The Intersection of Heart Disease and Breast Cancer: A Clinical Cardiologist’s Perspective

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Case Example

- A 57-year-old woman with a history of obesity and high blood pressure was referred to a cardio-oncology clinic during therapy for breast cancer.
- She had completed 4 cycles of chemotherapy with doxorubicin as well as 3 months of trastuzumab (Herceptin) of a planned 12-month course.
- She was asymptomatic, however, her echo showed changes.
Baseline
3-month echo
Left ventricular ejection fraction (LVEF) decreased from 60% to 49%
Medical therapy with carvedilol and lisinopril

Transition to a whole-food plant-based diet low in sodium (<2 grams/day)

Moderate physical activity of at least 30 minutes, 5 days/week
Following Treatment
Scope of the Problem, Risk Factors and Prevention

Chemotherapy cardio-toxicity
- Anthracyclines
- Trastuzumab

Prevention – The Whole-Food Plant-Based Diet
18 million cancer survivors projected to be 22 million by 2030

- Cancer patients are living longer
  - Higher odds of developing CV disease

- Changing therapies/targeted therapies
  - Improved cancer outcomes
  - More side effects, including cardiovascular

Source: American Cancer Society 2019
# Sites of New Cancer Cases and Deaths – 2022 Estimates

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td></td>
<td>Estimated New Cases</td>
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<tr>
<td>Prostate</td>
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<tr>
<td>Lung &amp; bronchus</td>
<td>117,910</td>
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<tr>
<td>Colon &amp; rectum</td>
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<td>Urinary bladder</td>
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<td>Melanoma of the skin</td>
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<td>Kidney &amp; renal pelvis</td>
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<td>Non-Hodgkin lymphoma</td>
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<td>Oral cavity &amp; pharynx</td>
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<tr>
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<td>Pancreas</td>
<td>32,970</td>
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<tr>
<td>All sites</td>
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</table>

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>68,820</td>
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<tr>
<td>Prostate</td>
<td>34,500</td>
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<tr>
<td>Colon &amp; rectum</td>
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<td>Pancreas</td>
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<tr>
<td>Leukemia</td>
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<tr>
<td>Brain &amp; other nervous system</td>
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<tr>
<td>All sites</td>
<td>322,090</td>
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</tbody>
</table>

Source: American Cancer Society 2022
CV Disease and Cancer in Women: Age-Adjusted Mortality Rates

Source: Mehta LS, et al. Circulation 2018
Cardio-Oncology Syndrome (COS): Neoplastic disorders and Cardiovascular disease whereby direct or indirect mechanisms associated with the one condition induces acute or chronic presence of the other.

**COS Type I**  
(Direct)  
Progressive development of cancer leads to CV disease

**COS Type II**  
(Indirect)  
Cancer associated treatments causing CV disease

**COS Type III**  
(Direct)  
Progressive scarring and remodeling of heart and kidney causing a pro-oncogenic environment

**COS Type IV**  
(Indirect)  
CV disease associated treatments and diagnostics causing a pro-oncogenic environment

**COS Type V**  
(Secondary)  
Systemic and genetic conditions causing both cancer and CV disease
Types of cardiovascular toxicity

- **Valve Disease**: Radiation, Anthracyclines, Endocrine Tx
- **Atherosclerosis**: Radiation, Endocrine Tx, Alkylating Agents, TKIs
- **Abnormal Conduction**: Radiation, Anthracyclines, Endocrine Tx, Alkylating Agents, Antimetabolites, ICIs, TKIs, Taxanes
- **Vasospasm, Myocardial Ischemia**: Taxanes, Endocrine Tx, Alkylating Agents, Antimetabolites, TKIs, Anti-tumor ab, Anti-CD20 Ab, PI
- **Cardiomyopathies**: Radiation, Anthracyclines, Endocrine Tx, Alkylating Agents, Antimetabolites, ICIs, TKIs, HER2 Ab
- **Pericardial Disease**: Radiation, Anthracyclines, Endocrine Tx, Alkylating Agents, ICIs
- **Myocarditis**: Anthracyclines, Alkylating agents, ICIs
- **Thrombosis**: Alkylating Agents, Endocrine Tx, PIs, TKIs, AntiMT agents
- **Hypertension**: Alkylating Agents, PIs, TKIs, AntiMT agents
- **Vasculitis**: ICIs
- **Vasospasm**: Alkylating Agents, Antimetabolites, AntiMT agents
- **Stenosis**: Endocrine Tx, TKIs
Risk Factors for CV Disease and Breast Cancer

Cardiovascular Disease
- Autoimmune Diseases
- Depression
- Diabetes Mellitus
- Gestational Diabetes Mellitus
- Dyslipidemia
- Hypertension
- Inflammation
- Personal history of Cardiovascular Disease
- Preeclampsia
- Pregnancy-Associated Hypertension
- Sleep Apnea

Breast Cancer
- Age
- Diet
- Family History
- Alcohol Intake
- Hormone Replacement
- Obesity/Overweight
- Physical Activity
- Tobacco Use
- BRCA Genes
- Dense Breasts
- Diethylstilbestrol Exposure
- Early Menstrual Period
- High Dose Chest Radiation
- Late or No Pregnancy
- Oral Contraception Pills
- Personal History of Breast Cancer
- Starting Menopause After Age 55

Source: Mehta LS, et al. Circulation 2018
Anthracyclines
Anthracyclines - Basics

- Have been used since the 1950s in adults and children
  - breast cancer, lymphoma, GU/Gyn cancers, ALL/AML, and sarcomas

- “Red Medicine”

- See heart failure and LV dysfunction
  - Incidence rises with increasing doses (7%, 18%, and 65% at cumulative doses of doxorubicin 150 mg/m2, 350 mg/m2, and 550 mg/m2, respectively)

Keefe DL. Semin Oncol. 2001
Toxicity Types

- **Acute**
  - During therapy (can be during infusion and within 2-3 days of administration)
  - E.g., palpitations due arrhythmias, EKG changes, and chest pain due to myopericarditis

- **Subacute**
  - Within 1 year

- **Chronic**
  - Late effects
  - Can be as late as 10-20 years due to a “second hit”
Monitoring

- Transthoracic Echocardiogram (TTE) is the main way to monitor patients
- Assess baseline LV function prior to therapy, after 4 cycles, and 6-12 months after completion of therapy
- Long-term monitoring is not well defined

Source: American College of Cardiology (acc.org/infographics)
Cardiac dysfunction affects cardiovascular outcomes as well as oncological therapeutic options.

LVEF at the end of chemo and the cumulative dose are independently associated with cardiotoxicity.

With therapy, over 80% of patients recover LVEF either fully or partially.

Cardiac surveillance based only on symptoms (e.g., shortness of breath or leg swelling) might miss the opportunity to treat early.
Trastuzumab
USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSIONS HER2

Dennis J. Slamon, M.D., Ph.D., Brian Leyland-Jones, M.D., Steven Shak, M.D., Hank Fuchs, M.D., Virginia Paton, Pharm.D., Alex Bajamonde, Ph.D., Thomas Fleming, Ph.D., Wolfgang Eiermann, M.D., Janet Wolter, M.D., Mark Pegram, M.D., Jose Baselga, M.D., and Larry Norton, M.D.*
Marked increase in progression-free survival and overall survival with trastuzumab

Lower rate of death at 1 year: 22% vs 33% (p=.008)

Slamon Dj et al. NEJM 2001
63/235 patients with symptomatic or asymptomatic cardiac dysfunction

Trastuzumab discontinued in 18/235 (8% overall) patients overall due to cardiac dysfunction, most of whom received an anthracycline as well.

Continued use of trastuzumab did not cause deterioration of cardiac function in most patients.

Cardiac function improved in 75% of patients who received trastuzumab who received standard medical therapy for LV dysfunction.

Slamon Dj et al. NEJM 2001
Risk Factors for Cardio-toxicity

- Combination with anthracyclines
  - Either concomitant or past
  - Increases at higher doses (>250 mg/m² doxorubicin)
- Pre-existing Cardiac Conditions
  - HF, LV systolic dysfunction, CAD, Afib, Htn, HLD
- DM
- Obesity (BMI ≥ 30 kg/m²)
- Renal Failure
- Age (≥ 60)
- Black Race
Drug Monitoring (per FDA)

- Baseline LVEF measurement immediately prior to initiation of Trastuzumab
- LVEF measurements every 3 months during and upon completion of Trastuzumab
- LVEF measurements every 6 months for at least 2 years following completion of Trastuzumab as a component of adjuvant therapy
  - This would come out to 9 echos/person for a typical 1-year course

Source: Trastuzumab drug label (fda.gov)
Drug Discontinuation

- Withhold Trastuzumab for ≥ 16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values

- Measure LVEF every 4 weeks if agent is held for cardiomyopathy

- Trastuzumab may be resumed if, within 4–8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤ 15%

- Permanently discontinue Trastuzumab for a persistent (> 8 weeks) LVEF decline or for suspension of Trastuzumab dosing on more than 3 occasions for cardiomyopathy

Source: Trastuzumab label (fda.gov)
An Ounce of Prevention: The Whole-Food Plant-Based Diet
A whole-foods plant-based diet means eating foods:

- That are whole with little to no processing
- That come from plants, including vegetables, whole grains, nuts, seeds, legumes and fruits
- With no animal products (no dairy, eggs, etc.) and small amounts of healthy fats
Why a whole-food plant-based diet?

- The more fruits and vegetables we eat the less room we will have for high fat, high sodium, high cholesterol and processed foods.

- Processing robs foods of vital nutrients and their main purpose which is to nourish.

- Plants are naturally low in fat, sugar, and salt, are cholesterol free (only animals make cholesterol - beef, chicken, fish, and pork), plus high in fiber, phytochemicals, and antioxidants.
What is the difference between Vegan and WFPB diet?

<table>
<thead>
<tr>
<th>Food</th>
<th>Vegan Diet</th>
<th>Whole Food, Plant-Based Diet</th>
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<tbody>
<tr>
<td>Fresh Vegetables</td>
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<td>Yes</td>
</tr>
<tr>
<td>Dairy</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Raw Honey</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Refined Sugar</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Most Breads</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Olive Oil</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Source: UC Davis Integrative Medicine (www.ucdintegrativemedicine.com)
THE PLANT-BASED HEALTHY PLATE

Use this plate to help you portion your food in a healthy way and make meal planning easier. Portions are based on a small dinner plate.

Fill one-quarter of your plate with a plant-based protein source, such as cooked beans, lentils, or tofu.

Fill half of your plate with non-starchy vegetables, such as carrots, broccoli, spinach, cabbage, green beans, peppers, zucchini, onions, greens, tomatoes, or romaine lettuce.

Fill one-quarter of your plate with healthy grains or starches, such as brown rice, whole-wheat pasta, quinoa, bulgur, corn, peas, barley, farro, amaranth, 1 slice of whole-grain bread, 2 corn tortillas, or 1 whole-wheat tortilla.

For good nutrition also choose each day:
- 3 servings of fruit. A serving is a small orange, banana, or apple, or 1 cup of berries or melon.
- 2 to 3 cups of a milk substitute, such as almond, soy, or hemp.
- A small amount of healthy fats

Kaiser Permanente
Ideas for meals and snacks

These sample meals and snacks include foods from the shopping list below, and follow the tips on the other side. Use these ideas to build healthy, tasty meals. Or create your favorite combinations!

### Breakfast
- 4 oz. sprouted-grain or wheat bagel with almond butter or cashew cheese
- 1 cup diced melon
- 2 oz. whole-grain muesli cereal
- 1/2 banana, 1/2 cup berries
- 10 walnuts
- 1 cup nondairy milk
- 1 cup plain almond or soy yogurt, mixed with 1 Tbsp. chia seeds and 2 Tbsp. raisins or 1/2 cup diced fruit
- 1 small bran muffin
- 2 slices sprouted-grain or wheat toast
- 1 cup berries
- 1 cup nondairy milk

### Lunch and Dinner
Add 1 cup nondairy milk to each meal (optional)

#### Chinese cuisine
- 1/2 cup brown rice, wild rice, or quinoa
- 1 cup broccoli tofu (sautéed in broth)
- 1 cup vegetarian hot-and-sour soup

#### Indian cuisine
- 1/2 cup beans or 1 cup lentil soup (dal)
- 1 whole-grain flatbread
- 1 cup diced cauliflower, onions, and tomatoes

#### Mexican cuisine
- 2 bean tacos made with 2 corn tortillas, 1 cup whole beans, 2 Tbsp. avocado, salsa, shredded lettuce or cabbage, and tomatoes
- Diced mango

### Snacks
- 1/2 cup baked sweet potato
- 2 tbsp. dried fruit or nuts
- Fresh fruit
- 3 cups air-popped or light microwave popcorn
- 1/4 cup roasted garbanzo beans
- Raw vegetables with hummus or vegetable pâté
- Medium apple with 1-2 Tbsp. "natural" peanut butter
- 3 large rice wafer crackers
- Fresh nonstarchy vegetables

### Healthy meals start at the store. Use this shopping list to help you prepare.

- Fruits—fresh, frozen, canned in their own juice, or dried
- Vegetables—fresh, frozen, or low-sodium canned
- Plain nondairy milk (fortified soy, rice, oat, or almond)
- Plain nondairy yogurt (soy or almond)
- "Natural" peanut or other nut butter
- Cultured cashew cheese
- Olive or organic canola oil
- Light soy sauce, tamari, or Bragg’s liquid aminos
- Sauerkraut or kimchee
- Whole beans (canned or dried), or lentils
- Hummus, bean spreads, or tahini
- Tofu (silken, firm), tempeh
- Avocado, olives, or sun-dried tomatoes
- Unsalted nuts and seeds
- Nutritional yeast
- Vegetable broth
- 100% whole-wheat or sprouted-grain bread, rolls, or bagels
- Rye wafer or whole-wheat crackers
- Brown rice or whole-wheat pasta
- Whole-grain cereal (oats, or muesli)
- Whole grains (bulgur, whole cornmeal, hulled barley, farro, millet, whole-wheat couscous, brown rice, or quinoa)
- Tortillas (corn, or whole- or sprouted-wheat)

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This information is not intended to diagnose health problems or to take the place of medical advice or care you receive from your physician or other medical professional. If you have persistent health problems, or if you have additional questions, please consult with your doctor.

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The Daily Dozen

Source: Dr. Michael Greger: nutritionfacts.org
Thank You!
samir.r.thadani@kp.org