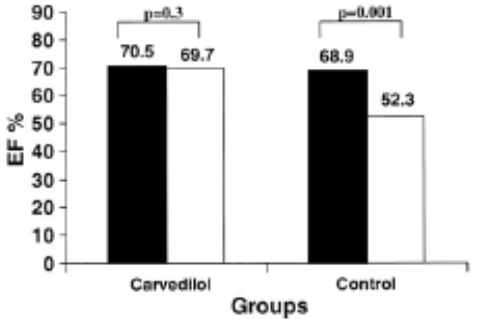


Figure 1. Comparison of left ventricular ejection fraction (EF) at baseline (black bars) and after chemotherapy (white bars) in the 2 groups. Data expressed as mean values.

Cardinale et al, Circulation 2006; Kalay JACC 2007
Blaes et al, Breast Cancer Res Treat 2010
MANTICORE Pituskin E et al, J Clin Oncol. 2016 Nov 28

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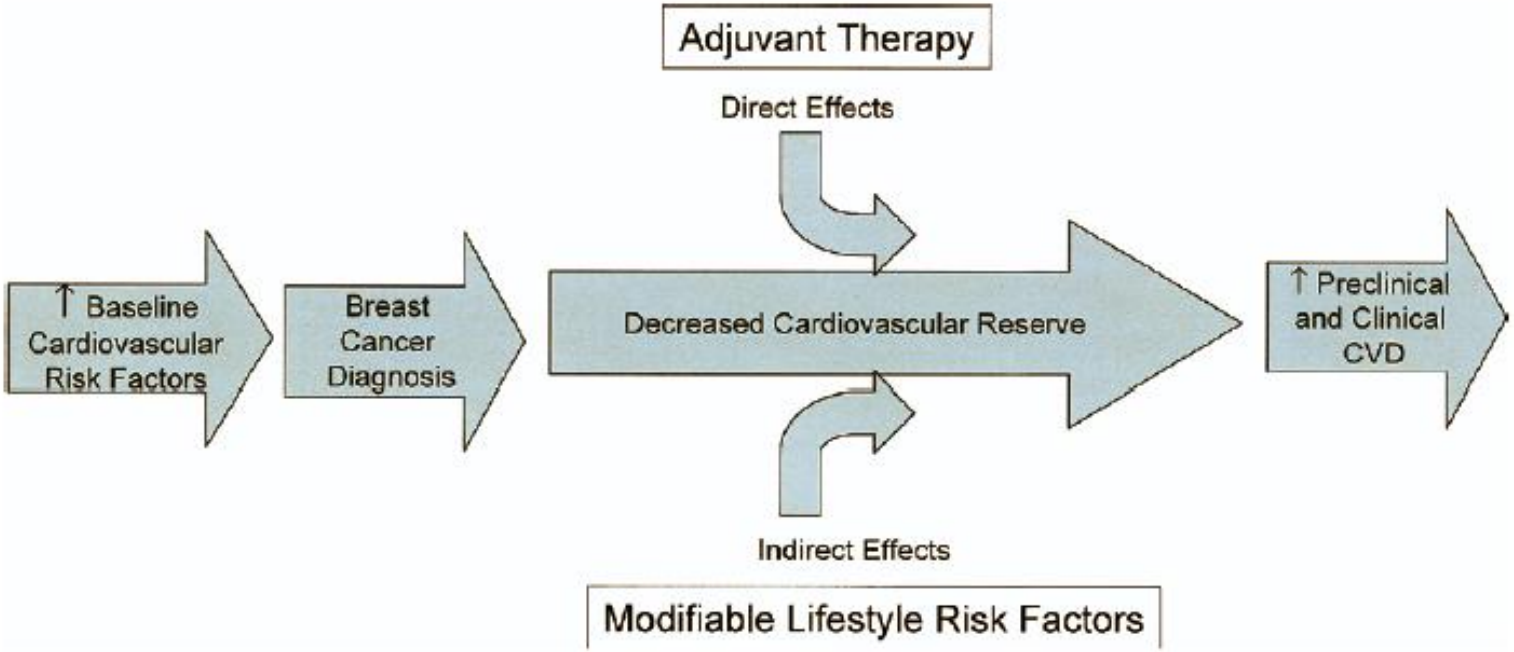
Other Practical Tips

- Avoid Tobacco Use
- Have a primary care provider
- Control blood pressure and cholesterol
- Healthy diet
- Stay Active
  - *Cancer Rehab, YMCA Livestrong



Cancer and Cardiovascular Disease

- Risk factors for chemotherapy-related cardiac complications should be assessed in all patients diagnosed with breast cancer
- Biologic data to support the overlap of the pathogenesis of these two diseases
- Management of risk factors is important not only during treatment and post treatment, but also in the prevention of these two diseases
- Treatment of cardiac risk factors including htn, hyperlipidemia, diabetes in cancer patients may actually improve overall outcomes

Questions