Physical Issues Cancer Survivors Face and Interventions for Improved Physical Well-Being

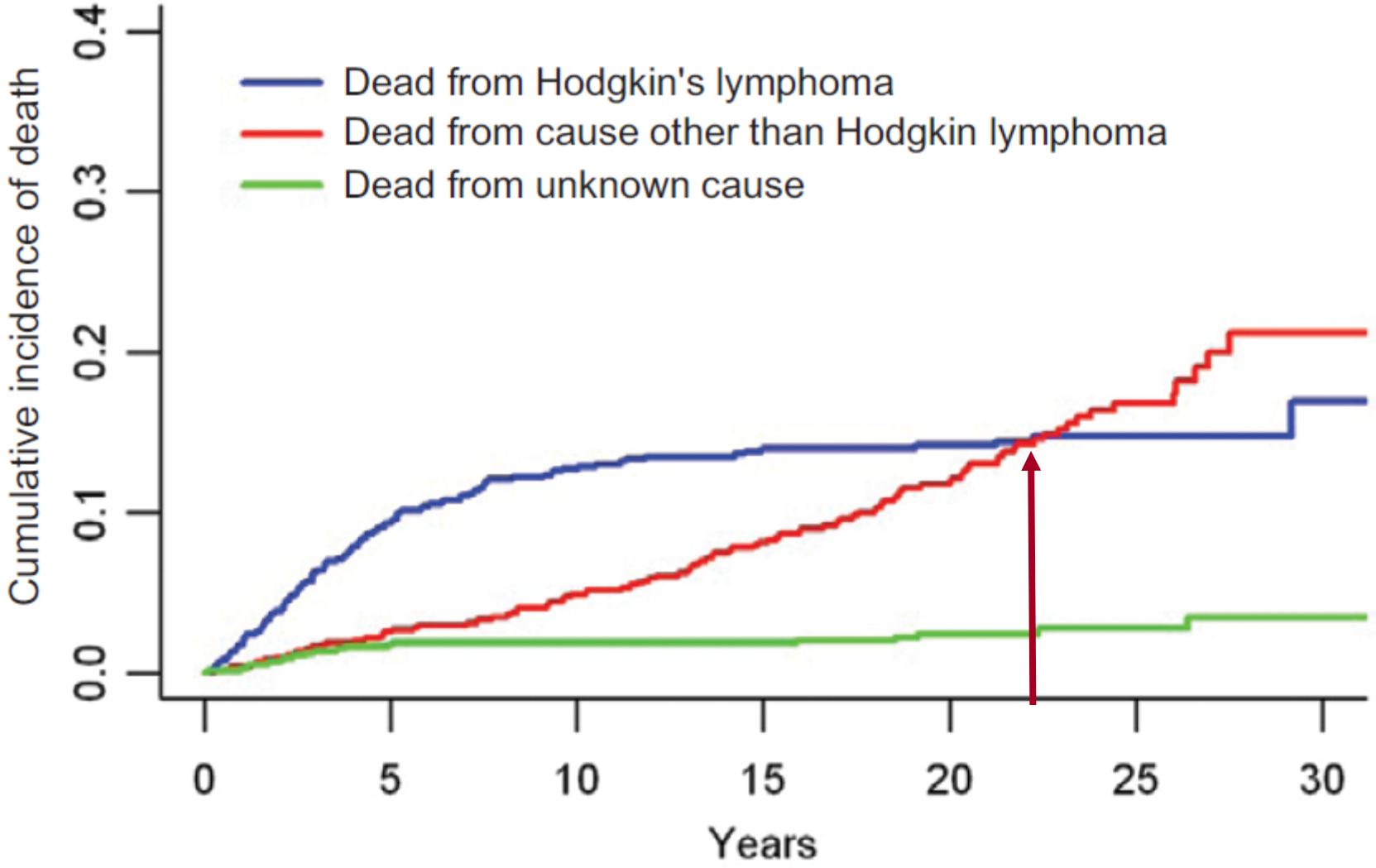
Kevin C. Oeffinger, MD
Director, Duke Center for Onco-Primary Care
Director, Duke Cancer Supportive Care and Survivorship Center

Duke Cancer Institute

National Cancer Policy Forum
Long-Term Survivorship Care
July 25, 2017

Late Mortality Among 5+ Year HL Survivors

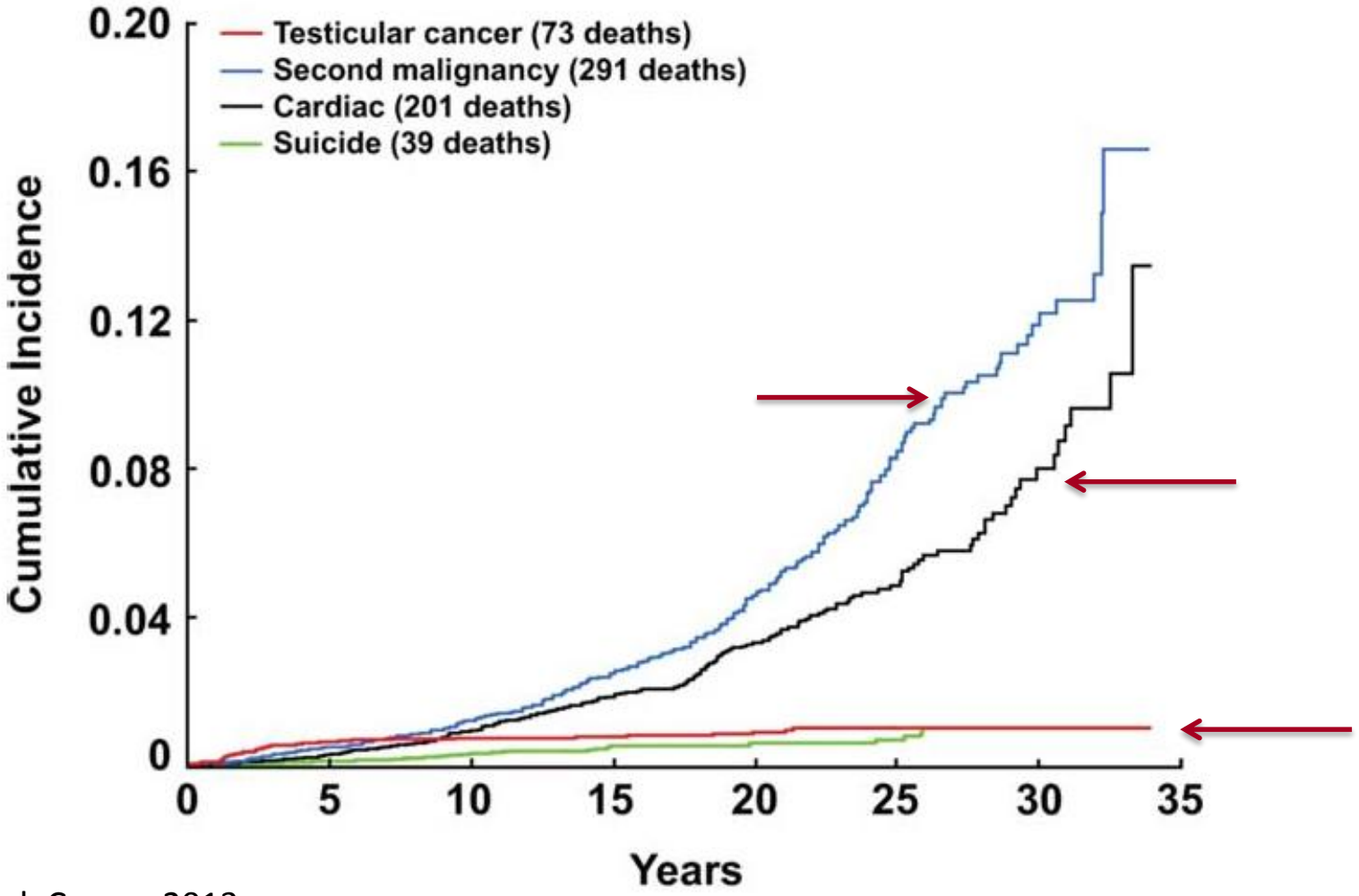
MSKCC Adult Hodgkin Lymphoma Study (1975-2000; N=747)



Matasar M, et al. J Natl Cancer Inst, 2015

Cumulative Incidence by Causes of Death for Patients With Stage I Testicular Seminoma

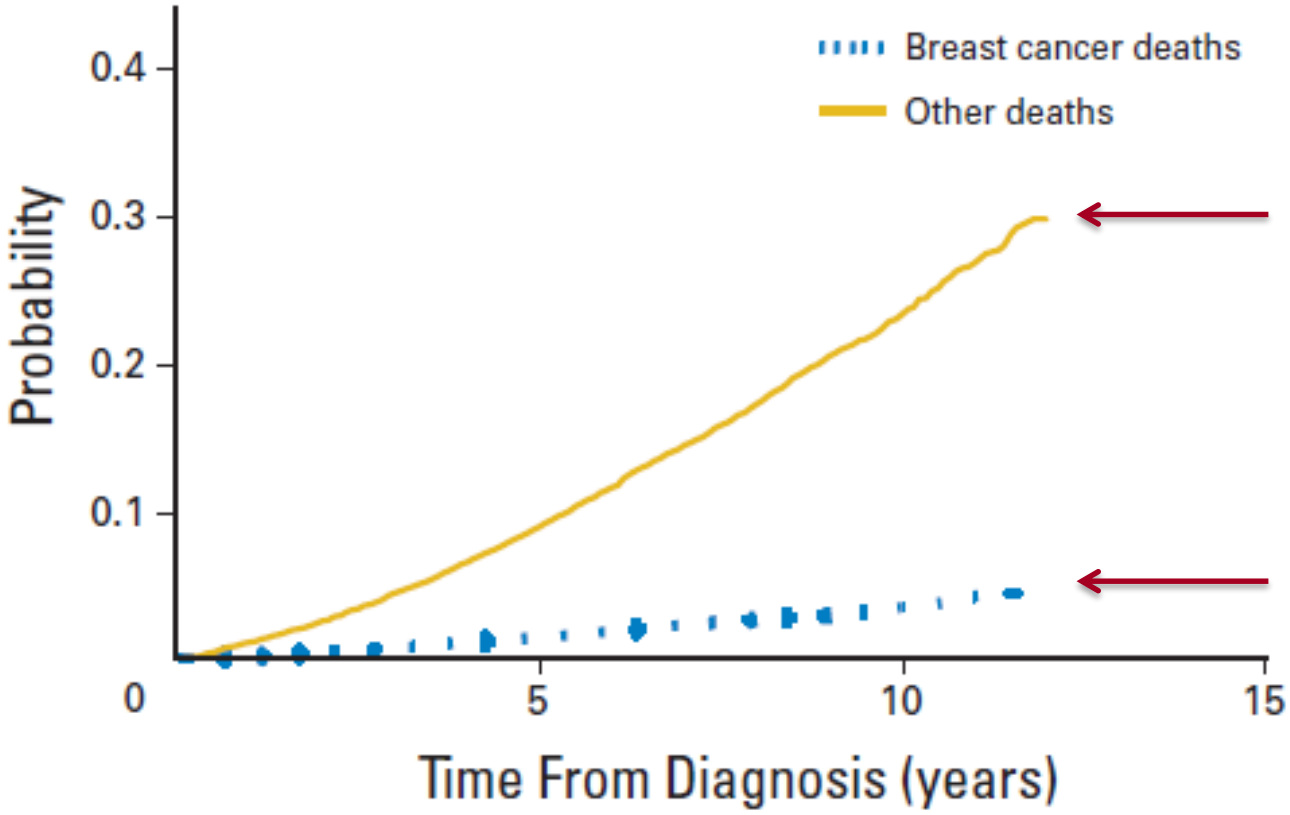
SEER Registry: N=9193 men; Diagnosed 1973-2001



Beard CJ, et al. Cancer 2013

Probability of death from breast cancer or other causes among women age 50 and older with ER+ early stage breast cancer

SEER: 1988-2001



Hanrahan EO, et al. J Clin Oncol, 2007

Outline

- Selected 'physical' issues
  - Second (and subsequent) primary cancers
  - Cardiovascular disease
  - Accelerated aging
- Interventions
  - Risk-stratified screening and surveillance
  - Management of comorbidities
  - Interception?
  - Healthy lifestyles [Wendy Demark-Wahnefried, PhD]
- Focus – survivors of adult cancers

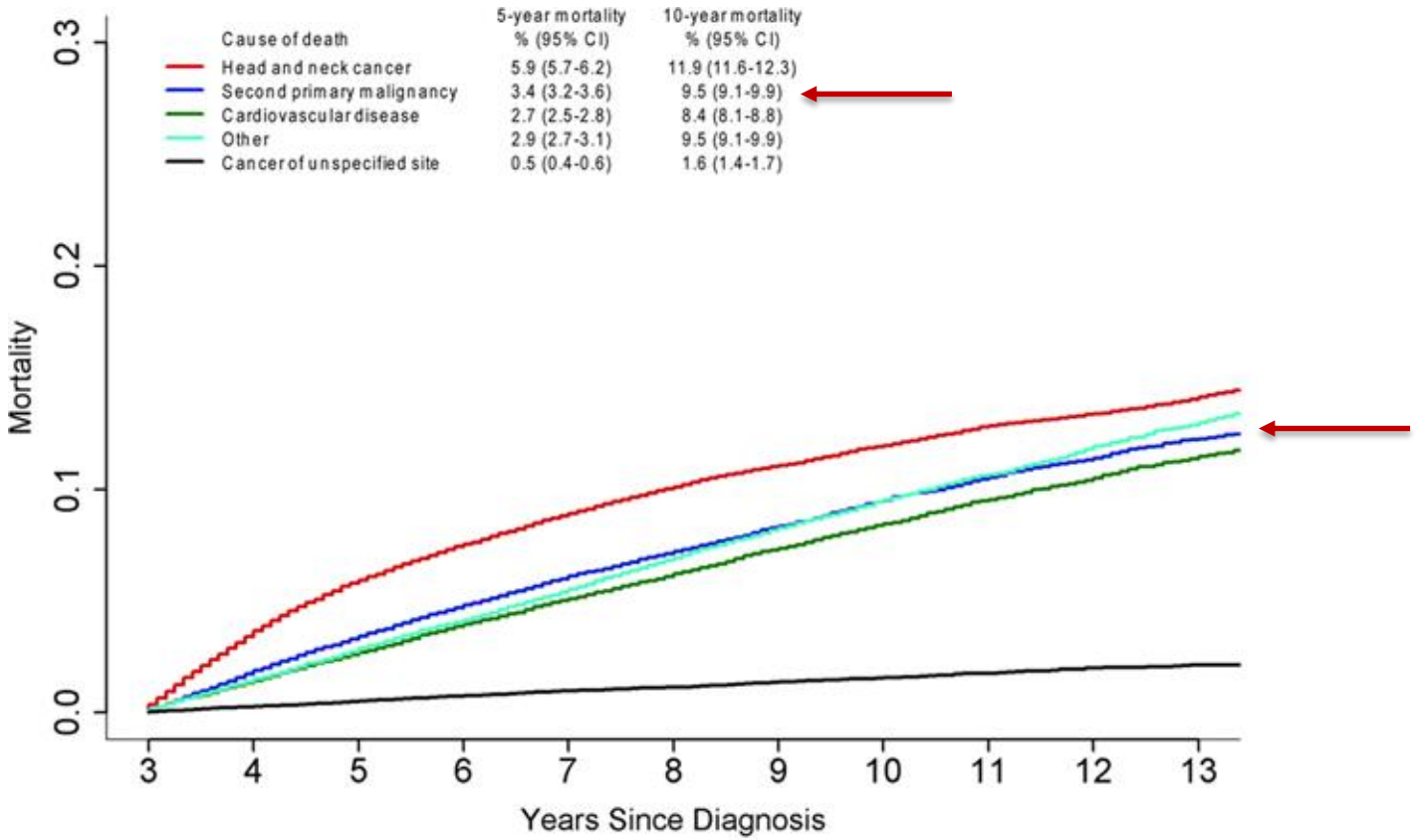
Second Primary Cancer (SPC)

- 20% of incident cancers are a second (or subsequent) primary cancer
- Causal pathways:
  - Lifestyle habits
  - Aging
  - Genetic factors
  - Treatment exposures for the first cancer
  - All of the above (interactions)

SPC after Head / Neck Cancer

SEER – 1992 – 2005

Cause-specific mortality among
3-year survivors of head and neck cancer



Duke Cancer Institute

Baxi SS, et al. Cancer, 2014

SPC after Head / Neck Cancer

Risk prediction model – 10-year cumulative risk of SPC

Cohort of 293,435 from 12 French registries

Age at H/N cancer	Calendar period	10-yr cumulative risk of SPC	Difference with general population
55 - 64 years	2001 - 2003	41.0%	+25.9%
	2004 - 2006	40.6%	+25.7%
	2007 - 2010	41.1%	+26.9%

Moitry M, et al. Cancer Epidemiol, 2017

SPC after Head / Neck Cancer

SEER – 1975 – 2006

Treatment	SIR	95% CI	AER*
Any solid tumor	2.2	2.1-2.2	167.7
Lung	3.7	3.7-3.8	75.2
Head / neck	12.4	12.0-12.7	59.8
Esophagus	8.3	7.8-8.9	14.2

*per 10,000 person-years

Morris LG, et al. J Clin Oncol, 2011

Aging and SPC

SEER – 1992 – 2008

Risk of SPC based upon age at first cancer

Age at first cancer	Females HR (95% CI)	Males HR (95% CI)
51 – 65 years	4.7 (4.3-5.0)	8.8 (7.8-9.9)
66 - 80	7.1 (6.6-7.6)	15.1 (13.4-17.0)
> 80	6.2 (5.7-6.7)	15.2 (13.5-17.2)

Donin N, et al. Cancer, 2016

SPC after Breast or Colorectal Cancer

Risk prediction model – 10-year cumulative risk of SPC

Cohort of 293,435 from 12 French registries

FEMALES

Calendar period for first cancer – 2007-2010

	First Breast Cancer		First Colorectal Cancer	
Age at first cancer	10-yr cumulative risk	Difference with general population	10-yr cumulative risk	Difference with general population
55 - 64 yrs	6.8%	+1.5%	10.0%	+3.0%
65 - 74	9.3%	+1.9%	10.7%	+2.2%
≥ 75	10.5%	+2.0%	10.6%	+1.6%

Moitry M, et al. Cancer Epidemiol, 2017

SPC after Prostate or Colorectal Cancer

Risk prediction model – 10-year cumulative risk of SPC

Cohort of 293,435 from 12 French registries

MALES

Calendar period for first cancer – 2007-2010

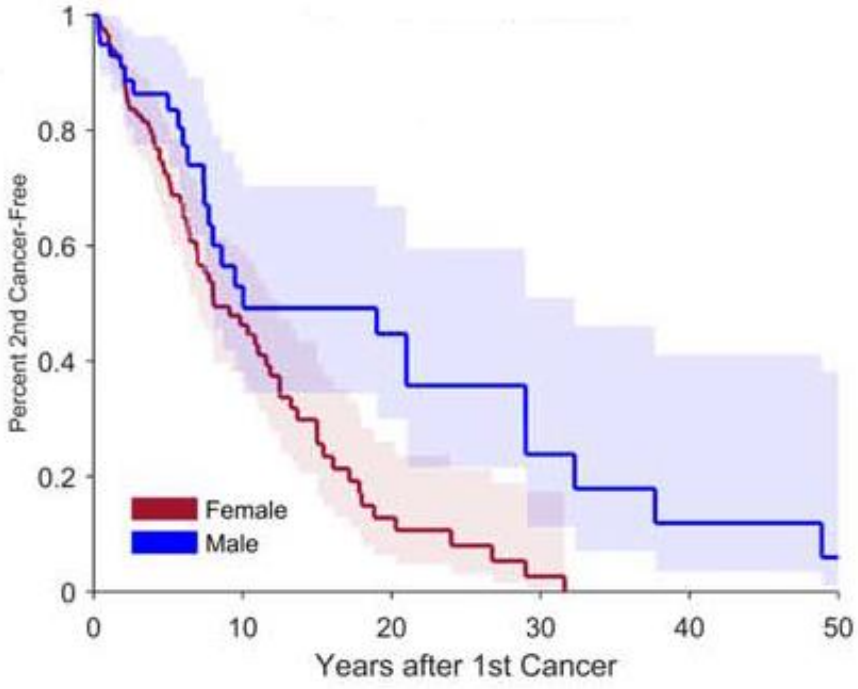
	First Prostate Cancer		First Colorectal Cancer	
Age at first cancer	10-yr cumulative risk	Difference with general population	10-yr cumulative risk	Difference with general population
55 - 64 yrs	13.1%	+5.5%	19.4%	+6.3%
65 - 74	16.0%	+5.0%	21.7%	+3.1%
≥ 75	16.4%	+2.5%	22.1%	+4.4%

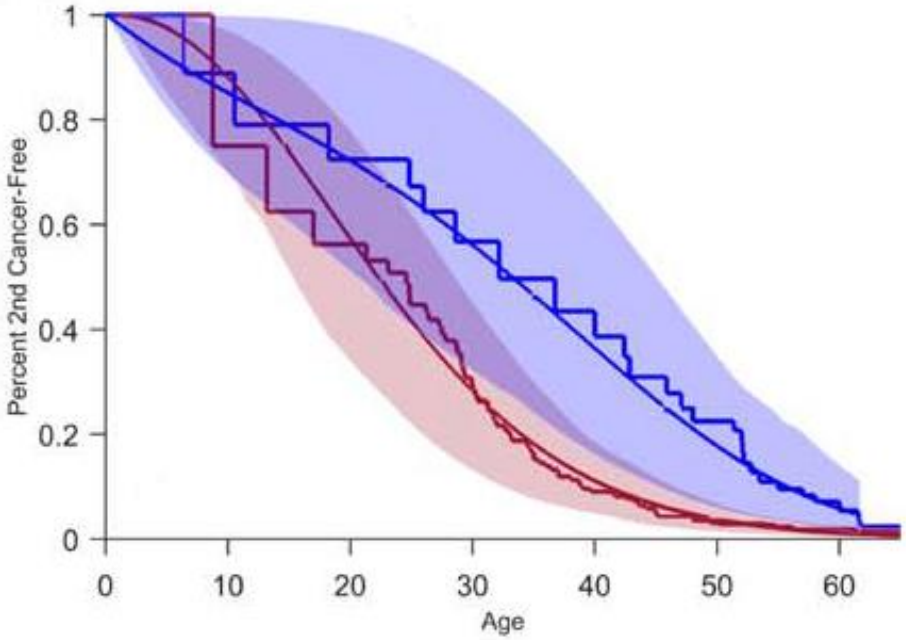
Moitry M, et al. Cancer Epidemiol, 2017

SPC in TP53 carriers

NCI Li-Fraumeni Syndrome Cohort (N=286)

Risk of SPC by time since first cancer and by age





Duke Cancer Institute

Mai PL, et al. Cancer, 2016

SPC in Mismatch Repair (MMR) genes

Colon Cancer Family Registry (N=764)

Cumulative risk of extracolonic cancer following CRC

	10 years		20 years	
Cancer site	**Risk, %**	**(95% CI)**	**Risk, %**	**(95% CI)**
Both sexes				
Kidney etc.*	1.90	(0.87 to 3.17)	5.15	(2.86 to 7.68)
Urinary bladder	1.61	(0.65 to 2.75)	3.15	(1.37 to 5.20)
Small intestine	0.92	(0.28 to 1.73)	4.00	(1.92 to 6.41)
Stomach	0.66	(0.13 to 1.40)	1.15	(0.19 to 2.48)
Hepatobiliary tract†	0.83	(0.16 to 1.69)	1.42	(0.42 to 2.73)
Men				
Prostate	2.74	(0.86 to 4.77)	5.90	(2.69 to 9.76)
Women				
Endometrium	12.12	(7.66 to 17.11)	23.99	(16.79 to 32.84)
Breast	1.94	(0.58 to 3.83)	11.38	(0.63 to 16.69)
Ovary	0.94	(0.00 to 2.11)	2.08	(0.50 to 4.14)

* Kidney etc. included kidney, renal pelvis, ureter and other and unspecified urinary organs.

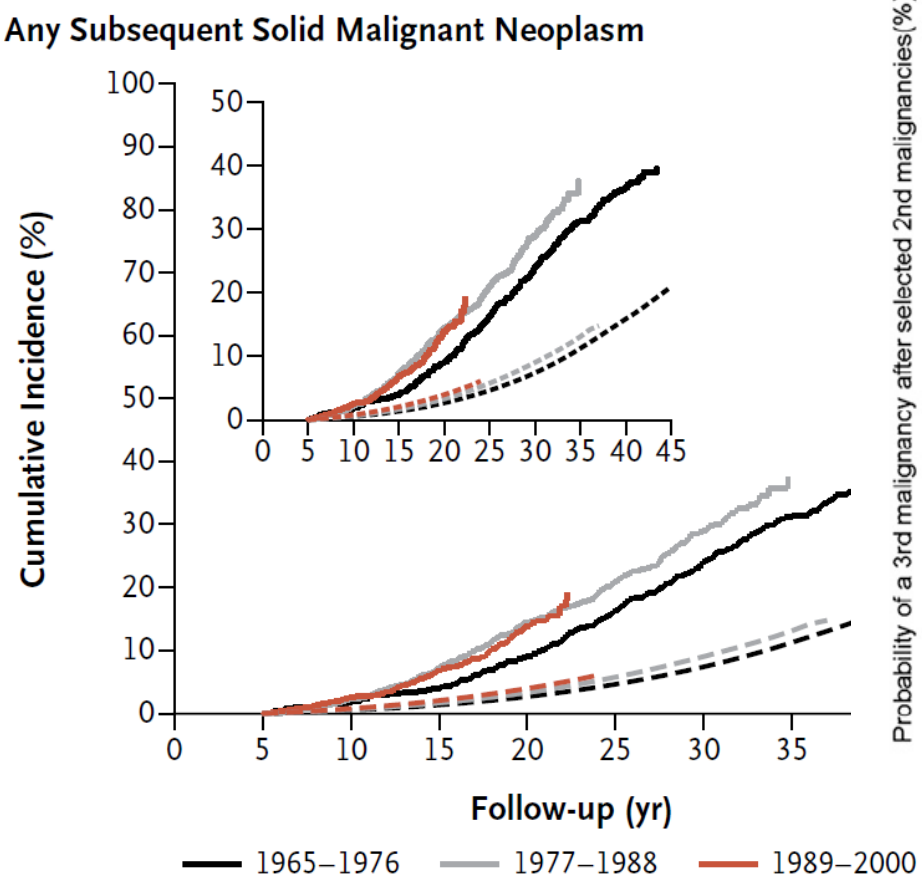
† Hepatobiliary tract included liver and intrahepatic bile duct, gall bladder, and other and unspecified parts of biliary tract.

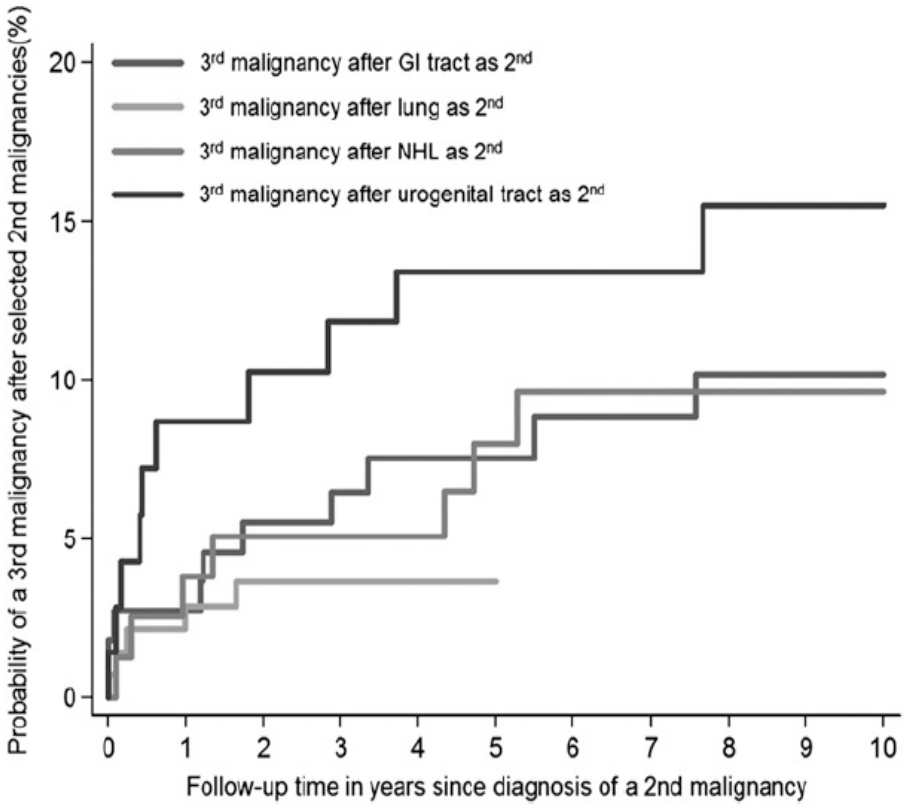
Win AK, et al. J Natl Cancer Inst, 2012

SPC following Hodgkin Lymphoma

Dutch HL Cohort (N=3905)

Age 15-50 at HL diagnosis, 1965-2000





Schaapveld M, et al. N Engl J Med, 2015

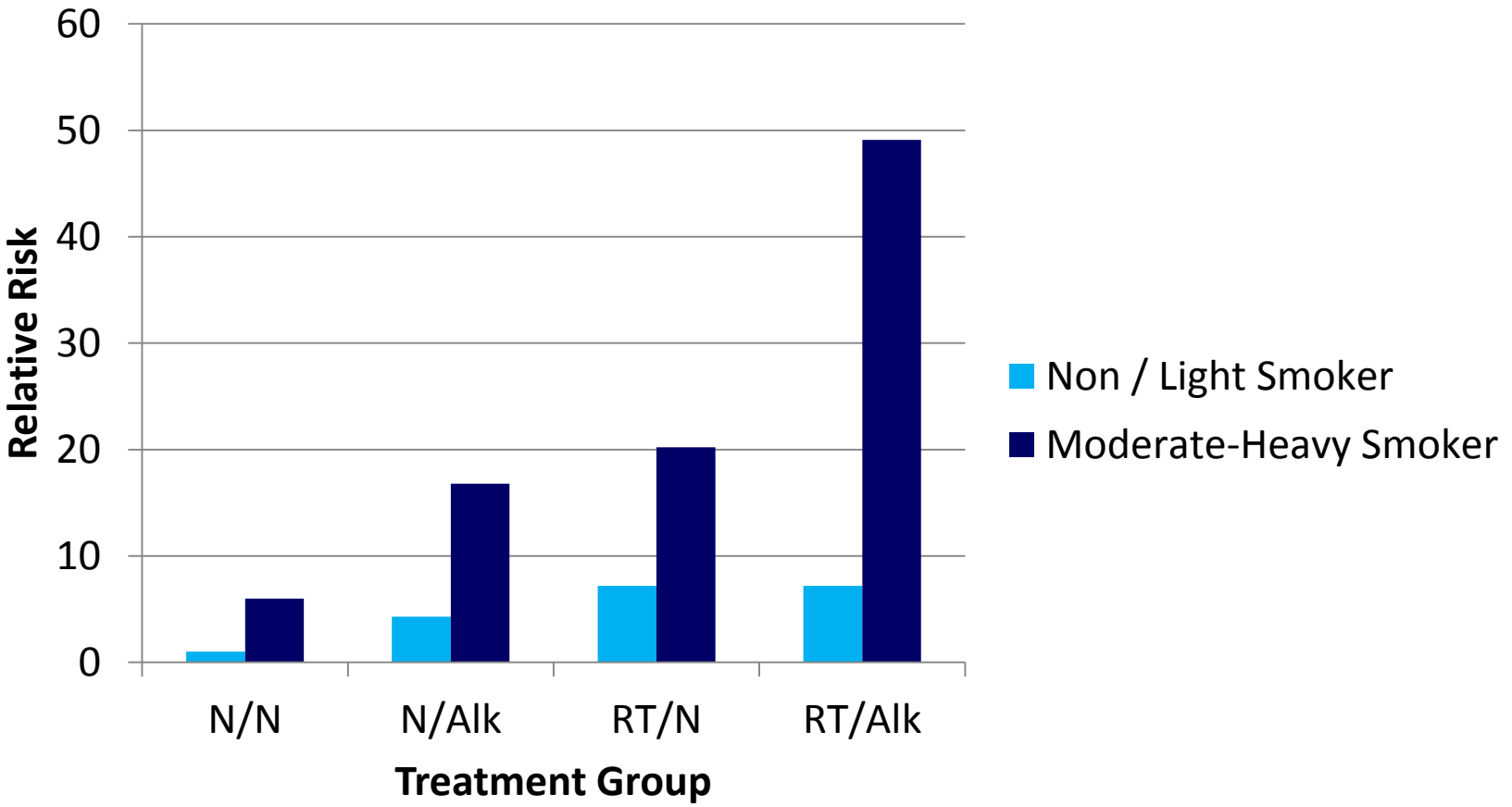
Van Eggermond AM, et al. Blood, 2014

Duke Cancer Institute

Lung cancer after Hodgkin lymphoma

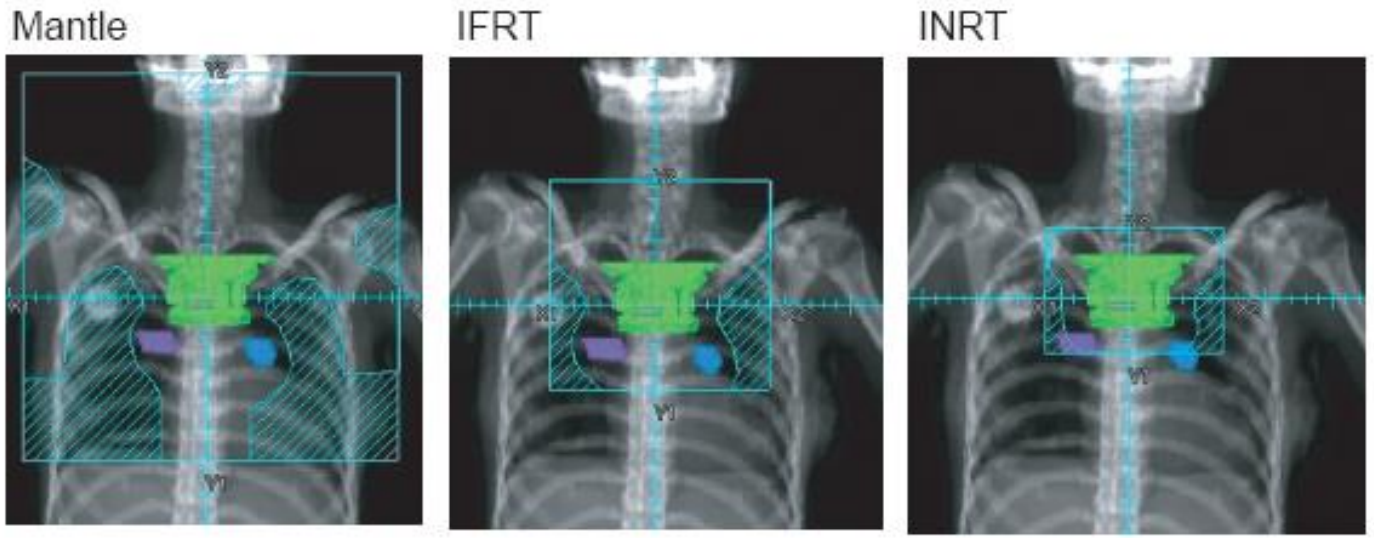
Case-Control study from population-based registry

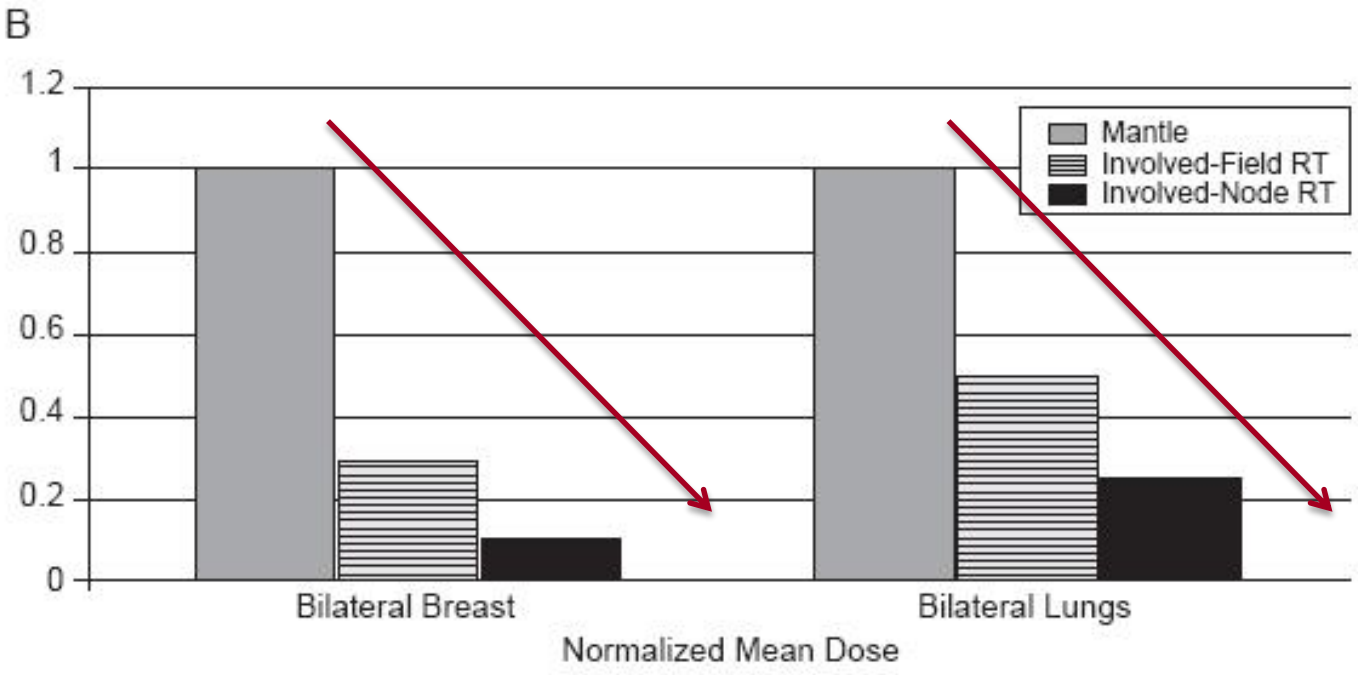
Age at Hodgkin lymphoma – median 50 years



Duke Cancer Institute

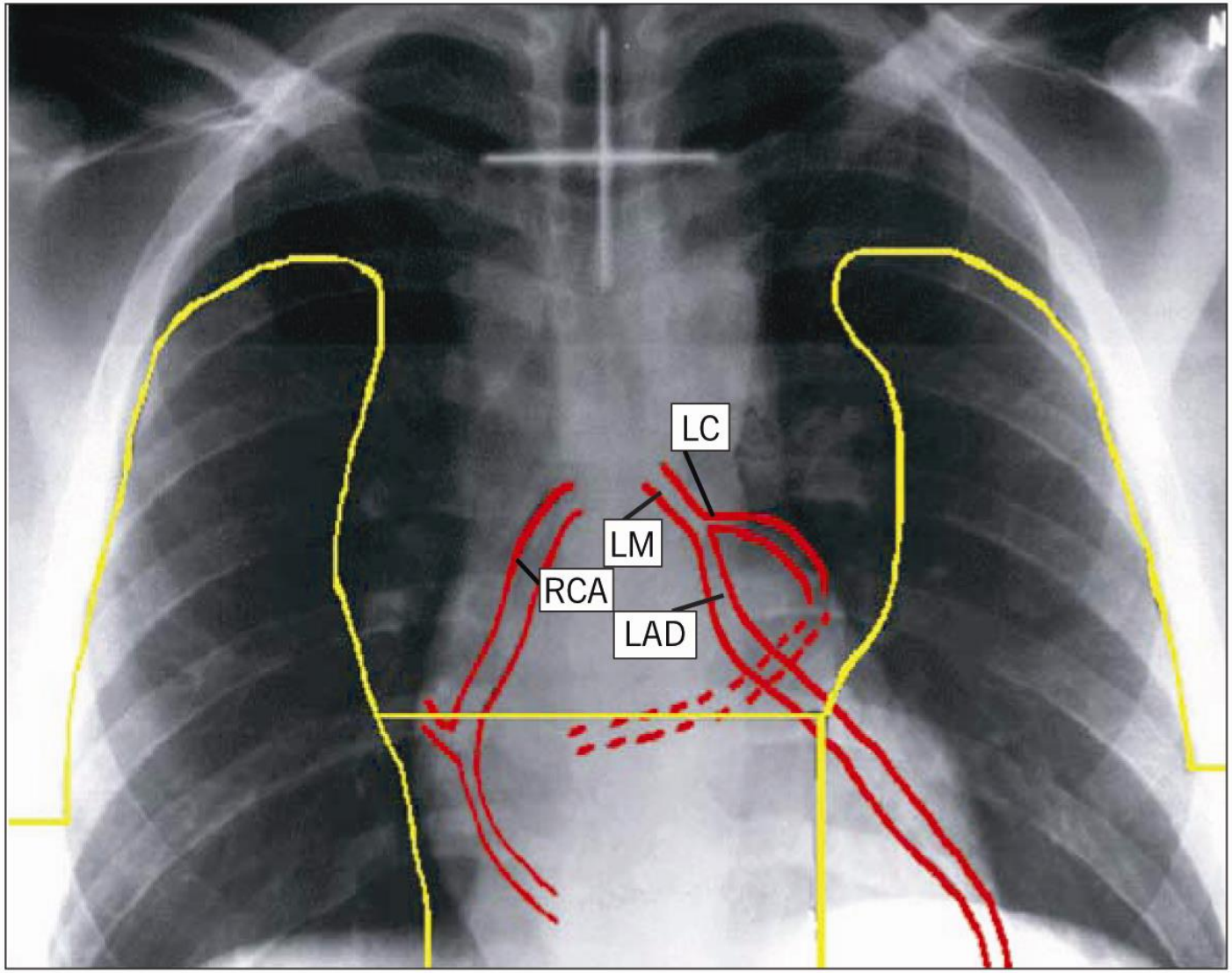
Travis LB, et al. J Natl Cancer Inst, 2002





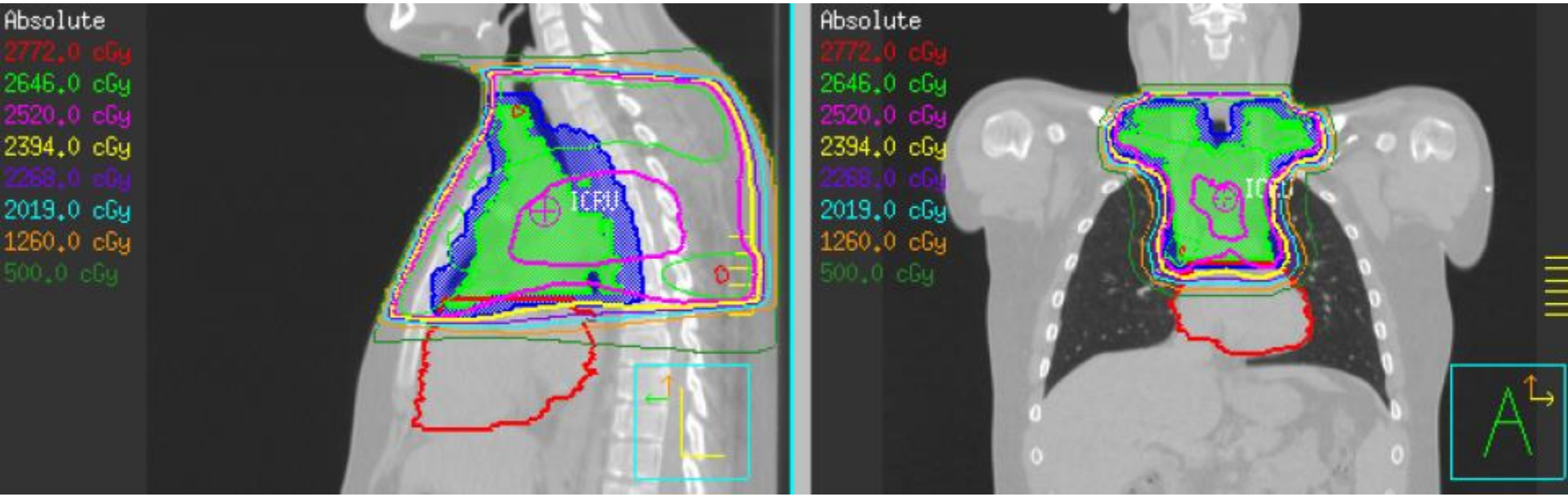
Hodgson DC, et al. Semin Radiat Oncol 2007

30 Gy Irradiation to 20 year-old with Hodgkin lymphoma



Courtesy of Constine LS.

Involved Nodal Radiation



Courtesy of Hodgson D.

Mantle / Mediastinal Radiotherapy

Men and women treated with mediastinal radiotherapy have a substantially elevated risk of coronary artery disease.

- 20 yrs post moderate-dose RT (37.2 Gy), actuarial risk of symptomatic CAD = **21.2%**

  Reinders JG, et al. Radiother Oncol, 1999

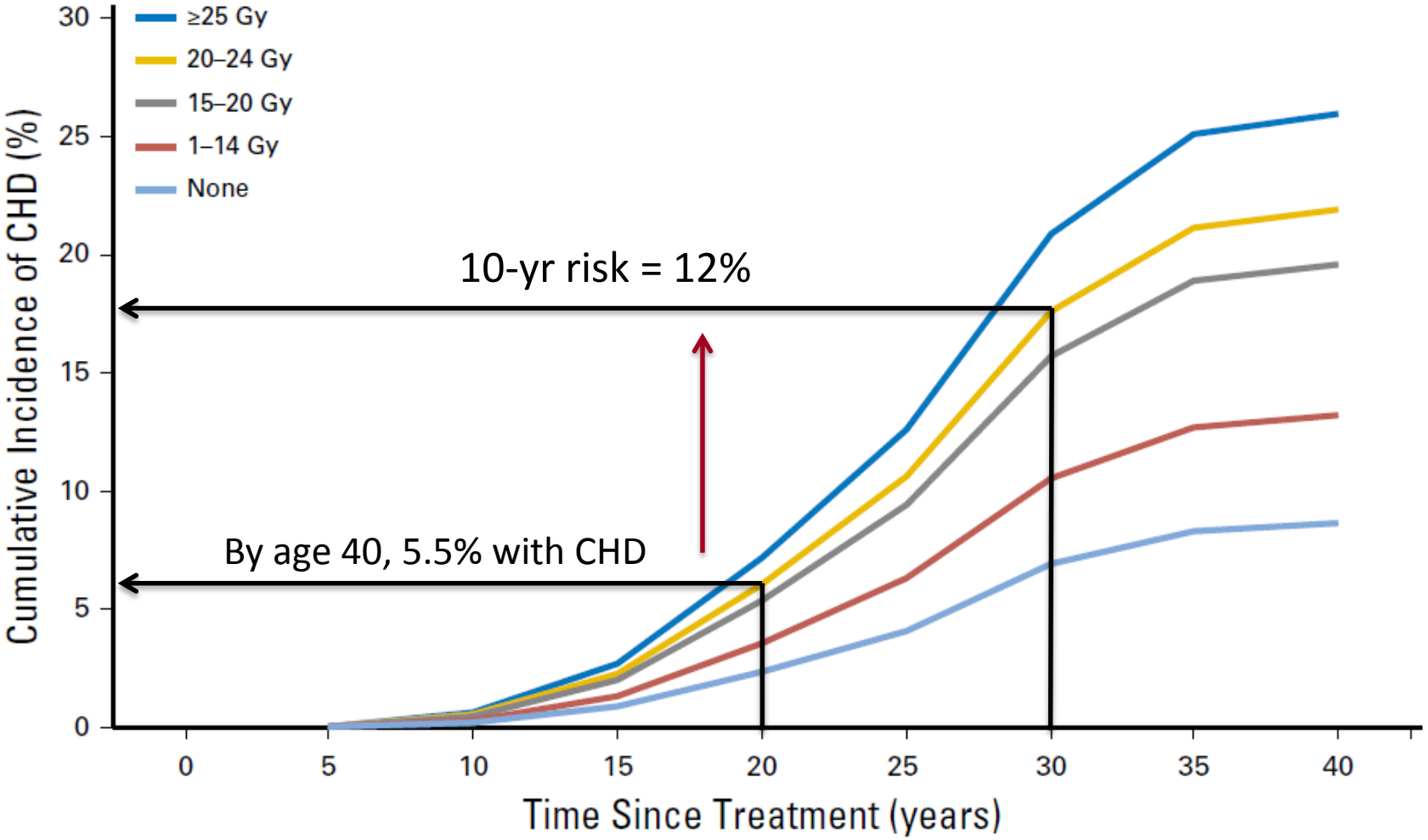
- By 30 yrs, incidence of MI = **12.9%**

  Aleman BM, et al. Blood, 2007

- Standardized Mortality Ratio with MI = **3.2**

  Swerdlow AJ, et al. JNCI, 2007

Cumulative incidence of coronary heart disease in HL survivors diagnosed prior to age 51 (1965-1995)



van Nimwegen FA, et al. J Clin Oncol, 2016

American Heart Association.

AMERICAN COLLEGE of CARDIOLOGY

2013 Prevention Guidelines Tools

CV RISK CALCULATOR

Figure 1. Implementation of Risk Assessment Work Group Recommendations

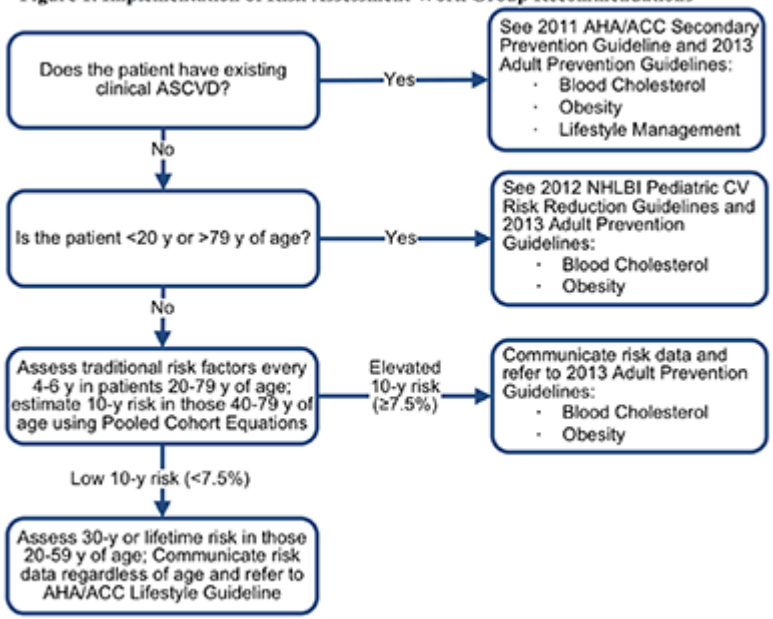


Figure 1. Implementation of Risk Assessment Work Group Recommendations

Pooled Cohort Risk Assessment Equations

Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event

Pooled Cohort Risk Assessment Equations

Predicts 10-year risk for a first ather
cardiovascular disease (ASCVD) eve

Risk Factors for ASCVD

Gender: Male / Female

Age: 40 years

Race: White or othe

Total Cholesterol: 232 mg/dL

HDL Cholesterol: 38 mg/dL

Receivin treatmer blood pr (if SBP > mmHg)

Diabetes

Smoker

Reset | Calculate

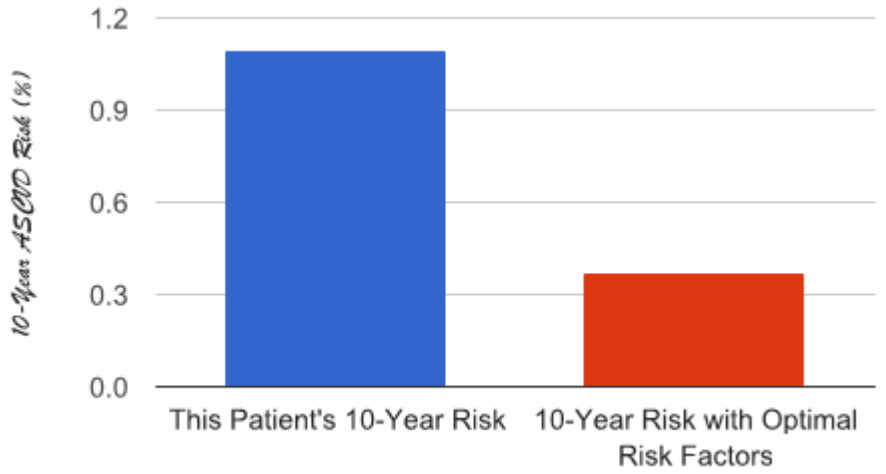
US units

10-year risk = 12%

ASCVD Risk Evaluation

10-year risk of atherosclerotic ... 1.1%

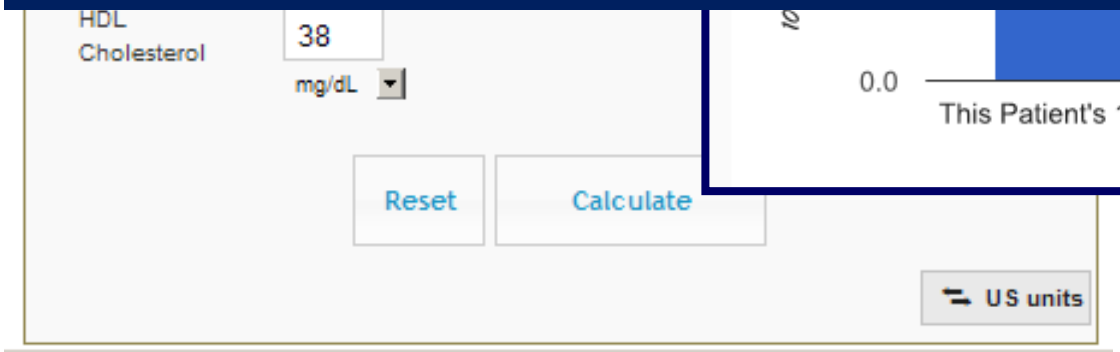
...t with 0.4%



Pooled Cohort Risk

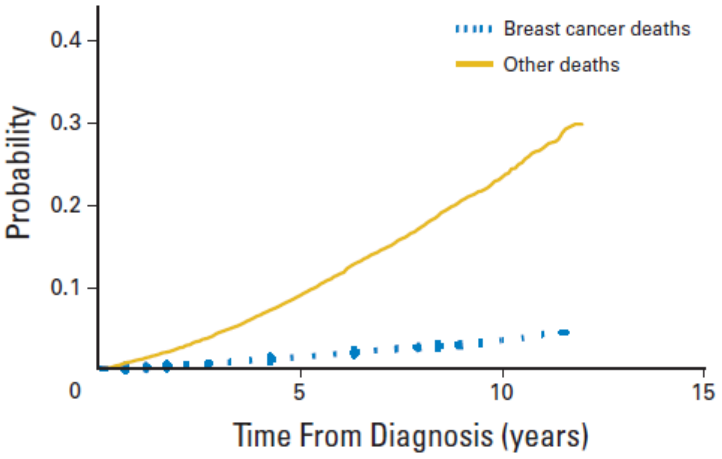
Need for validated
CAD risk prediction models
for cancer survivors

Salz T, et al
MSK and Danish Cancer Institute



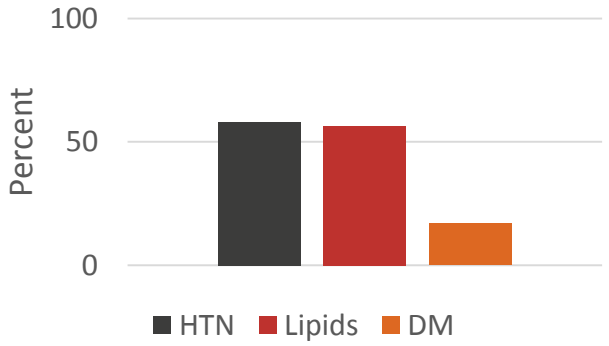
ClinCalc.com

Probability of death from breast cancer or other causes among women age 50 and older with ER+ early stage breast cancer
SEER: 1988-2001



Hanrahan EO, et al. J Clin Oncol, 2007

Percent of women with a early stage breast cancer and a cardiovascular risk factor
SEER-Medicare: 2000-2007



Chen J, et al. J Am Coll Cardiol, 2012

Caveats:

- Most women with breast cancer will not die of breast cancer
- Continued monitoring and management of common comorbidities may be as important for longevity / QoL as treatment of the breast cancer
- Lack of standardized approaches to manage HTN, DM, and lipid disorders

Hypertension (pre/during/post cancer) is a key risk factor in development of heart failure in breast cancer survivors treated with anthracyclines and/or trastuzumab

Jawa Z, et al. Medicine, 2016
Chen J, et al. J Am Coll Cardiol, 2012

VOLUME 35 · NUMBER 8 · MARCH 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Saro H. Armenian, Christina Lacchetti, Ana Barac, Joseph Carver, Louis S. Constine, Neelima Denduluri, Susan Dent, Pamela S. Douglas, Jean-Bernard Durand, Michael Ewer, Carol Fabian, Melissa Hudson, Mariell Jessup, Lee W. Jones, Bonnie Ky, Erica L. Mayer, Javid Moslehi, Kevin Oeffinger, Katharine Ray, Kathryn Ruddy, and Daniel Lenihan

Clinical Question 3: Which preventive strategies are effective in minimizing risk during the administration of potentially cardiotoxic cancer therapy?

Recommendation 3.1. Clinicians should screen for and actively manage modifiable cardiovascular risk factors (eg, smoking, hypertension, diabetes, dyslipidemia, obesity) in all patients receiving potentially cardiotoxic treatments.

Table 4. Multivariable Cox Regression Analyses of Cardiovascular Disease Deaths in Men Diagnosed With Testicular Nonseminoma According to Baseline Characteristics

Variable	All Cardiovascular Deaths (n = 104)		
	HR	95% CI	*P*
Initial treatment by time since TC diagnosis			
< 1 year			
Surgery (no RT)	—	—	Ref
Chemotherapy (no RT)	4.86*	1.25 to 32.08	.04
1-4 years			
Surgery (no RT)	—	—	Ref
Chemotherapy (no RT)	1.35	0.54 to 3.45	.53
≥ 5 years			
Surgery (no RT)	—	—	Ref
Chemotherapy (no RT)	0.90	0.51 to 1.58	.72
Age at diagnosis, years			
< 30	—	—	Ref
30-39	3.47*	1.99 to 6.13	< .01
40-49	8.97*	4.73 to 17.02	< .01
≥ 50	34.26*	17.81 to 66.17	< .01

Fung C, et al. J Clin Oncol, 2015

‘Accelerated Aging’ and Frailty

Deficit-Accumulation Index (DAFI):

- 51-items
- Demographics
- ADLs
- Patient-rated KPS
- Falls
- Polypharmacy
- Comorbidities
- Nutritional status
- Psychosocial status
- Social support
- Health care professional questionnaire
- Basic lab values

$$\text{DAFI} = \frac{\text{Actual Deficit Score}}{\text{Potential Deficit Score}} \quad \text{e.g.} \quad \frac{15}{78} = \text{FI } .19$$

Robust	0.0 - < 0.2
Prefrail	0.2 - < 0.35
Frail	≥ 0.35

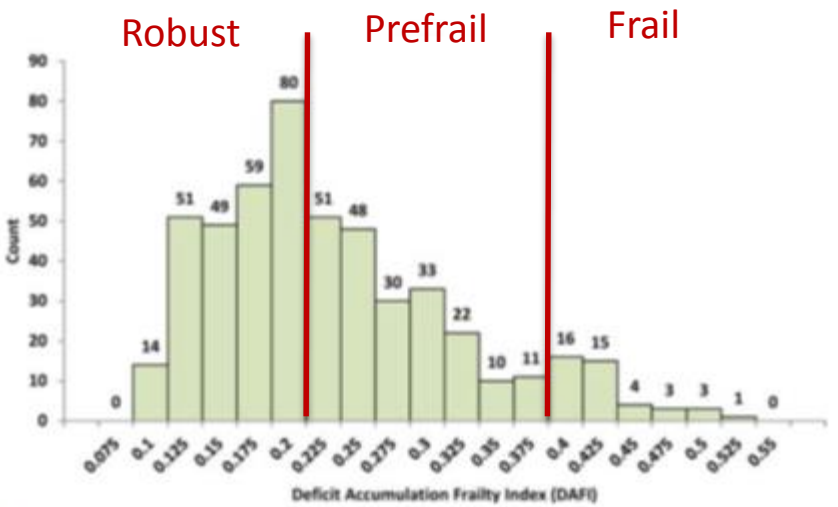


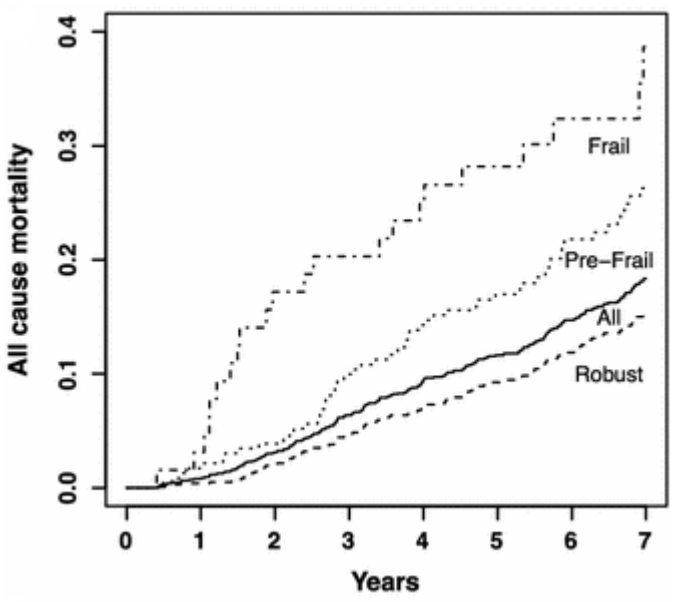
Figure 2. The distribution of frailty scores in the Cancer and Aging Research Group cohort is illustrated according to the frailty index (FI). DAFI indicates deficit-accumulation frailty index.

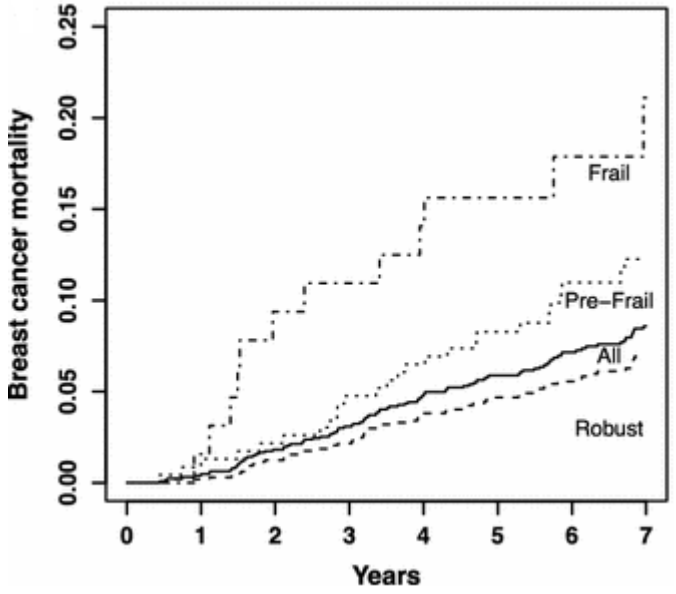
Duke Cancer Institute

Cohen HJ, et al. Cancer, 2016

Frailty and Mortality

Older breast cancer patients: CALGB 369901 (Alliance)





St. Jude Lifetime Cohort Study

Table 4. Risk for Death by Frailty Status

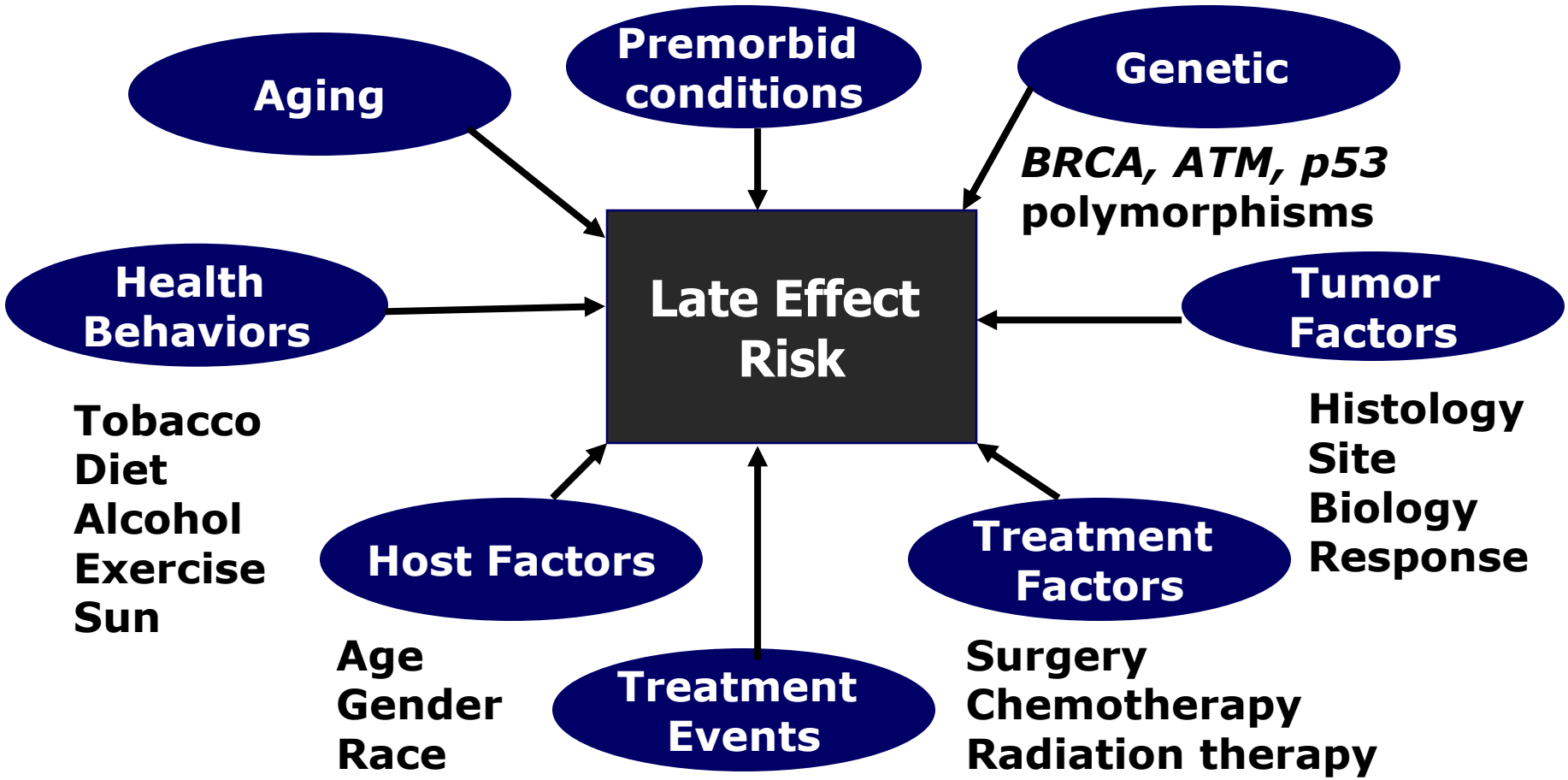
	Total				Women				Men			
Phenotype*	No. of Patients	Deaths (%)	HR†	95% CI	No. of Patients	Deaths (%)	HR	95% CI	No. of Patients	Deaths (%)	HR†	95% CI
Frail	151	4.6	2.6	1.2 to 6.2	125	3.2	1.9	0.6 to 3.0	26	11.5	6.0	4.6 to 7.3
Not frail	1,771	1.4			831	1.3			940	1.4		

Abbreviation: HR, hazard ratio.
*Frail is defined as at least three from among low lean muscle mass, exhaustion, low energy expenditure, slowness, weakness. Not frail is defined as two or fewer from among low lean muscle mass, exhaustion, low energy expenditure, slowness, or weakness.
†HR from Cox proportional hazards model.

Mandelblatt JS, et al. Breast Cancer Res Treat, 2017
Ness KK, et al. J Clin Oncol, 2013

System	Exposures	Potential Late Effects
Cardiac	Radiation therapy Anthracyclines AntiHER2 therapy	Myocardial infarction Congestive heart failure Valvular disease Arrhythmias
Pulmonary	Radiation therapy BCNU/CCNU Bleomycin	Restrictive lung disease Exercise intolerance
Renal/Urological	Radiation therapy Platinums Ifosfamide/Cyclophos	Atrophy or hypertrophy Renal insufficiency or failure
Endocrine	Radiation therapy Alkylating agents	Pituitary, thyroid, adrenal disease Ovarian or testicular failure Infertility
CNS	Radiation therapy Intrathecal chemotherapy ? other systemic chemotherapy	Cognitive dysfunction
Psychological	Cancer	Post-traumatic stress Employment & educational problems Insurance discrimination Adaptation/problem solving
Second malignancies	Radiation therapy Alkylating agents Epipodophyllotoxins	Solid tumors Leukemia Lymphoma

Factors contributing to late effects



Hudson MM. Cancer, 2005

Interventions for Improved Physical Well-Being

Risk-stratified screening for SPC

- Average-risk individuals according to existing guidelines
  - Considerations for screening interval?
- High-risk groups
  - Genetic risk (Li-Fraumeni, BRCA2)
  - Cancer therapy risk (Hodgkin lymphoma)
  - Lifestyle risk (Lung cancer)
- Interventions to increase screening rates

Risk-stratified screening for late effects

1. Which patients with cancer are at increased risk for developing cardiac dysfunction?

Recommendation 1.1. It is recommended that patients with cancer who meet any of the following criteria should be considered at increased risk for developing cardiac dysfunction.

- Treatment that includes any of the following:
  - High-dose anthracycline (eg, doxorubicin $\geq$ 250 mg/m^2, epirubicin $\geq$ 600 mg/m^2)
  - High-dose radiotherapy (RT; $\geq$ 30 Gy) where the heart is in the treatment field
  - Lower-dose anthracycline (eg, doxorubicin $<$ 250 mg/m^2, epirubicin $<$ 600 mg/m^2) in combination with lower-dose RT ($<$ 30 Gy) where the heart is in the treatment field
- Treatment with lower-dose anthracycline (eg, doxorubicin $<$ 250 mg/m^2, epirubicin $<$ 600 mg/m^2) or trastuzumab alone, and presence of any of the following risk factors:
  - Multiple cardiovascular risk factors ($\geq$ two risk factors), including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after completion of therapy
  - Older age ($\geq$ 60 years) at cancer treatment
  - Compromised cardiac function (eg, borderline low left ventricular ejection fraction [50% to 55%], history of myocardial infarction, $\geq$ moderate valvular heart disease) at any time before or during treatment
- Treatment with lower-dose anthracycline (eg, doxorubicin $<$ 250 mg/m^2, epirubicin $<$ 600 mg/m^2) followed by trastuzumab (sequential therapy)

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Armenian SH, et al. J Clin Oncol, 2016

Risk-stratified screening for late effects

5. What are the preferred surveillance and monitoring approaches after treatment in patients at risk for cardiac dysfunction?

Recommendation 5.2. An echocardiogram may be performed between 6 and 12 months after completion of cancer-directed therapy in asymptomatic patients considered to be at increased risk (Recommendation 1.1) of cardiac dysfunction. (Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 5.4. No recommendations can be made regarding the frequency and duration of surveillance in patients at increased risk (Recommendation 1.1) who are asymptomatic and have no evidence of cardiac dysfunction on their 6- to 12-month post-treatment echocardiogram.

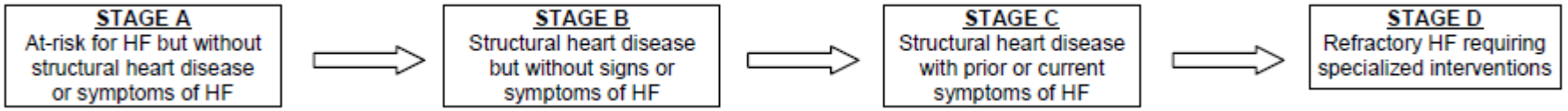
Recommendation 5.5. Clinicians should regularly evaluate and manage cardiovascular risk factors such as smoking, hypertension, diabetes, dyslipidemia, and obesity in patients previously treated with cardiotoxic cancer therapies. A heart-healthy lifestyle, including the role of diet and exercise, should be discussed as part of long-term follow-up care. (Evidence based and consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Armenian SH, et al. J Clin Oncol, 2016

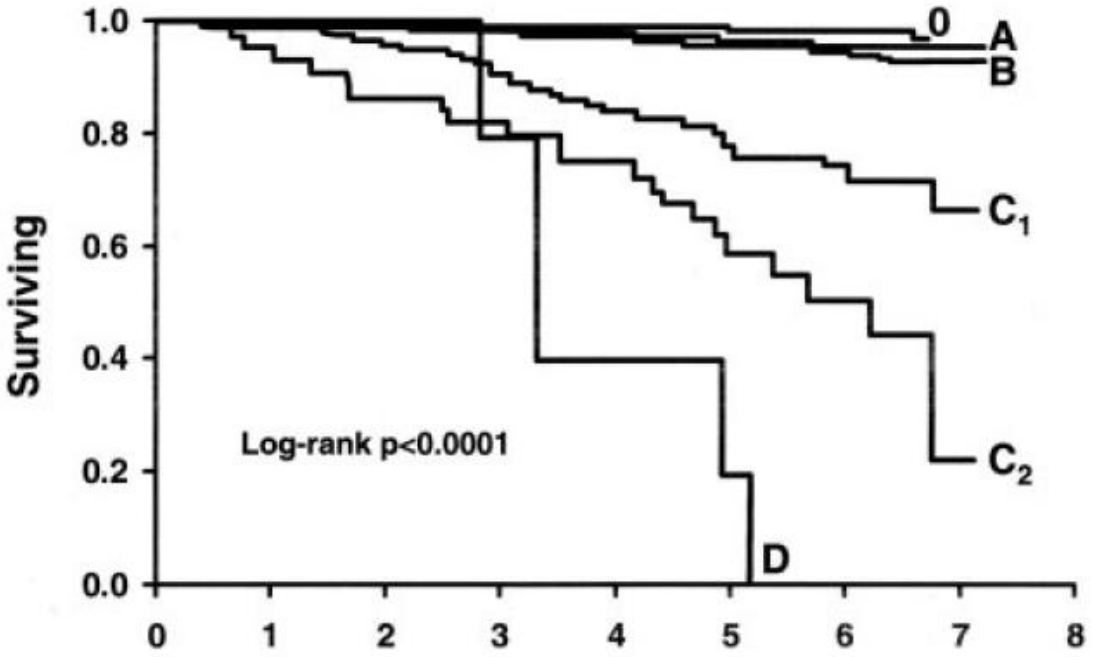
Risk-stratified screening for SPC

- Barriers to generating evidence:
  - NIH funding favors intervention > observation
  - Will early intervention improve outcomes?
    - Heart failure as an example

Heart Failure



Hunt SA, et al. J Am Coll Cardiol, 2009

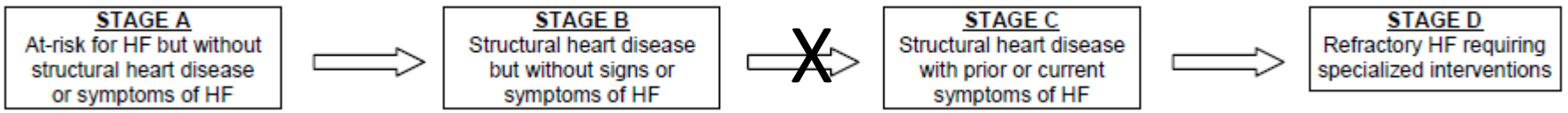


Ammar KA, et al. Circulation, 2007

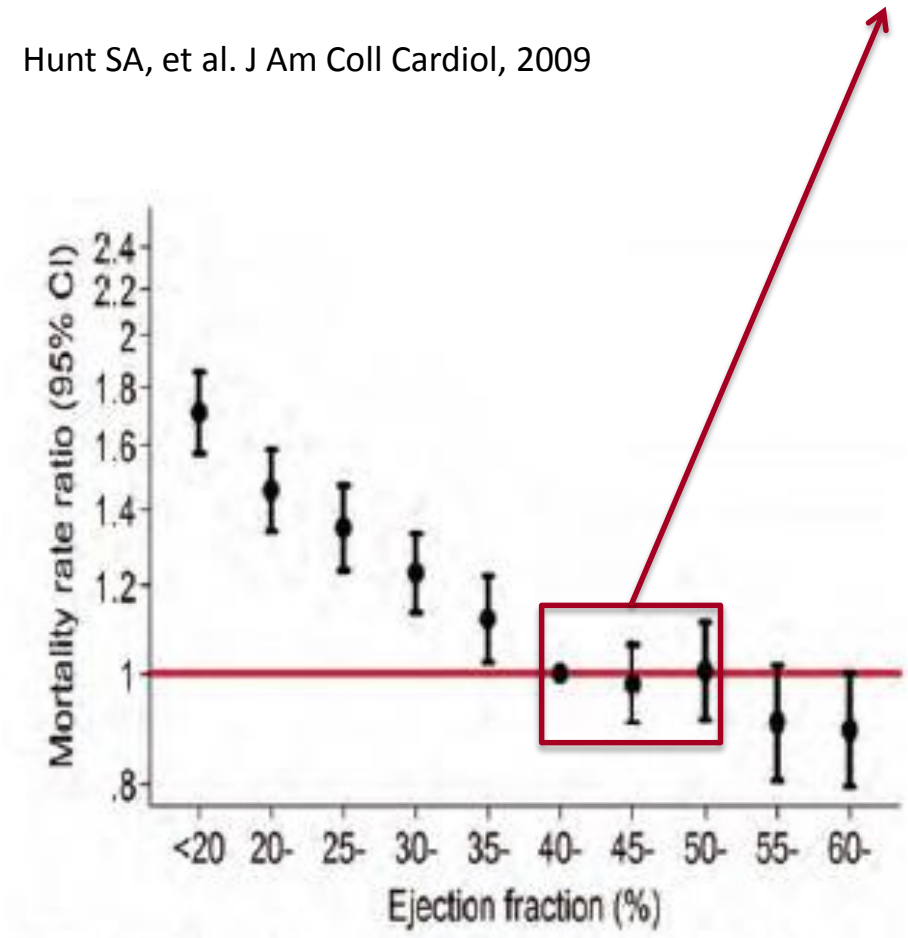
Key points

- 5-yr survival for stage C: 75%
- Transitioning from stage B to stage C was associated with a 5-fold increased mortality risk

Heart Failure



Hunt SA, et al. J Am Coll Cardiol, 2009



Key points

- Meta-analysis of 39,372 patients
- Importance of 5 unit incremental changes in LVEF on survival

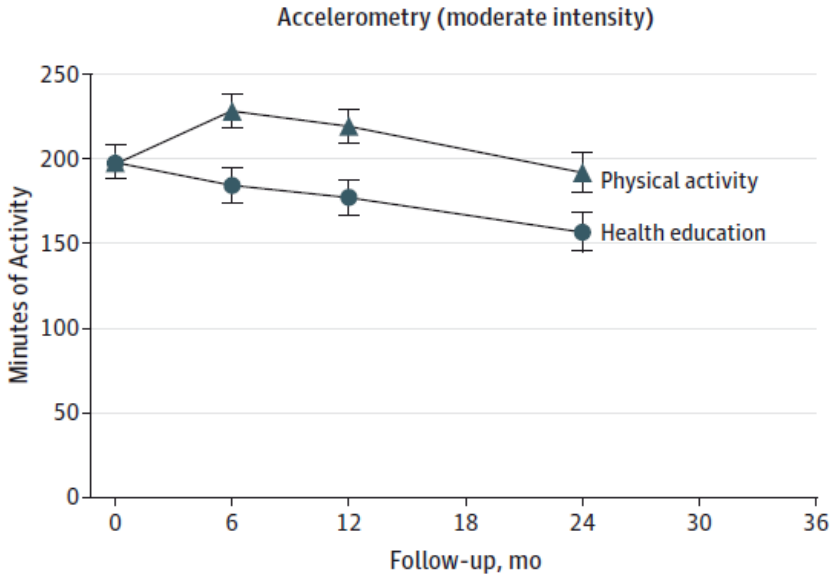
Duke Cancer Institute

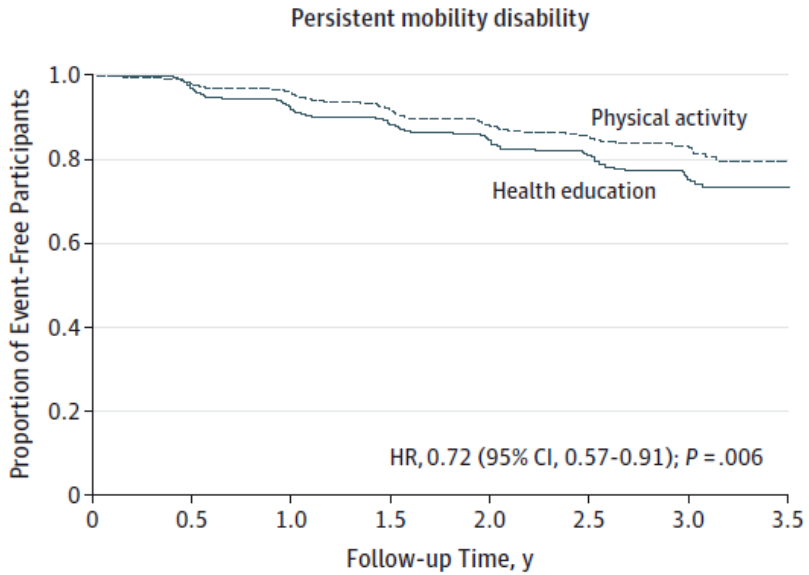
Pocock SJ, et al. Eur Heart J, 2013

Can we prevent frailty?

LIFE Study

818 sedentary individuals age 70 – 89 years
Structured, moderate-intensity physical activity program
vs health education program





Duke Cancer Institute

Pahor M, et al. JAMA, 2014

Precision Screening and Chemoprevention

- 'Liquid biopsy'
  - circulating cell-free DNA (cfDNA)
  - circulating tumor cells (CTC)

    Vockley JG and Niederhuber JE. BMJ, 2015

    Meyskens FL, et al. J Natl Cancer Inst, 2016

    Albini A, et al. Clin Cancer Res, 2016
- Epigenetic-marker based system with detection rate of breast cancer similar to mammography

  Uehiro N, et al. Breast Ca Res, 2016
- Cancer interception
  - Example: ErbB2 and lapatinib

    Li D, et al. Oncotarget, 2017

Summary

- Survival rates continue to improve
- Incidence and magnitude of risk of selected long-term and late effects is robust
- Evidence supporting risk-stratified surveillance and early intervention is needed
- Lifestyle modifications are evidence-based (Dr. Demark-Wahnefried's talk)

Thank You!

kevin.oeffinger@duke.edu