

# Cardiovascular Disease Prevention in Cancer Survivors



Heather M. Johnson, MD, MS, MMM, FAHA, FACC  
Preventive Cardiologist,  
Christine E. Lynn Women's Health & Wellness Institute  
Boca Regional Hospital/Baptist Health South Florida  
**[hjohnson@baptisthealth.net](mailto:hjohnson@baptisthealth.net)**  
**Clinic phone: 561-955-2131**

# 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

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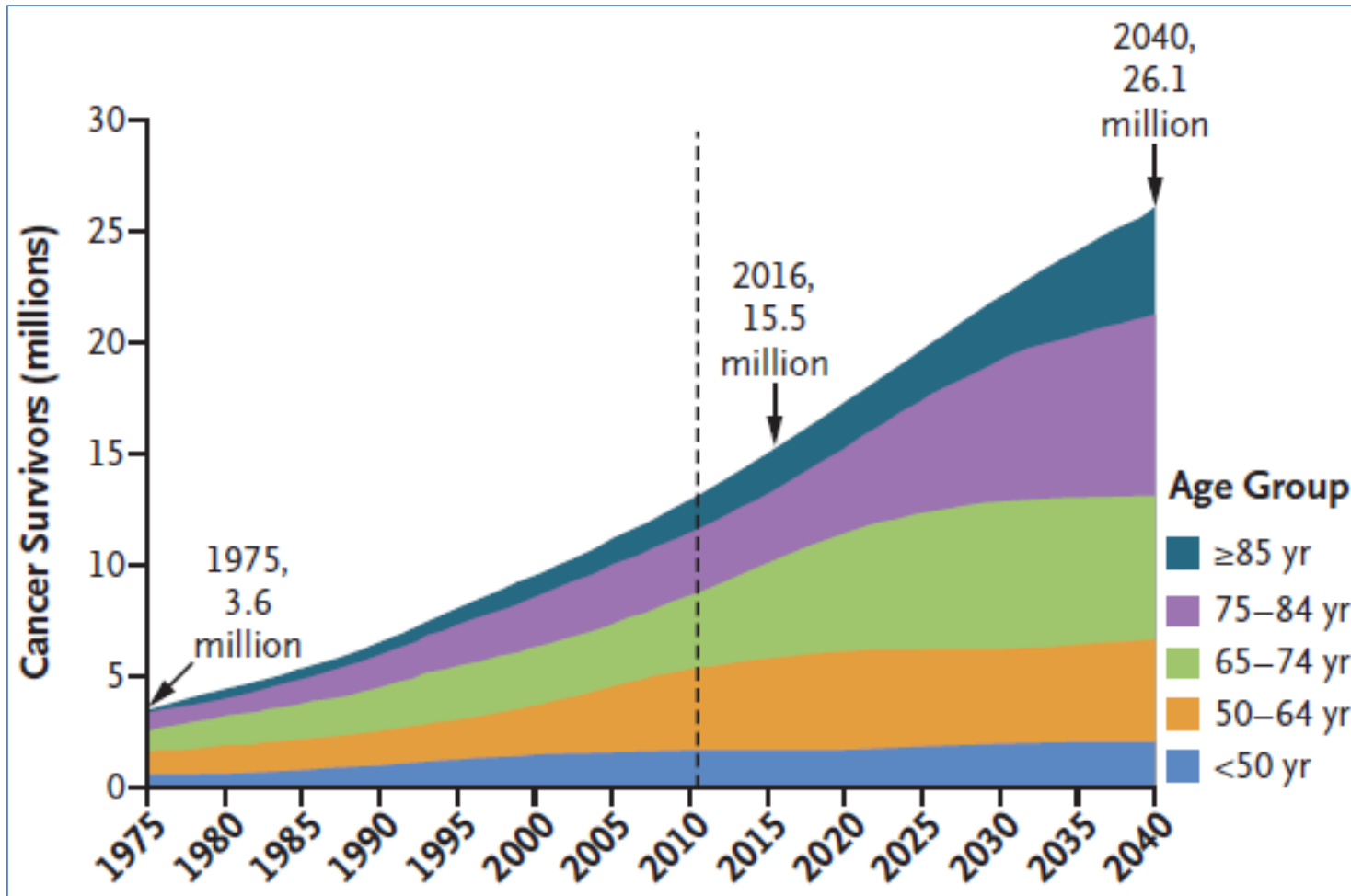
This talk will NOT focus on management of Cardiotoxicity.

# U.S. Cancer Survivors, January 2019



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

# Growing Prevalence of US Cancer Survivors

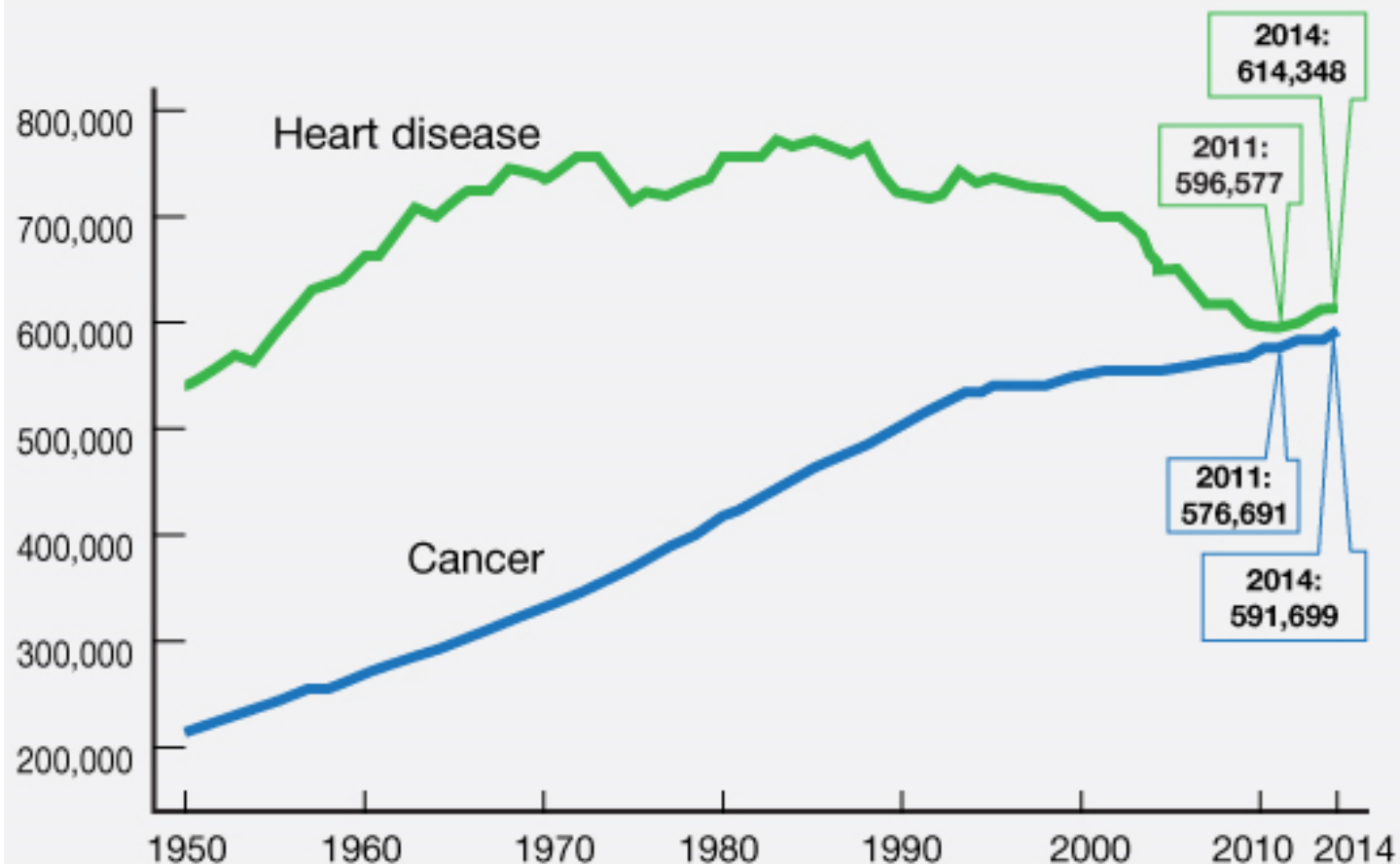




# TOP TWO KILLERS

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

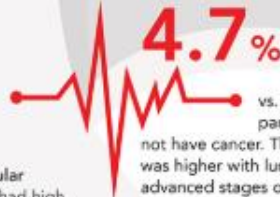
Number Check



**43%**

The percent of testicular cancer survivors who had high blood pressure vs. 31 percent of men who did not have cancer. Testicular cancer survivors were more likely to have high cholesterol and metabolic syndrome and to be overweight.

Source: HealthDay. News article. April 2, 2018.



**4.7%** The rate of heart attack or stroke within six months of cancer diagnosis, vs. 2.2 percent in study participants who did not have cancer. The risk of an event was higher with lung cancer and more advanced stages of cancer.

Source: Journal of the American College of Cardiology. 2017;70:926-36.



**30%**

The increased risk of death in lung

cancer patients whose radiation shifted slightly toward their heart during therapy, vs. those who radiation shifted away from their heart. A 50 percent difference was seen in patients with throat cancer.

Source: HealthDay. News article. April 23, 2018.

## CANCER AND HEART DISEASE



**87%**

The proportion of women with breast cancer who had one or more cardiovascular disease risk factors.

Additionally, 62 percent had two or more risk factors and one-third had three or more. The number of significant risk factors was associated with overall survival and risk of a cardiac event.

Source: Journal of Clinical Oncology 2018; March 27 [Epub ahead of print].



**5**

The number of hours of moderate exercise per week before a breast

cancer diagnosis that was associated with a 40 percent lower likelihood of a cardiovascular event and 60 percent lower risk of dying from coronary heart disease, according to a Women's Health Initiative analysis.

Source: ACC.17 abstract 1157-05.



**25.7%**

The percent of endometrial cancer survivors diagnosed with heart disease five to 10 years after cancer diagnosis. Endometrial cancer survivors were 47 percent more likely to be diagnosed with heart disease between one to five years after cancer diagnosis and 33 percent more likely to be diagnosed with heart disease between five to 10 years after initial cancer diagnosis.

Source: Oxford University Press. News release. May 8, 2018.



**4.5%**

The percent of childhood cancer survivors who had heart disease before they turned age 40, nearly eight years earlier than the general population.

Source: European Society of Cardiology. News release. March 8, 2018.

- Ischemic heart disease
- Stroke
- Heart failure



# 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

- 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)
- $\geq 40$  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

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**Table 1.** Study Participant Characteristics

Characteristic	Cancer Survivors* (N = 36,232)	Noncancer Controls* (N = 73,545)	P
Age at diagnosis, years			—
Median	60	60	
Range	40.0-96.0	40.0-96.0	
Sex, No. (%)			—
Female	19,055 (52.6)	39,225 (53.3)	
Male	17,177 (47.4)	34,320 (46.7)	
Race/ethnicity, No. (%)			< .01
Non-Hispanic white	23,395 (64.6)	35,087 (47.7)	
Hispanic	5,063 (14.0)	15,234 (20.8)	
Black	4,683 (12.9)	7,626 (10.4)	
Asian/Pacific Islander	3,019 (8.3)	6,379 (8.7)	
Other/unknown	72 (0.2)	9,129 (12.4)	
Follow-up time from index date, years			< .01
Median	4.4	4.5	
Range	0-8.0	0-8.0	
Hypertension, No. (%)†			< .01
No	12,344 (34.1)	29,790 (40.5)	
Yes	23,888 (65.9)	43,755 (59.5)	
Diabetes, No. (%)†			< .01
No	27,745 (76.6)	57,719 (78.5)	
Yes	8,487 (23.4)	15,826 (21.5)	
Dyslipidemia, No. (%)†			< .01
No	15,257 (42.1)	32,408 (44.1)	
Yes	20,975 (57.9)	41,137 (55.9)	
Overweight/obese, No. (%)†			< .01
No	20,502 (56.6)	47,497 (64.6)	
Yes	15,730 (43.4)	26,048 (35.4)	
Smoking, No. (%)†			< .01
Never	24,368 (67.3)	58,045 (78.9)	
Ever	11,864 (32.7)	15,500 (21.1)	

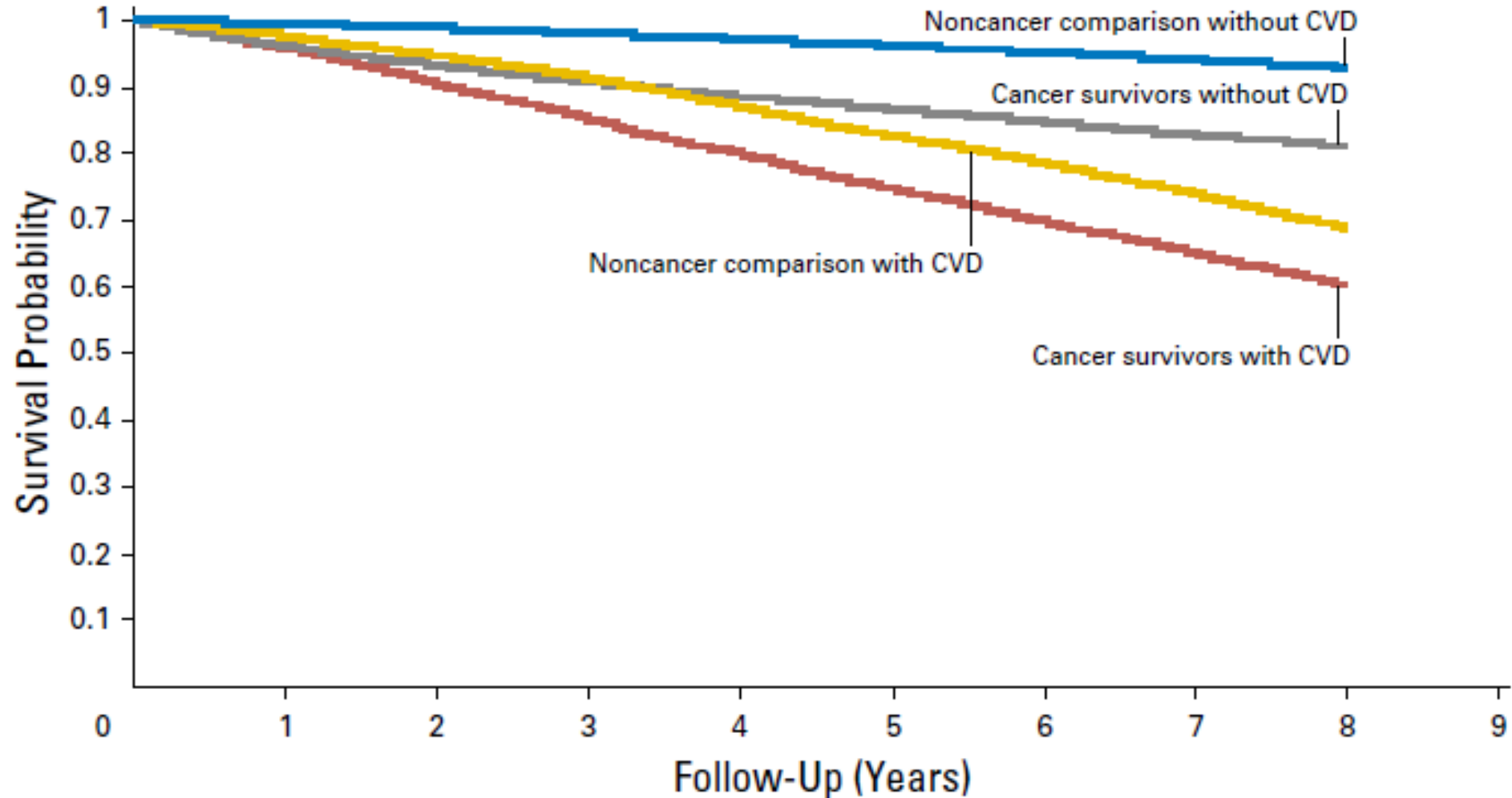


# Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study

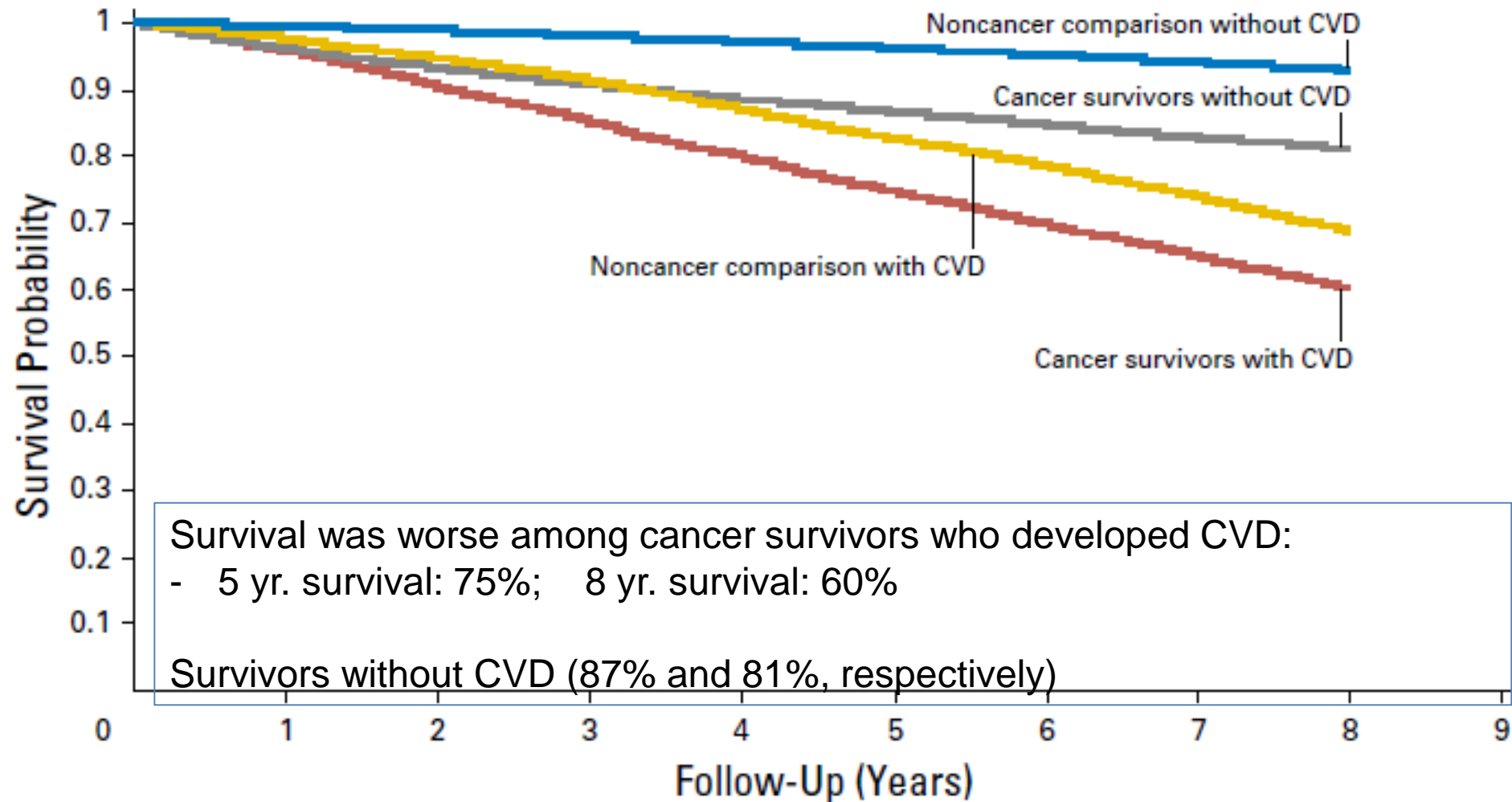
*Saro H. Armenian, Lanfang Xu, Bonnie Ky, Canlan Sun, Leonardo T. Farol, Sumanta Kumar Pal, Pamela S. Douglas, Smitta Bhatia, and Chun Chao*

- 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  $\geq 2$  CVD RFs
    - IRR: 1.83 to 2.59

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



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





## 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



	No. of cancer patients	Index-cancer deaths		CVD deaths		Heart disease deaths	
		No.	% of cancer patients	No.	% of cancer patients	No.	% of all CVD deaths
All patients	3 234 256	1 228 328	38.0	365 689	11.3	279 060	76.3
Sex							
Male	1 662 864	651 517	39.2	200 610	12.1	157 349	78.4
Female	1 571 392	576 811	36.7	165 079	10.5	121 711	73.7
Age at diagnosis							
0–19 years	43 263	10 156	23.5	278	0.6	232	83.5
20–39 years	210 699	54 047	25.7	2845	1.4	2330	81.9
40–59 years	932 545	326 003	35.0	41 356	4.4	32 622	78.9
60–79 years	1 636 489	656 668	40.1	224 173	13.7	171 137	76.3
80+ years	411 260	181 454	44.1	97 037	23.6	72 739	75.0
Year of diagnosis							
1973–82	564 129	294 723	52.2	109 144	19.3	82 941	76.0
1983–92	766 593	356 095	46.5	127 992	16.7	97 955	76.5
1993–2002	911 959	338 260	37.1	97 014	10.6	73 780	76.1
2003–2012	991 575	239 250	24.1	31 539	3.2	24 384	77.3
Race							
White	2 731 980	1 027 442	37.6	319 537	11.7	243 887	76.3
Black	297 188	127 077	42.8	30 924	10.4	24 233	78.4
Other	205 088	73 809	36.0	15 228	7.4	10 940	71.8
Marital status							
Single	399 184	141 885	35.5	28 848	7.2	22 463	77.9
Married	1 894 691	699 628	36.9	200 897	10.6	153 711	76.5
Separated	42 498	20 794	48.9	6740	15.9	5244	77.8
Divorced	237 000	98 579	41.6	18 723	7.9	14 557	77.7
Widowed	484 770	224 723	46.4	91 850	18.9	68 835	74.9
Stage at presentation							
Localized	1 059 957	169 107	16.0	148 767	14.0	111 465	74.9
Regional	632 242	282 521	44.7	65 304	10.3	49 420	75.7
Distant	528 923	389 794	73.7	25 220	4.8	20 052	79.5
Months since diagnosis							
2–11 months	3 234 256	519 279	16.1	45 592	1.4	35 925	78.8
12–59 months	2 533 198	498 282	19.7	105 581	4.2	81 355	77.1
60–179 months	1 493 858	176 561	11.8	148 842	10.0	112 673	75.7
180–239 months	490 191	20 554	4.2	34 398	7.0	25 802	75.0
240+ months	257 961	13 652	5.3	31 276	12.1	23 305	74.5



# Incident CVD Events by Primary Cancer Site, US



- 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

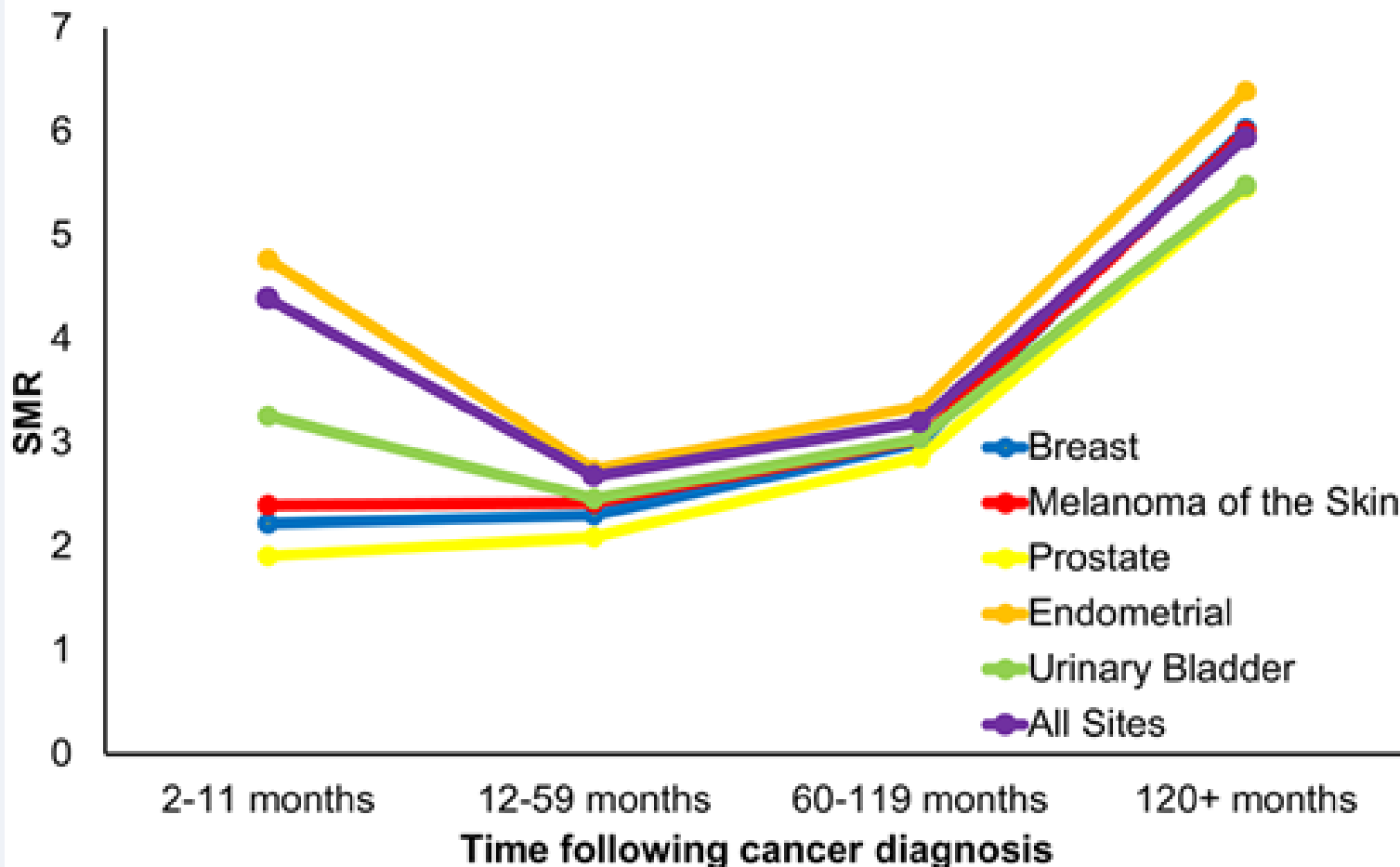
# SMR of CVD Among Survivors



- 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
- <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



## 2000-2015 Risk of Death from Heart Disease



- 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



# Number of Cardiovascular Deaths Rising Among Cancer Survivors, Study Finds

November 25, 2019

## Cancer patients are at higher risk of dying from heart disease and stroke

25 Nov 2019

HEALTH NEWS    NOVEMBER 27, 2019 / 2:58 PM / 9 MONTHS AGO



## Cancer patients, survivors face increased risk of heart disease deaths

<https://www.ajmc.com/view/number-of-cardiovascular-deaths-rising-among-cancer-survivors-study-finds>

<https://www.reuters.com/article/us-health-cancer-heart-death/cancer-patients-survivors-face-increased-risk-of-heart-disease-deaths-idUSKBN1Y12FV>

<https://www.escardio.org/The-ESC/Press-Office/Press-releases/Cancer-patients-are-at-higher-risk-of-dying-from-heart-disease-and-stroke>

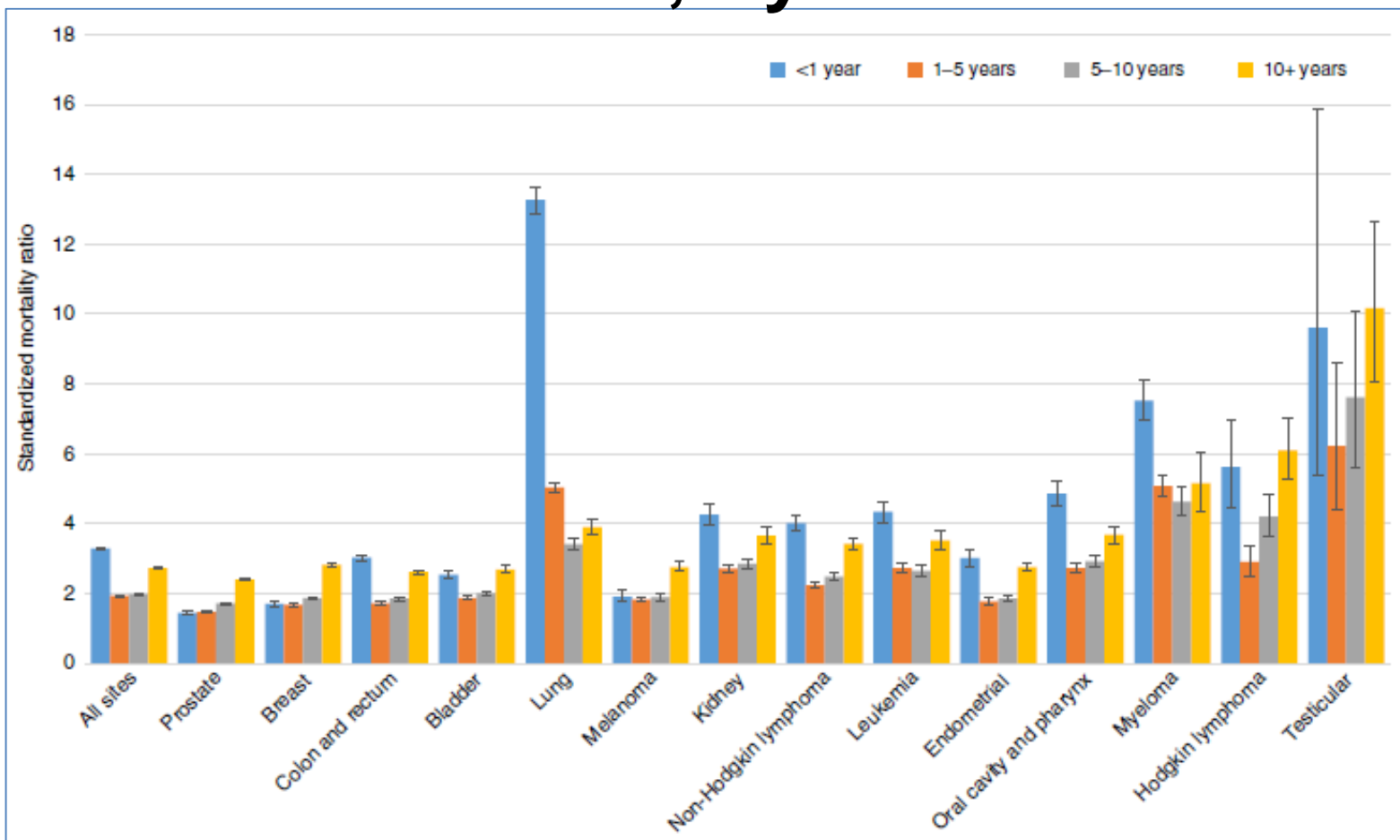
# Fatal heart disease among cancer patients

Kelsey C. Stoltzfus <sup>1</sup>, Ying Zhang<sup>2</sup>, Kathleen Sturgeon<sup>3</sup>, Lawrence I. Sinoway<sup>4</sup>, Daniel M. Trifiletti<sup>5</sup>,  
Vernon M. Chinchilli<sup>3</sup> & Nicholas G. Zaorsky <sup>1,3</sup> 

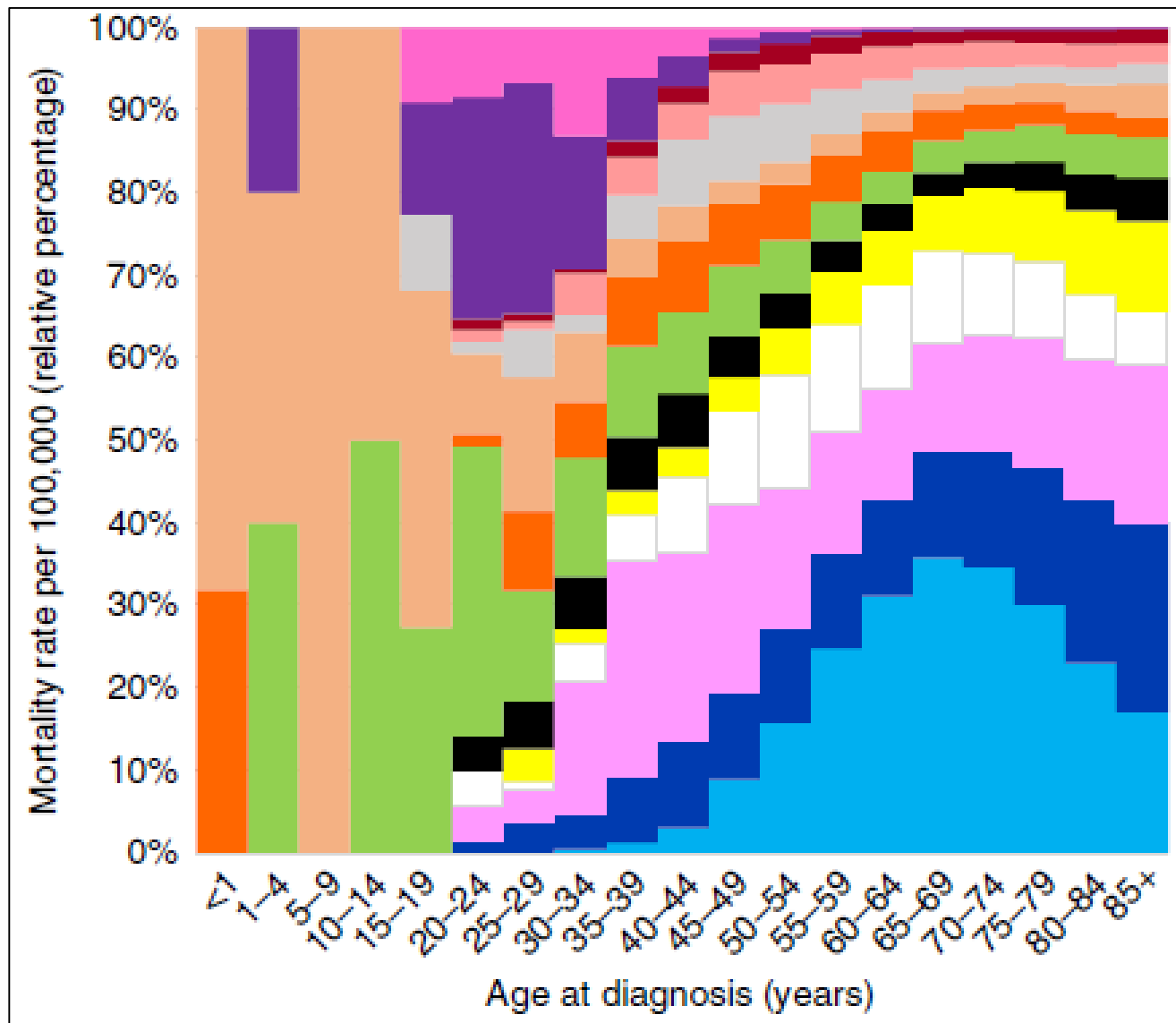


- Identify subgroups of cancer patients at greatest risk of fatal CVD compared to:
  - (1) the general population
  - (2) other cancer patients during the study time
  
- n= 7,529,481 cancer patients

# CVD death, By Cancer Site



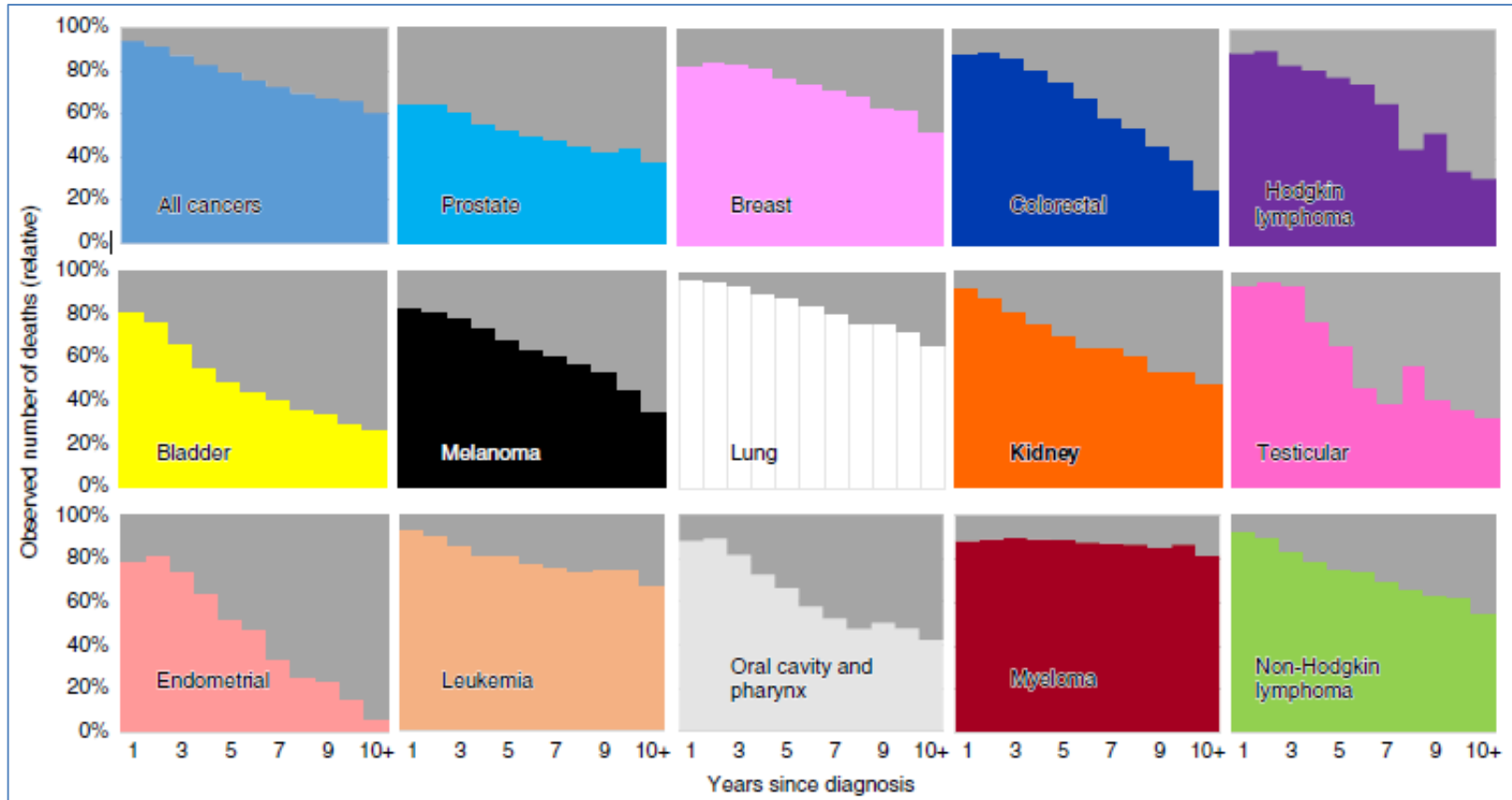
- All sites after diagnosis:
  - SMR at 1–5 years: 1.93 (95% CI: 1.91 -1.95)
  - SMR at >10 years: 2.73 (95% CI: 2.7 - 2.75)



- $<40$  yrs. old: breast cancer and lymphoma
- $\geq 40$  yrs. old: prostate, colon/rectum, breast, lung



# Death from Primary Cancer vs. CVD



- 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

# 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

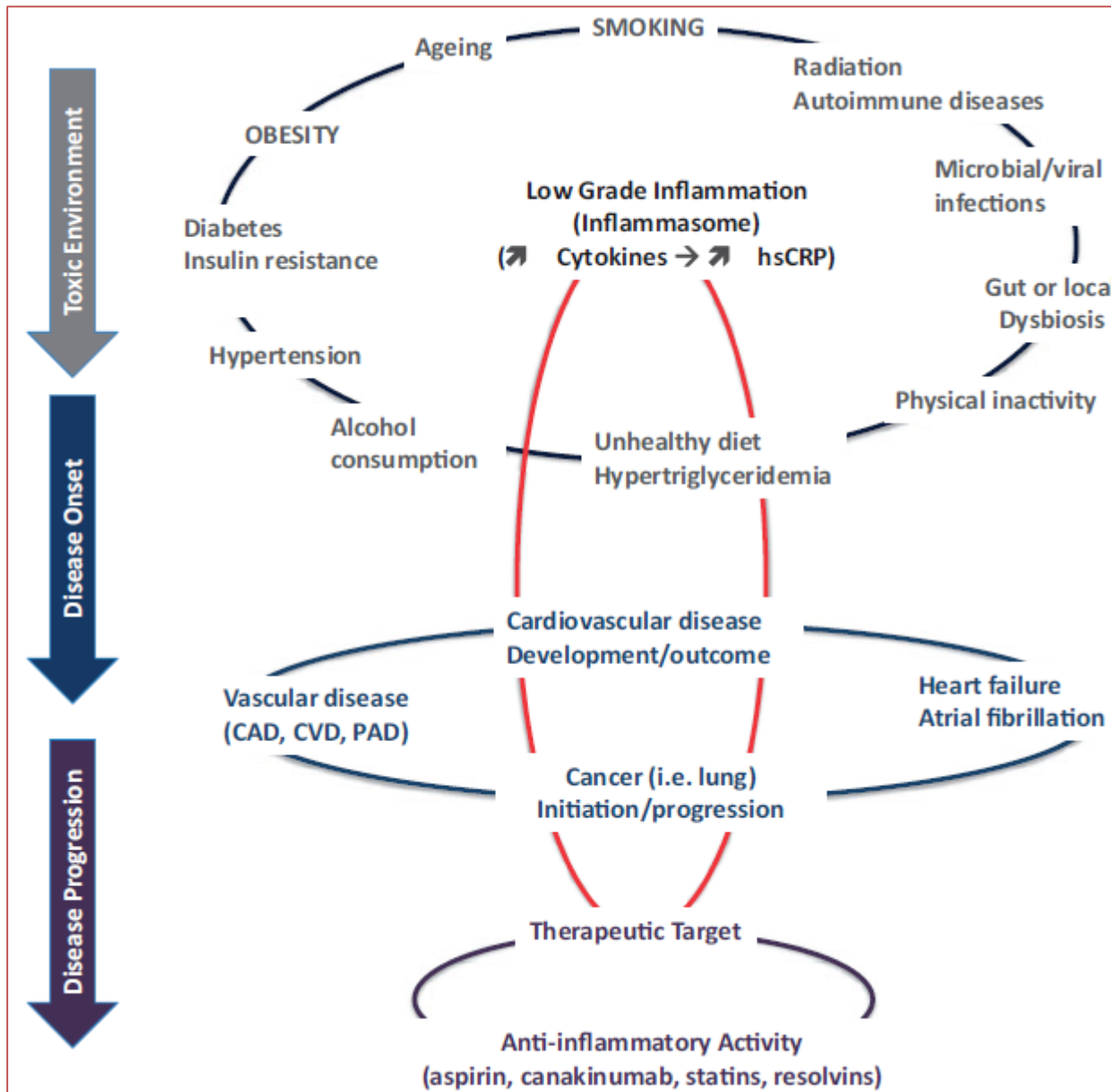
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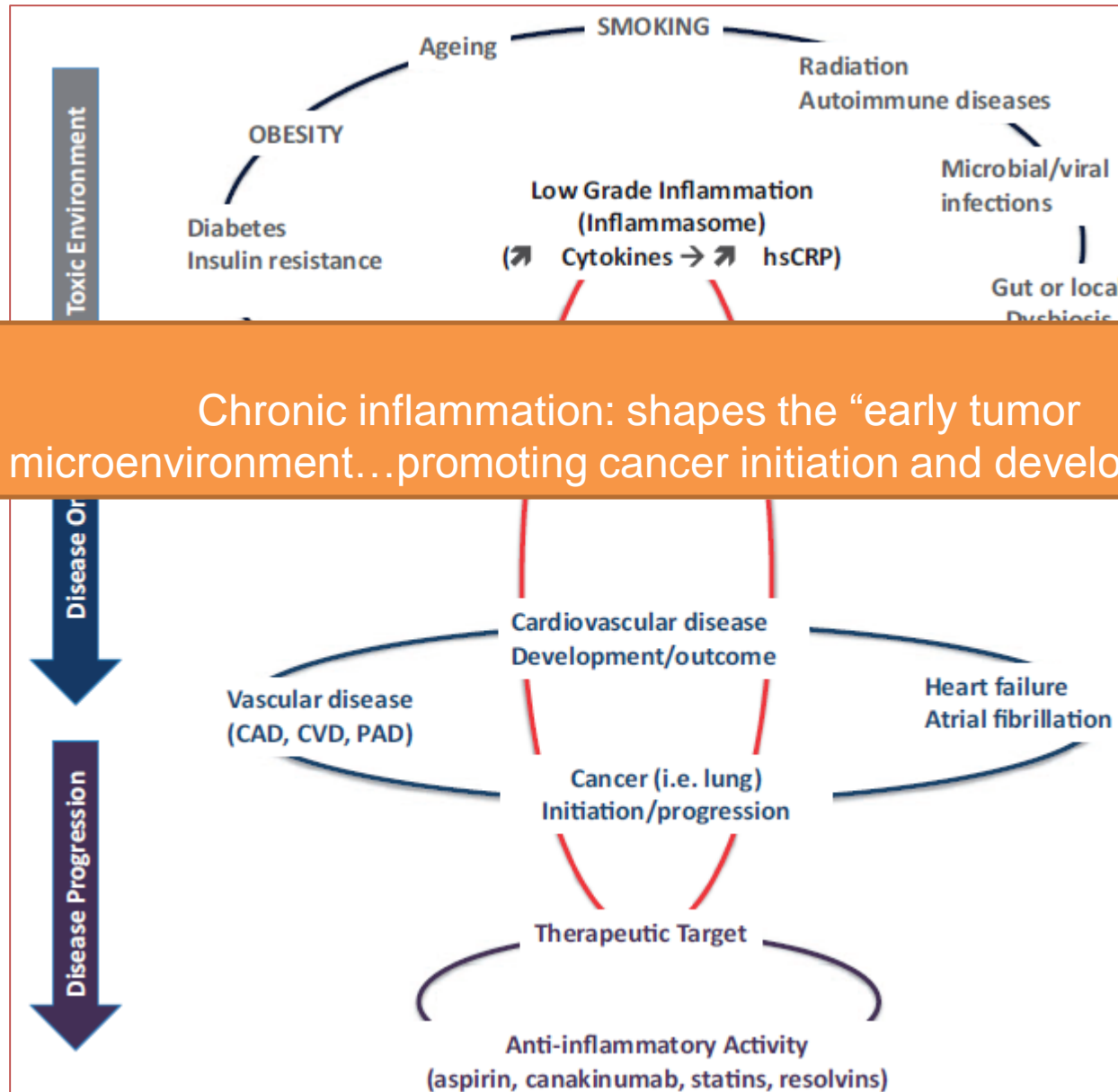
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# Inflammation, cardiovascular disease, and cancer: a common link with far-reaching implications



Lancellotti P, et al. European Heart Journal (2019) 40, 3910–3912.

# Inflammation, cardiovascular disease, and cancer: a common link with far-reaching implications



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

Lancellotti P, et al. European Heart Journal (2019) 40, 3910–3912.

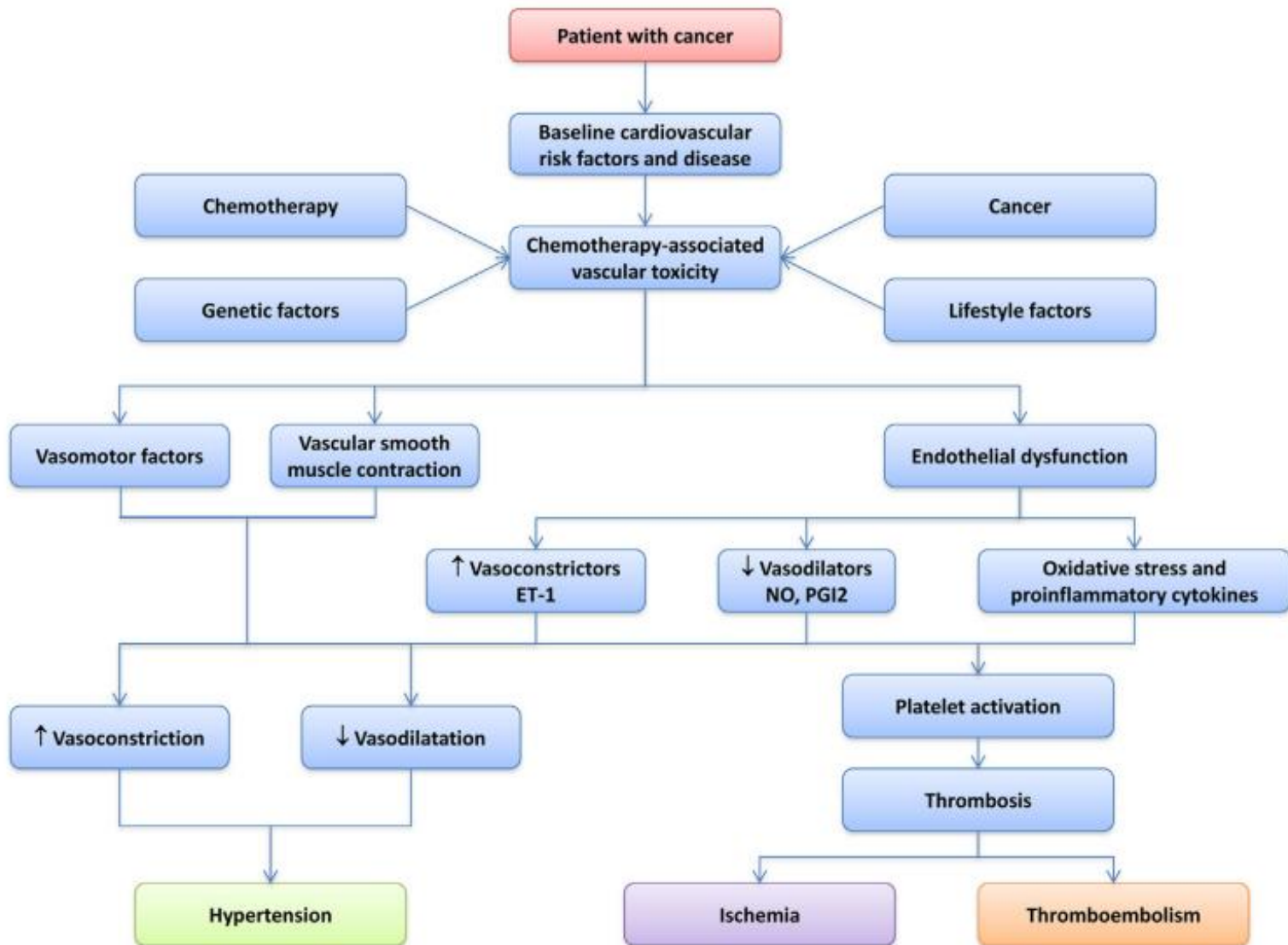
# Mechanisms of CVD Among Cancer Survivors



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3. Shared risk factors for CVD and cancer
  - Genetic, metabolic, and inflammatory

# Vascular Complications of Cancer Chemotherapy

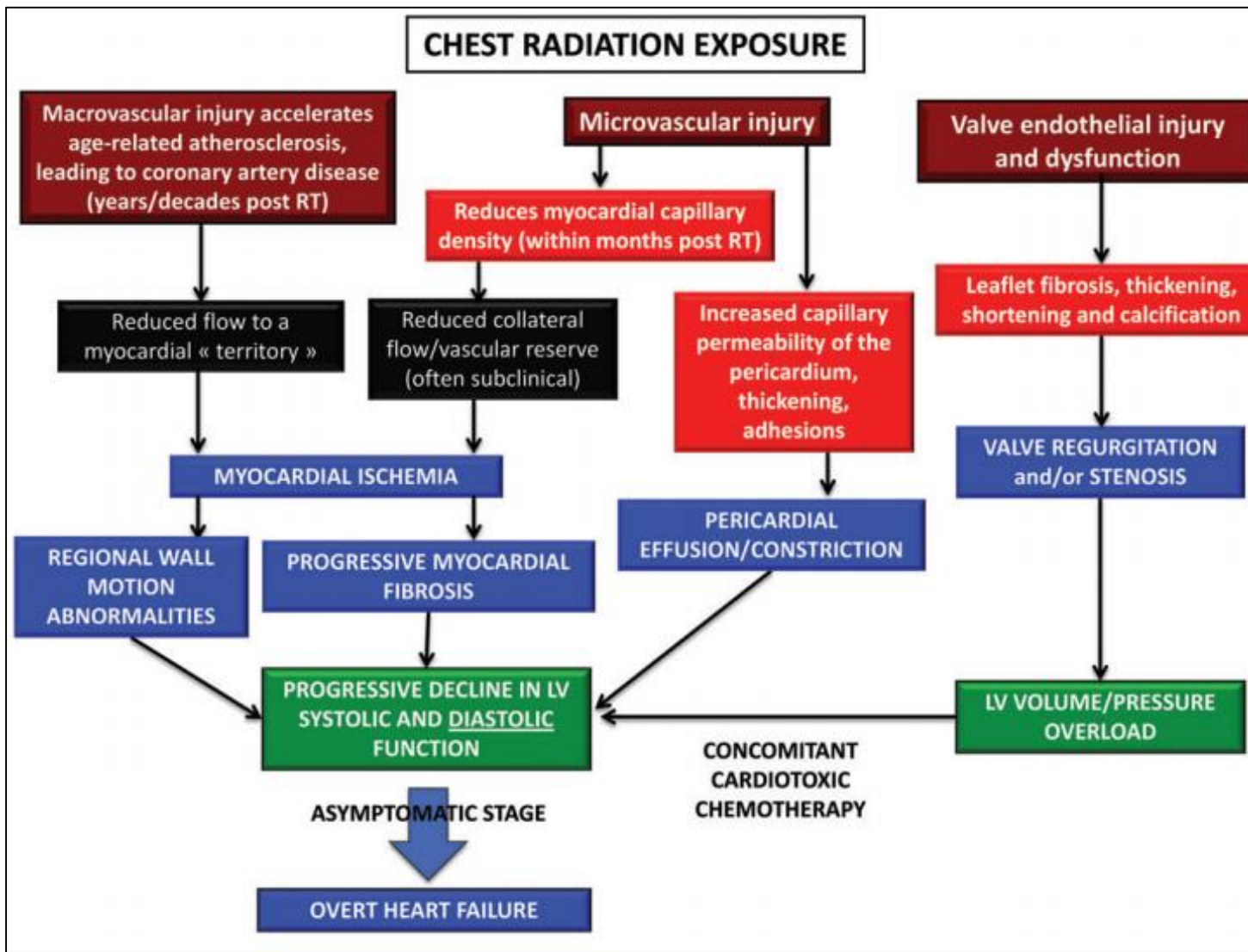


Cameron AC, et al. Canadian Jnl Cardiol. 2016;32: 852-862





**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**



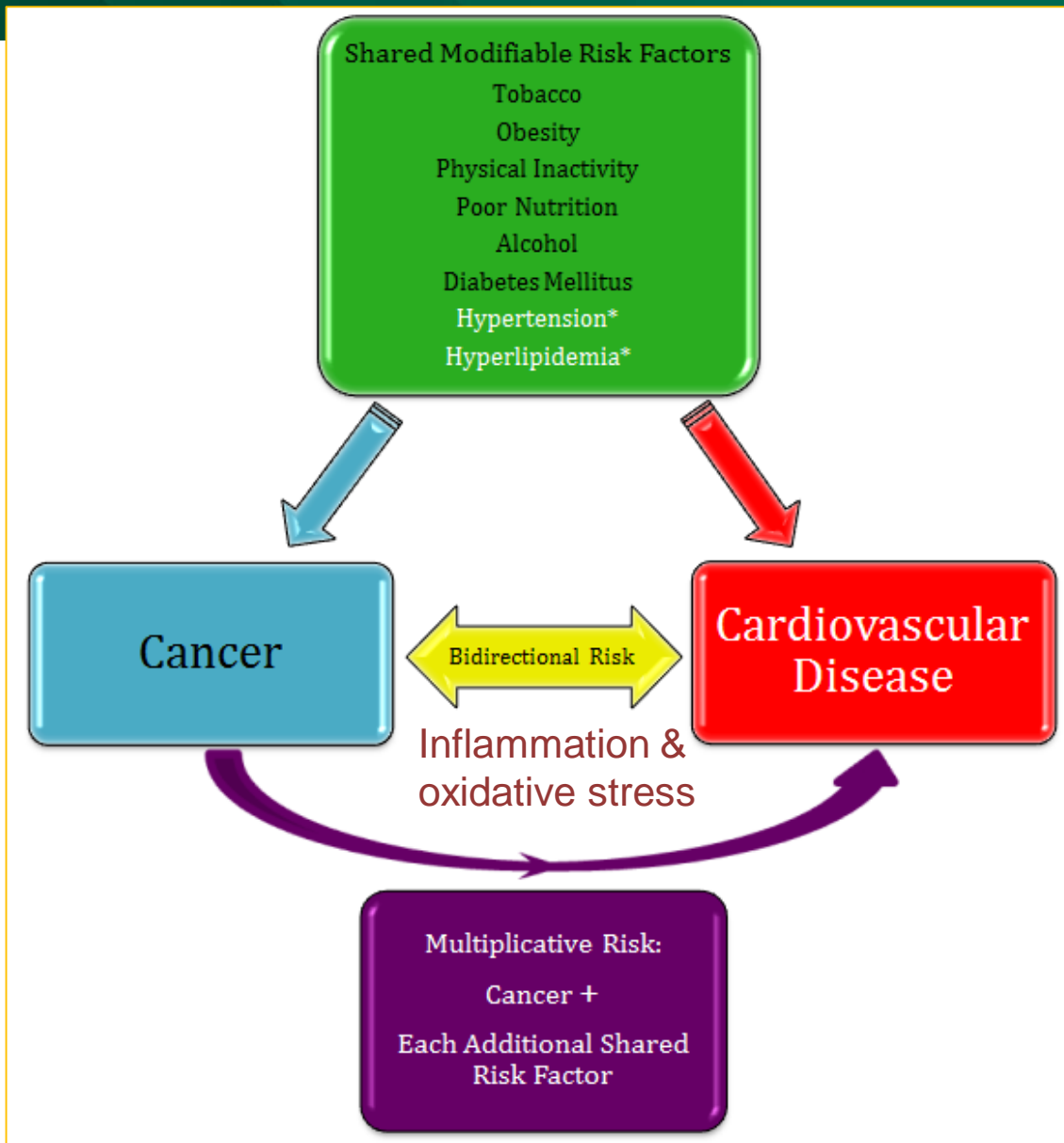
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# Cancer and CVD: Shared Modifiable Risk Factors



# Shared Modifiable CVD and Cancer Risk Factors



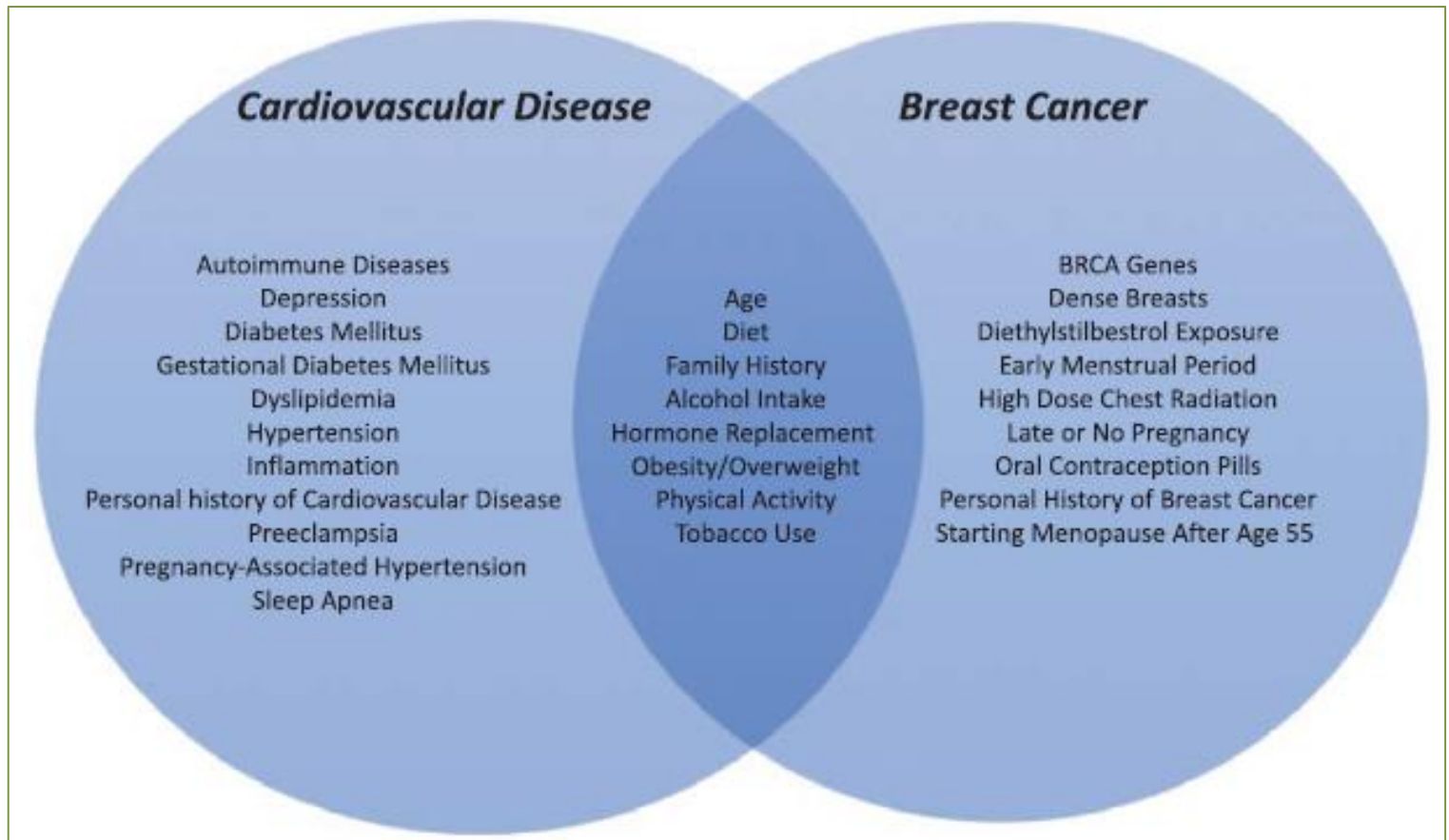
	Breast	Prostate	Lung	Colorectal
Physical activity	▼			▼▼ (colon)
Unhealthy diet	▲			▲▲
Obesity	▲▲			▲ (w) ▲▲▲ (m)
Diabetes	▲▲			▲▲
Hypertension			▲	▲
Tobacco smoking	▲	▲▲	▲▲▲	

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,



# Cardiovascular Disease and Breast Cancer: Where These Entities Intersect

A Scientific Statement From the American Heart Association



# Cancer Survivors: Hypertension



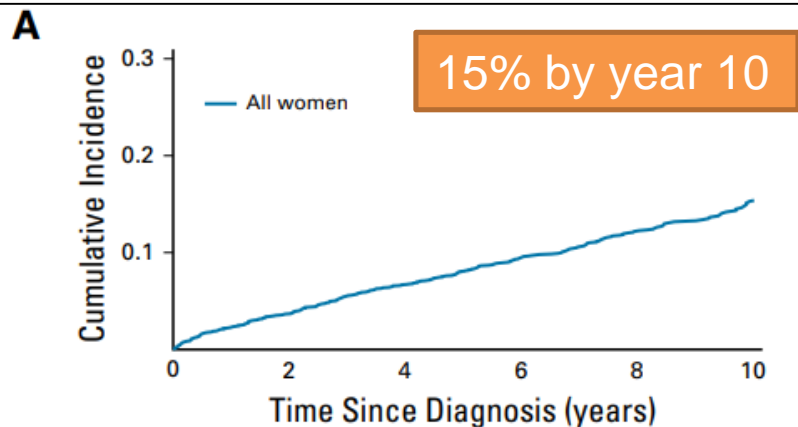
- Most common cardiovascular comorbidity among cancer survivors: 37%
- Several cancers and cancer-related treatments directly cause hypertension
  - high risk of developing new or worsening HTN
  - home blood pressure monitoring
- Increase in blood pressure has been shown to predict efficacy of cancer treatment

# Adipose Tissue Distribution and Cardiovascular Disease Risk Among Breast Cancer Survivors

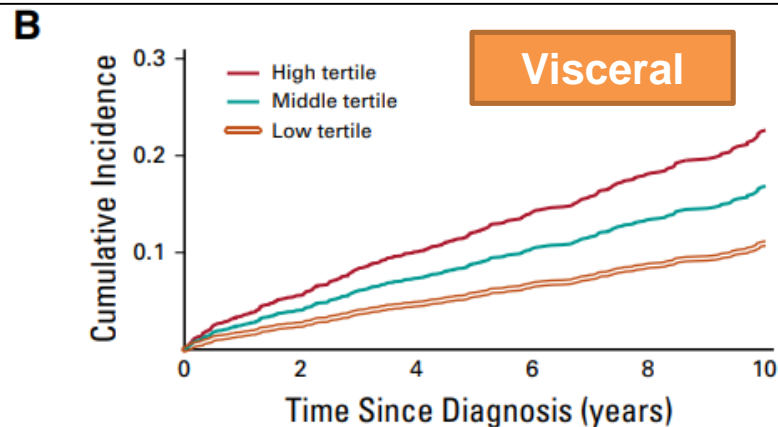


- n=2,943 patients with non-metastatic breast cancer without prior CVD
- Stage I to III invasive breast cancer with abdominal CT at diagnosis
- Outcomes:
  - acute myocardial infarction, ischemic stroke, heart failure
  - composite end point (any above +/- coronary revascularization +/- CVD-related deaths)

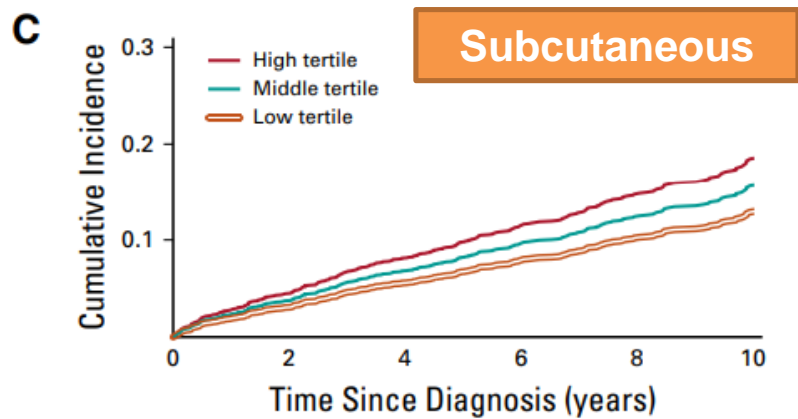
# Incident CVD Events: The Decade after a Non-metastatic Breast Cancer Diagnosis



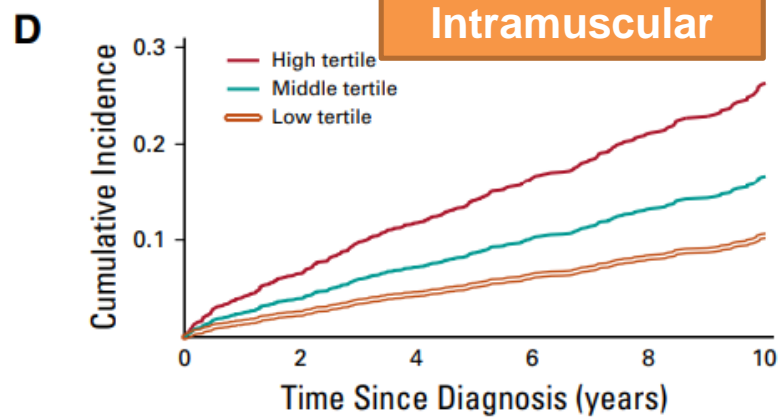
No. at risk	0	2	4	6	8	10
	2,943	2,568	2,207	1,558	862	373



No. at risk	0	2	4	6	8	10
High tertile	642	566	470	315	177	79
Middle tertile	899	789	686	477	258	107
Low tertile	1,402	1,213	1,051	766	427	187



No. at risk	0	2	4	6	8	10
High tertile	812	703	588	399	219	98
Middle tertile	965	850	731	520	279	119
Low tertile	1,166	1,015	888	639	364	156



No. at risk	0	2	4	6	8	10
High tertile	569	477	407	270	132	51
Middle tertile	901	790	675	459	266	119
Low tertile	1,473	1,301	1,125	829	464	203



# Association of BMI with Incident CVD in Breast Cancer Survivors



Body Mass Index	Underweight ( $< 18.5 \text{ kg/m}^2$ )	Normal weight ( $18.5 \text{ to } < 25 \text{ kg/m}^2$ )	Overweight ( $25 \text{ to } < 30 \text{ kg/m}^2$ )	Obese Class I ( $30 \text{ to } < 35 \text{ kg/m}^2$ )	Obese Class II ( $\geq 35 \text{ kg/m}^2$ )
kg/m <sup>2</sup> , mean $\pm$ SD	17.68 $\pm$ 0.64	22.42 $\pm$ 1.71	27.35 $\pm$ 1.39	32.18 $\pm$ 1.40	39.78 $\pm$ 4.45
No. events/No. at risk	8/47	83/1,006	89/898	76/563	72/429
Hazard ratio (95% CI)	2.16 (1.06 to 4.43)	Reference	1.01 (0.75 to 1.37)	1.32 (0.95 to 1.83)	1.70 (1.20 to 2.42)

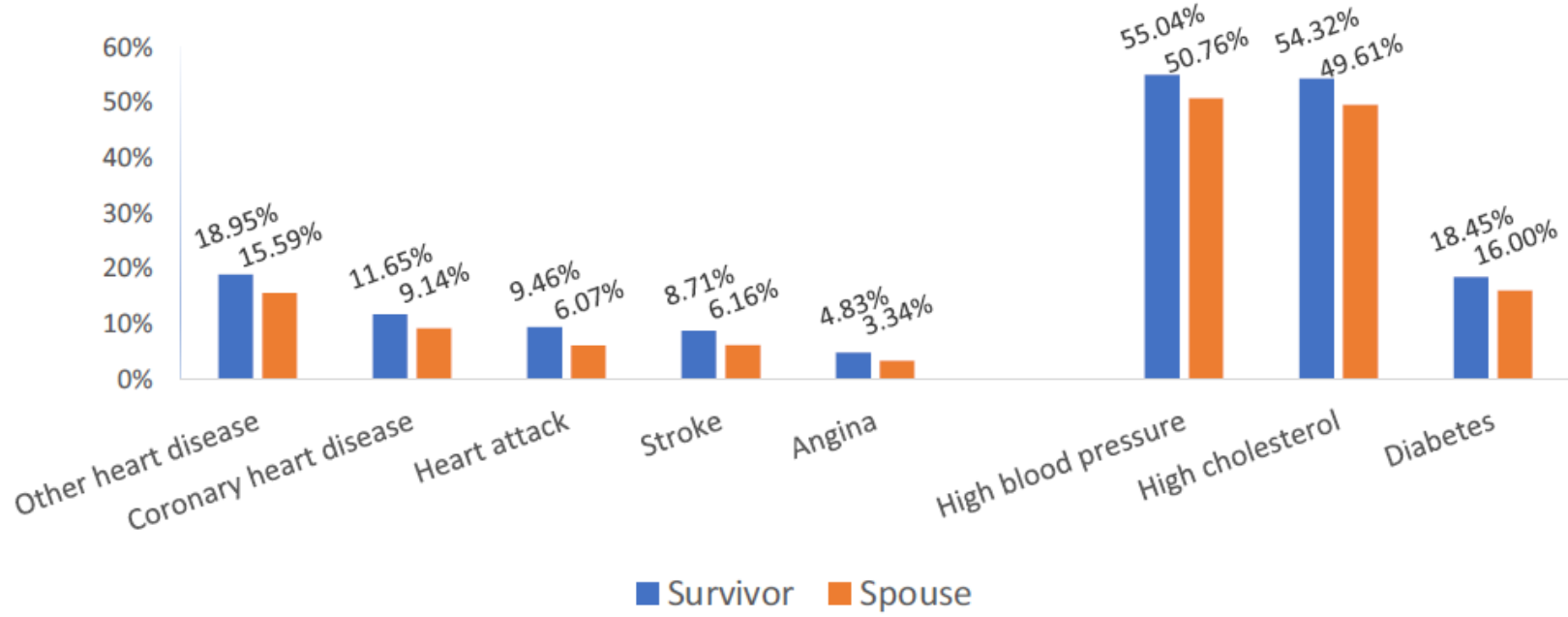
Models are accounting for competing risks, adjusted for: age, race/ethnicity, cancer stage, estrogen receptor/progesterone receptor, human epidermal growth factor receptor 2 status, type of chemotherapy (none, anthracycline containing, or other), smoking history, diabetes, hypertension, and dyslipidemia.



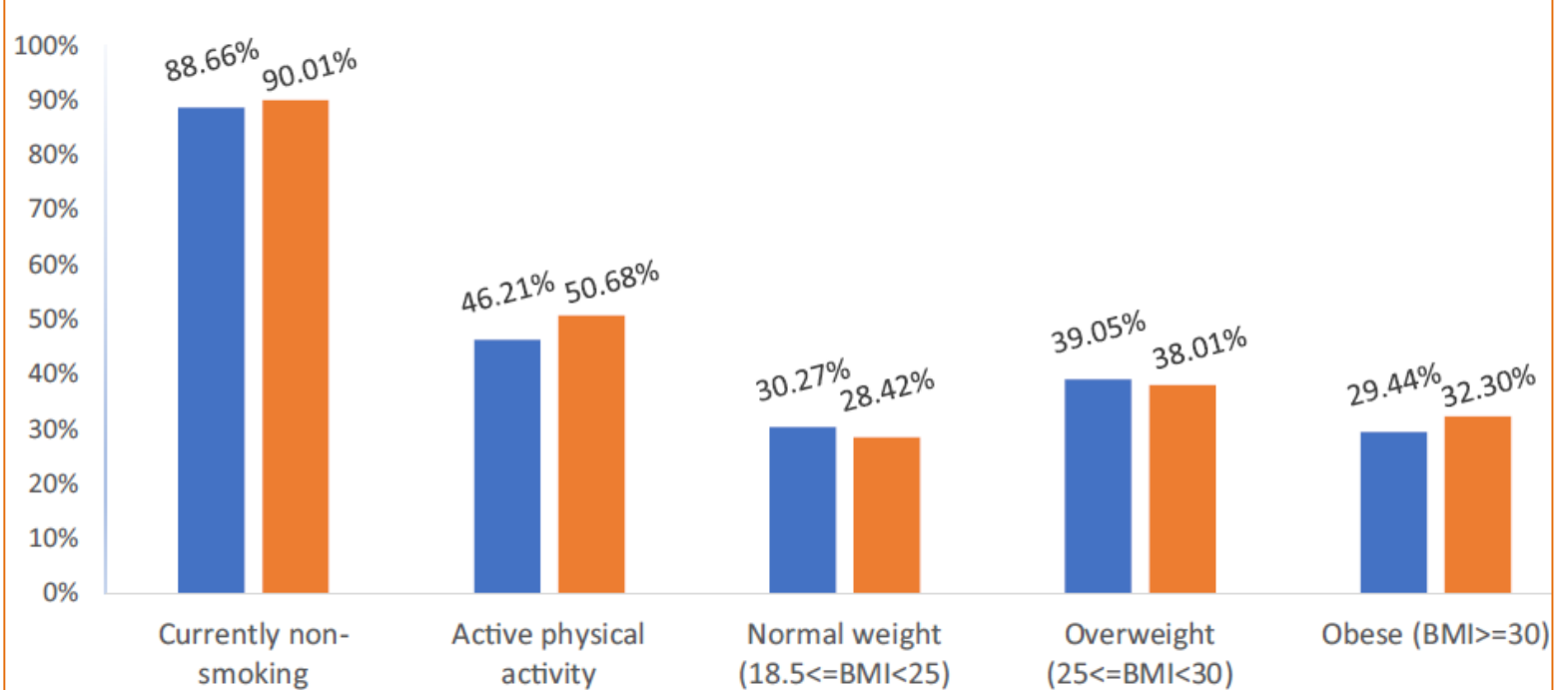
- Significant others of cancer survivors:
  - Have persistent psychological stress
  - Also at increased risk for CVD
- n=1,026 survivor-spouse dyads
  - Survivors  $\geq 18$  years old, self-reported cancer
- 2010-2015 (MEPS) Medical Expenditure Panel Survey



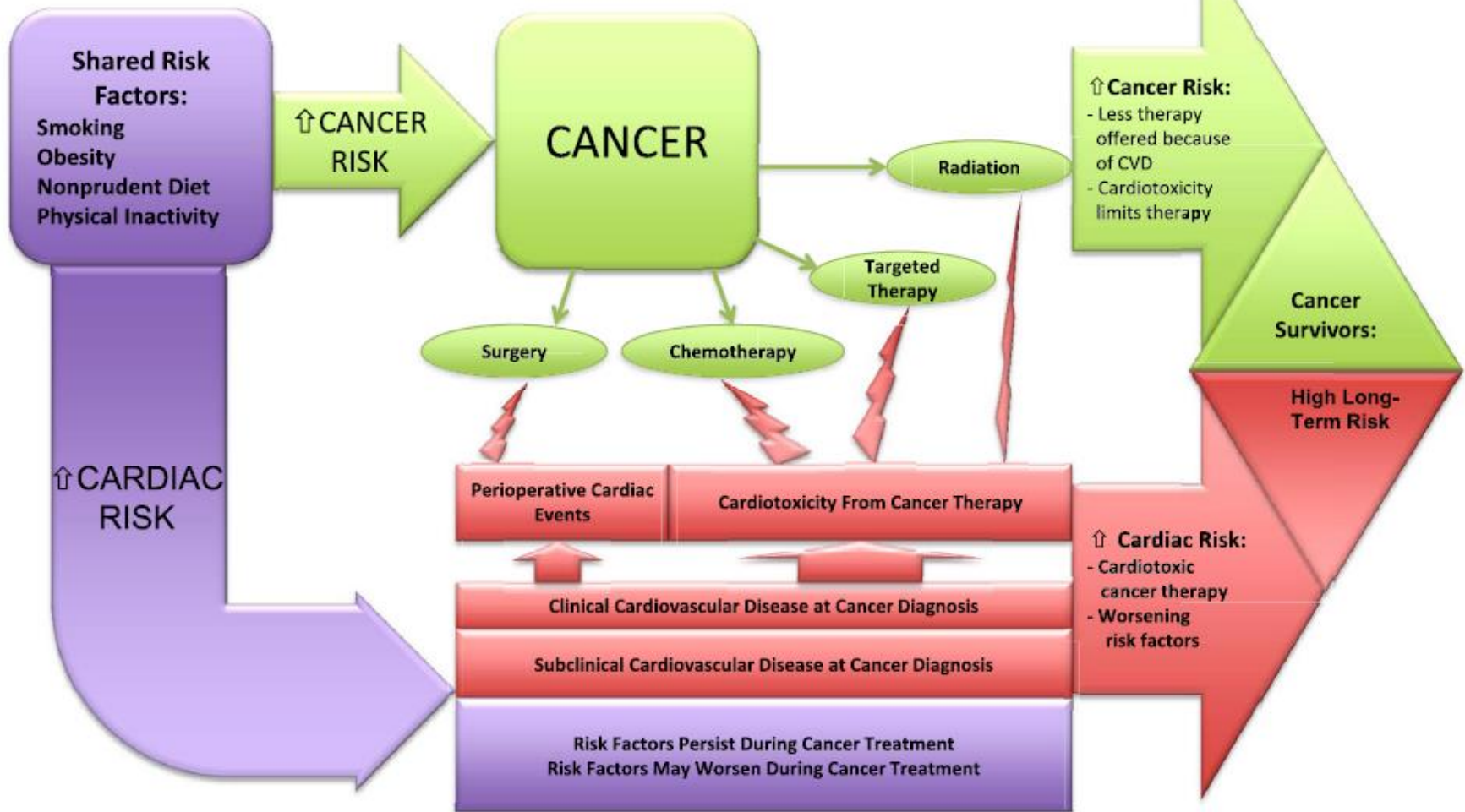
**A Prevalence of the CVD and CVD risk factors**



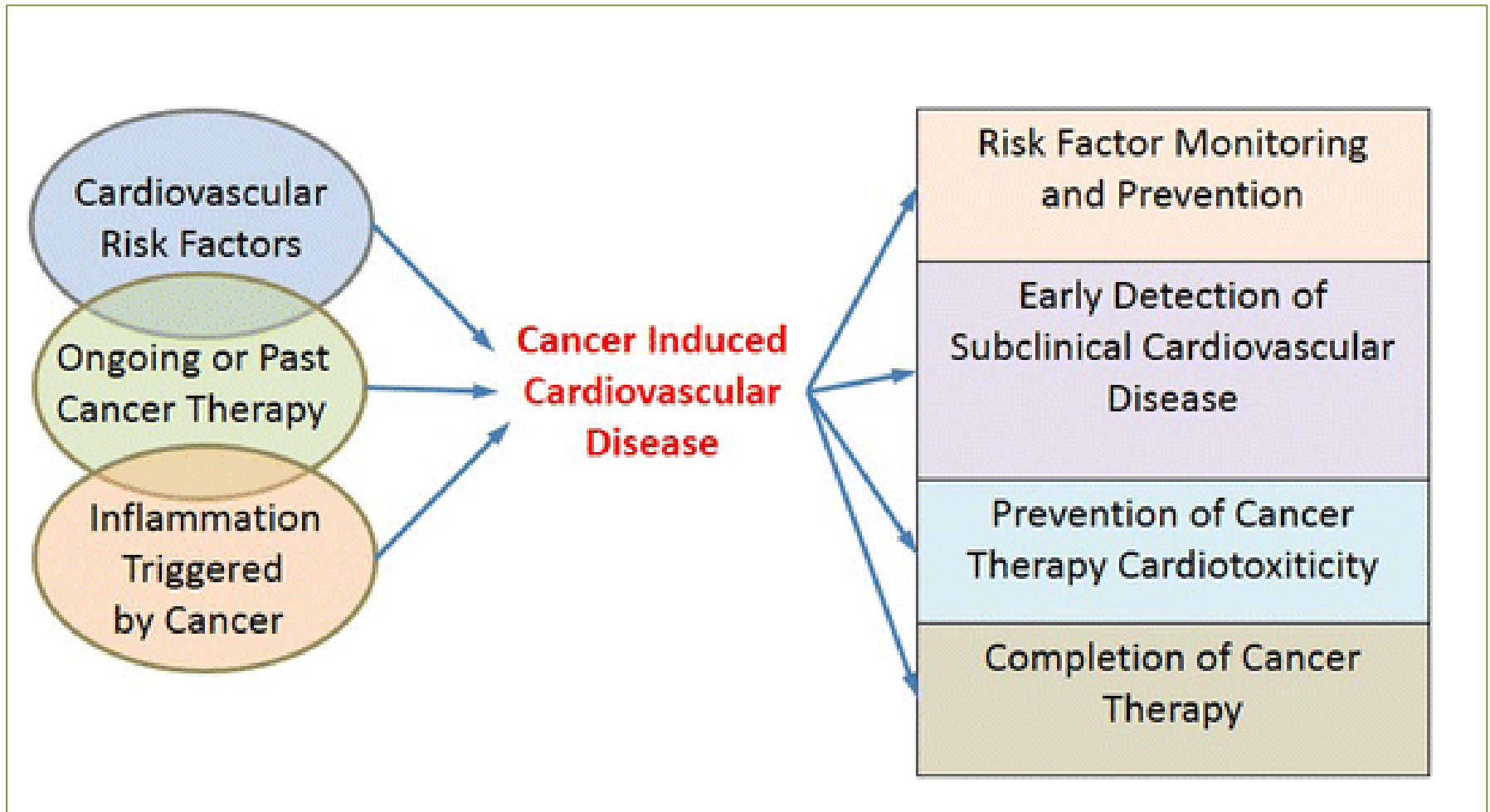
**B Prevalence of health behaviors**



# Putting It All Together: Cancer Survivorship and CVD Risk



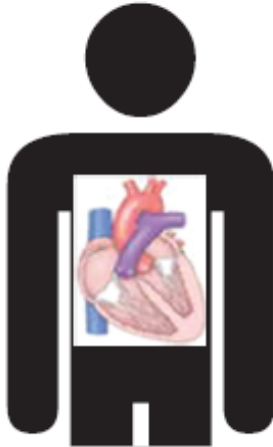
# CVD Prevention Among Cancer Survivors



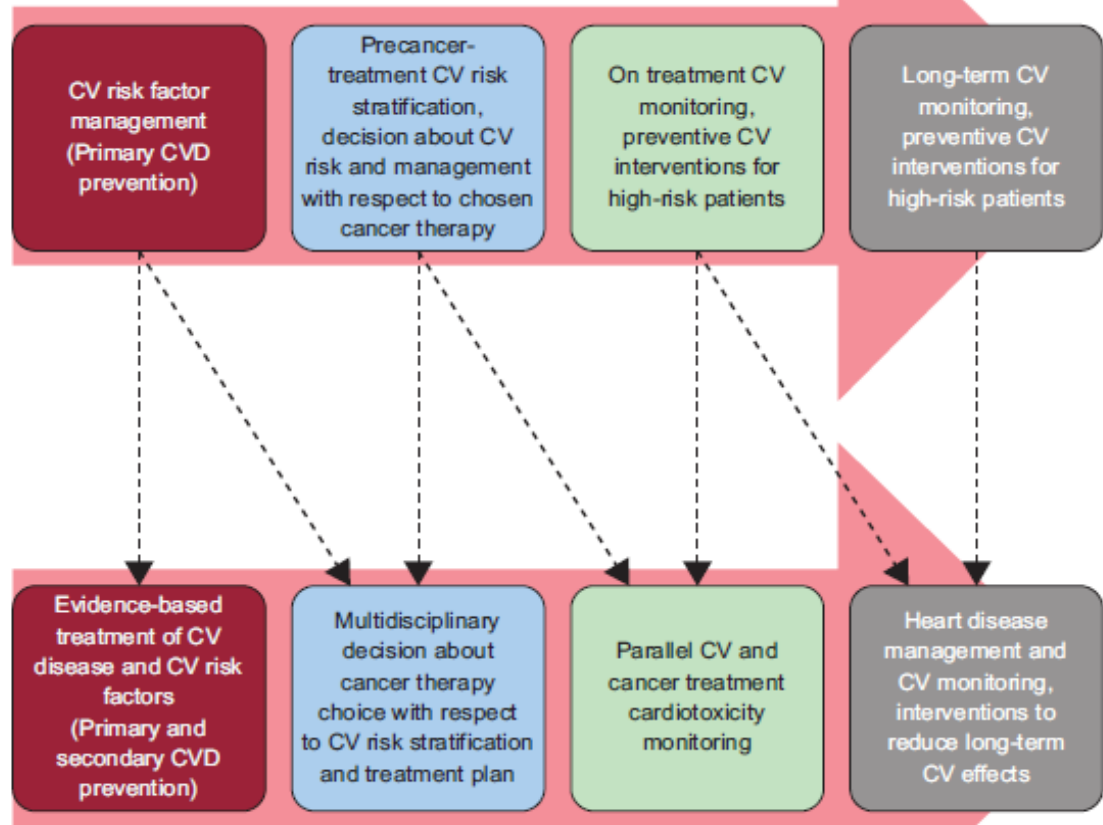
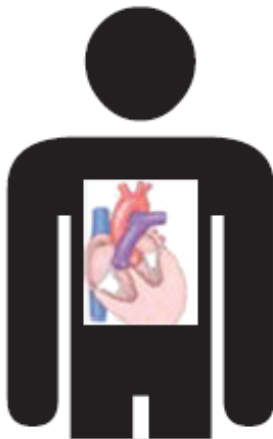
# Longitudinal Multidisciplinary Focus



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



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



# Preventive Cardiovascular Assessment: Diagnosis thru Survivorship



## 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<sup>a</sup>
- Depression screening
- Menopausal status
- EKG and evaluation of LV function by echocardiography or cardiac magnetic resonance
- Baseline biomarkers (NT-proBNP and BNP)

## Management goals

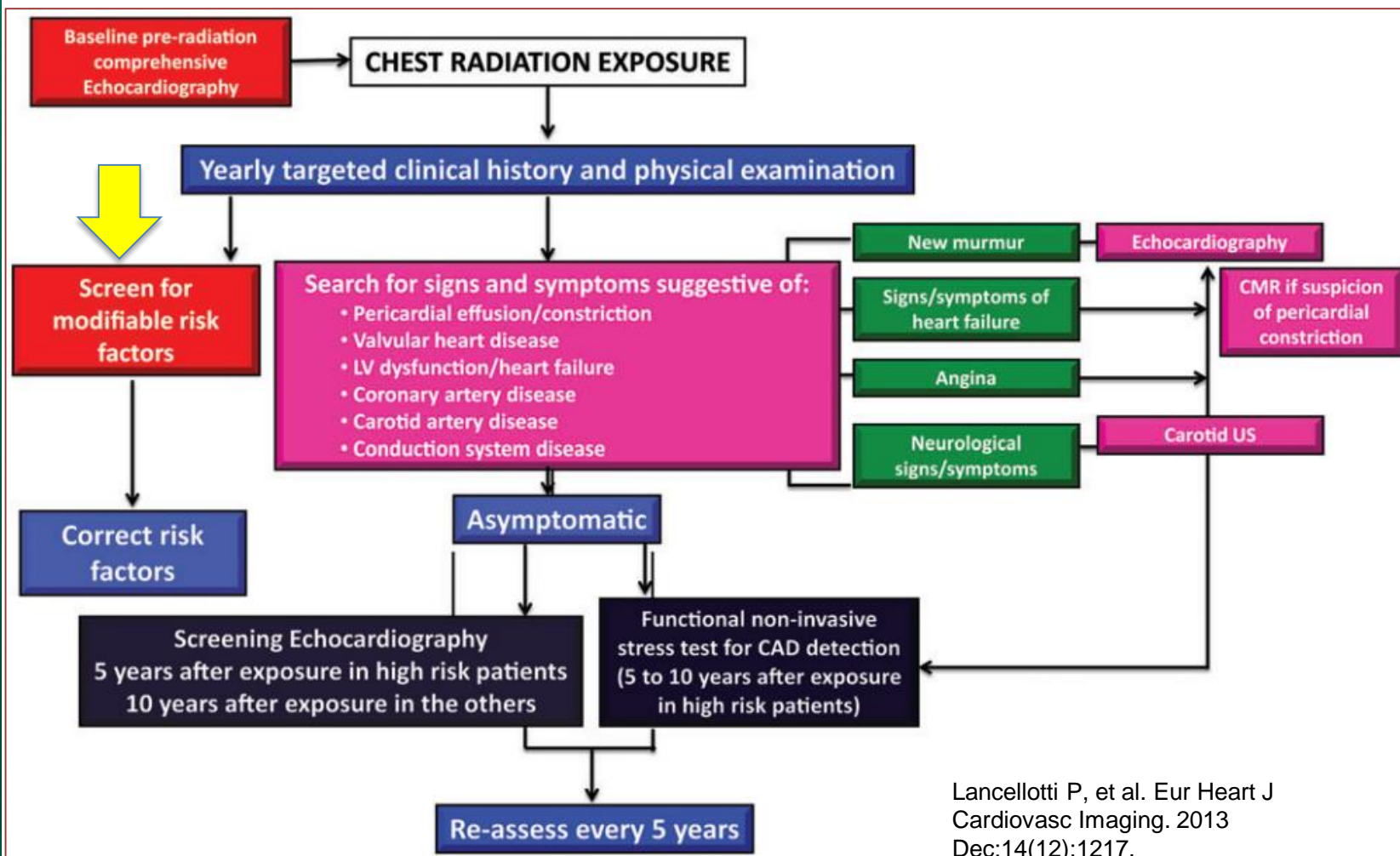
- Referral to cardiology
  - » For known CVD
  - » For decreased LV function
  - » For monitoring and treatment with carvedilol and/or ACE inhibitors
- Lifestyle behaviors<sup>b</sup>
- Lipid management
  - » LDL < 100 mg/dL (< 70 mg/dL for high-risk patients)
  - » Total cholesterol < 200 mg/dL
  - » 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
- Waist circumference
  - » < 35 inches for women
  - » < 40 inches for men
- Maintain glucose < 100 mg/dL
- Insulin < 15 mg/dL or HgA1c < 5.7 mg/dL

## 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!



Heather M. Johnson, MD, MS, MMM, FAHA, FACC  
Preventive Cardiologist,  
Christine E. Lynn Women's Health & Wellness Institute  
Boca Regional Hospital/Baptist Health South Florida  
**[hjohnson@baptisthealth.net](mailto:hjohnson@baptisthealth.net)**  
**Clinic phone: 561-955-2131**

# Additional Slides



# Time-Varying Analysis (1973 - 2012)

