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Cardiovascular Outcomes from Radiation Exposure

Radiation Epidemiology & Dosimetry Course

National Cancer Institute www.dceg.cancer.gov/RadEpiCourse

Disclosures

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- Clinigen: Consultant

National Cancer Institute
Childhood Cancer Survivor Study (CCSS)

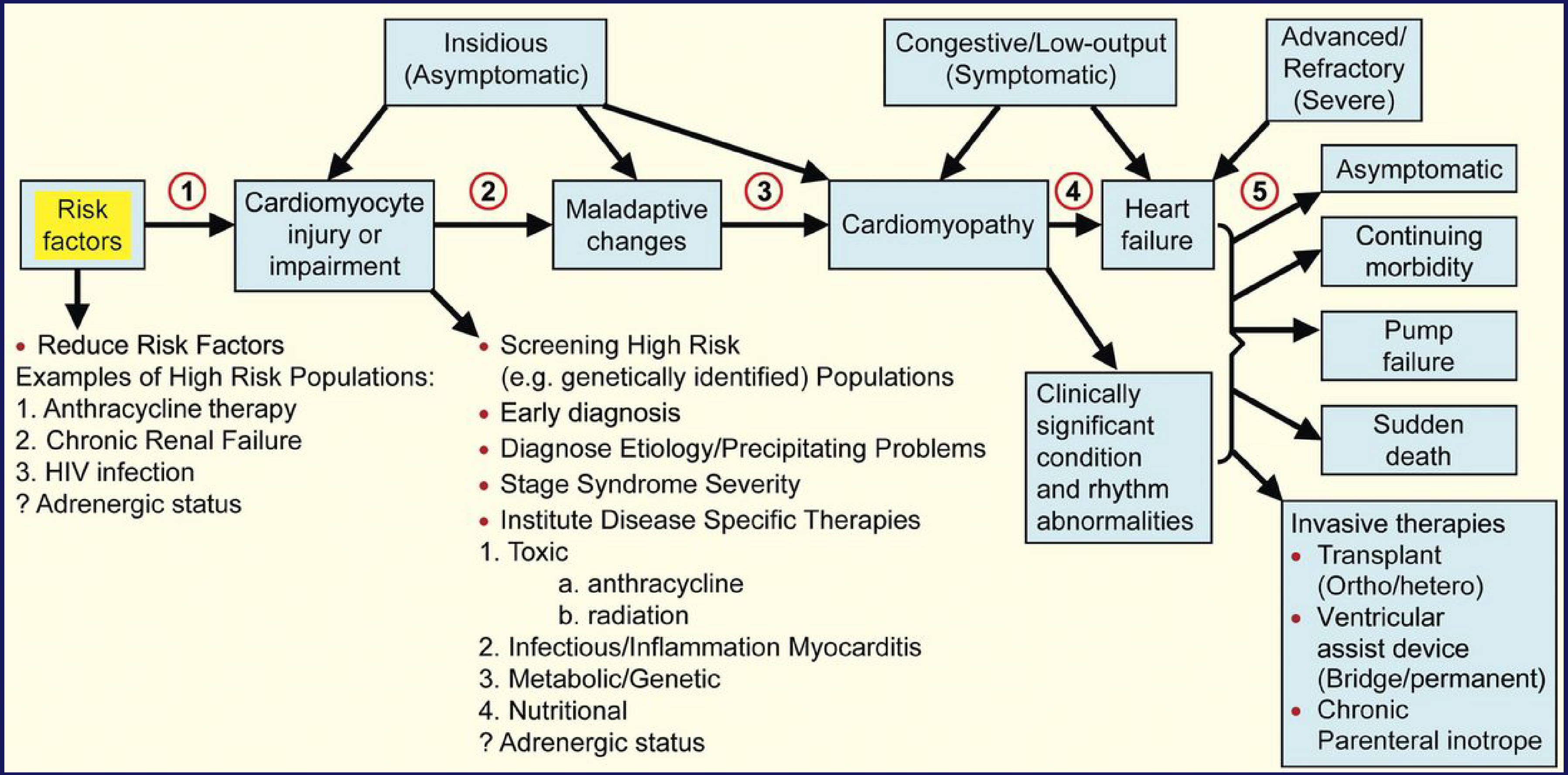
Common late effects and relative morbidity 30 years after childhood cancer treatment:

- Neurocognitive (severe cognitive dysfunction, RR* = 10.5)
- Psychological (depression, post-traumatic stress)
- Cardiopulmonary (decreased lung volume, heart dysfunction)
  (CAD, RR = 10.4; CHF, RR = 15.1; cerebrovascular accident, RR = 9.3)
- Endocrine (growth and fertility; ovarian failure, RR = 3.5)
- Musculoskeletal (major joint replacement, RR = 54.0)
- Second malignancies (RR = 14.8)

*RR = Relative risk of survivors vs. sibling controls

Institute of Medicine, American Cancer Society
Oeffinger et al., NEJM 2006

Stages in the Course of Pediatric Ventricular Dysfunction



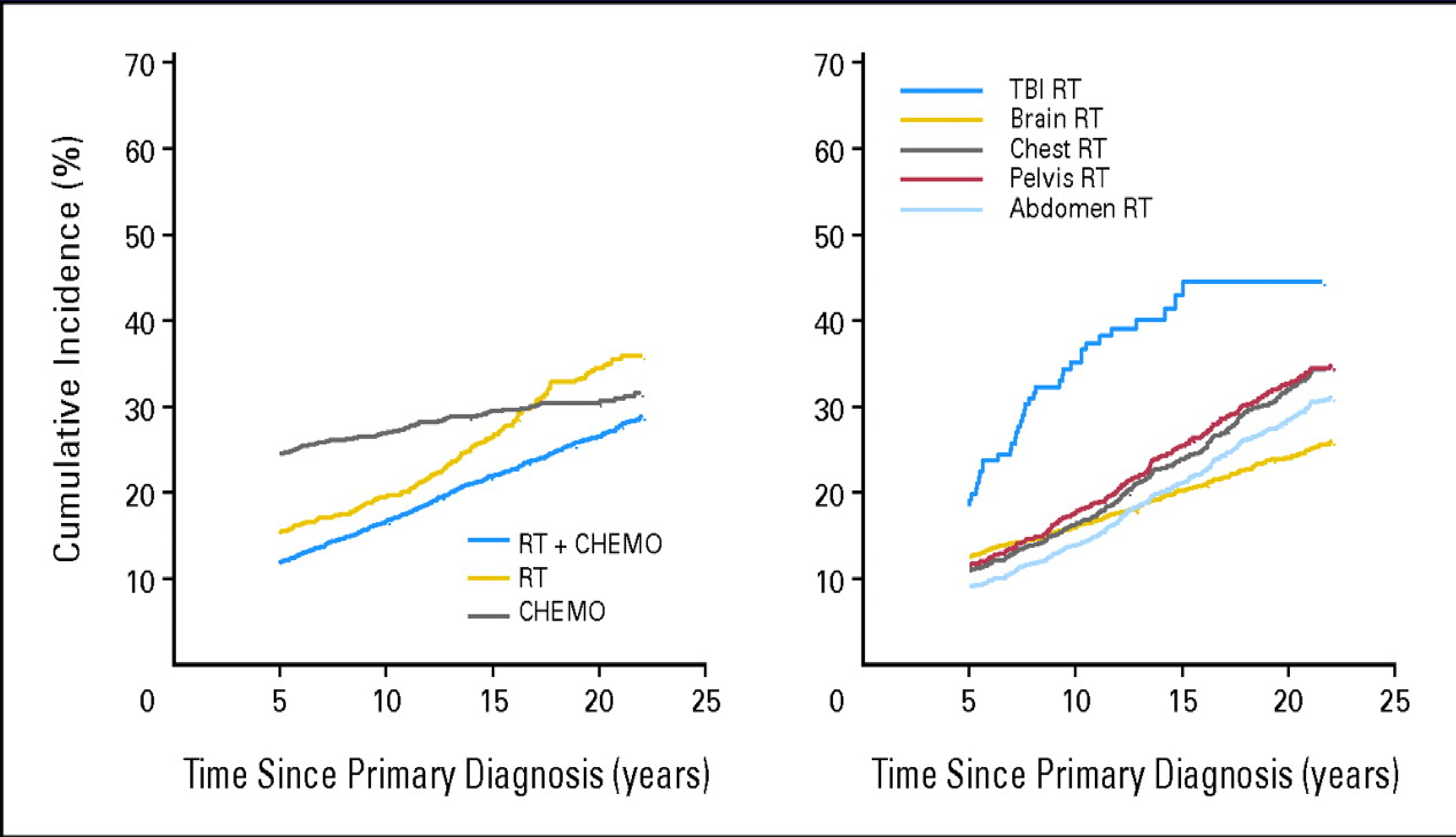
Preventive Strategies: Progressively less effective as the number increases.
Primary prevention is possible at number 1.
Secondary prevention is possible at numbers 2, 3, and 4.

Treatment Strategies: Greater impact with higher numbers but longer effects with lower numbers.
Treatment is possible at numbers 4 and 5 to reduce sequelae.

Biomarkers/Surrogate Endpoints:
Potentially more useful with lower numbers for alteration of course with interventions.
Potentially more useful with higher numbers for decisions about transplantation.

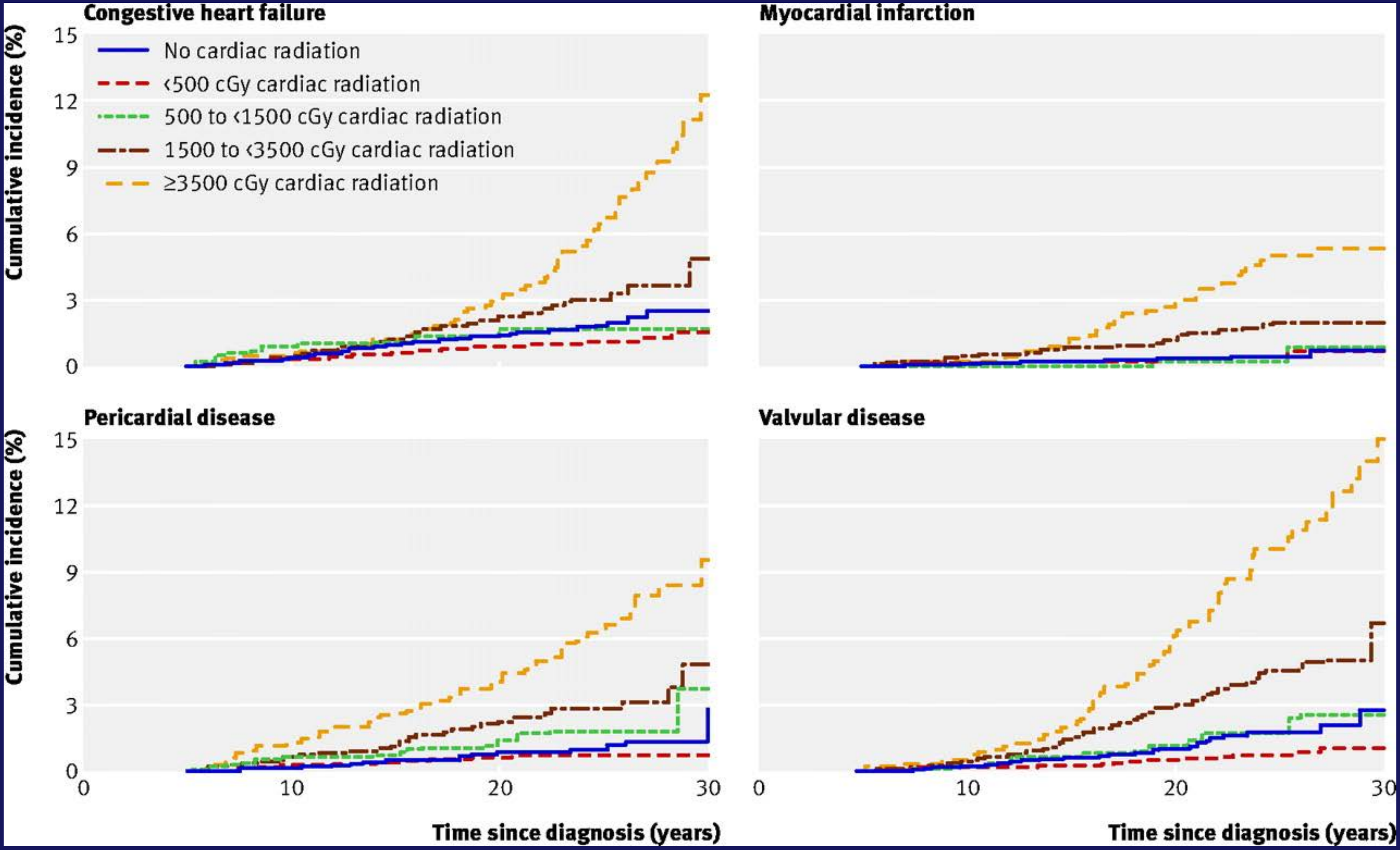
Lipshultz, et al., Prog Pediatric Cardiol 2000
Lipshultz, Eur Heart J 2012

CCSS: Cumulative Incidence of Chronic Health Conditions by Exposure (grade 3 to 5 only)



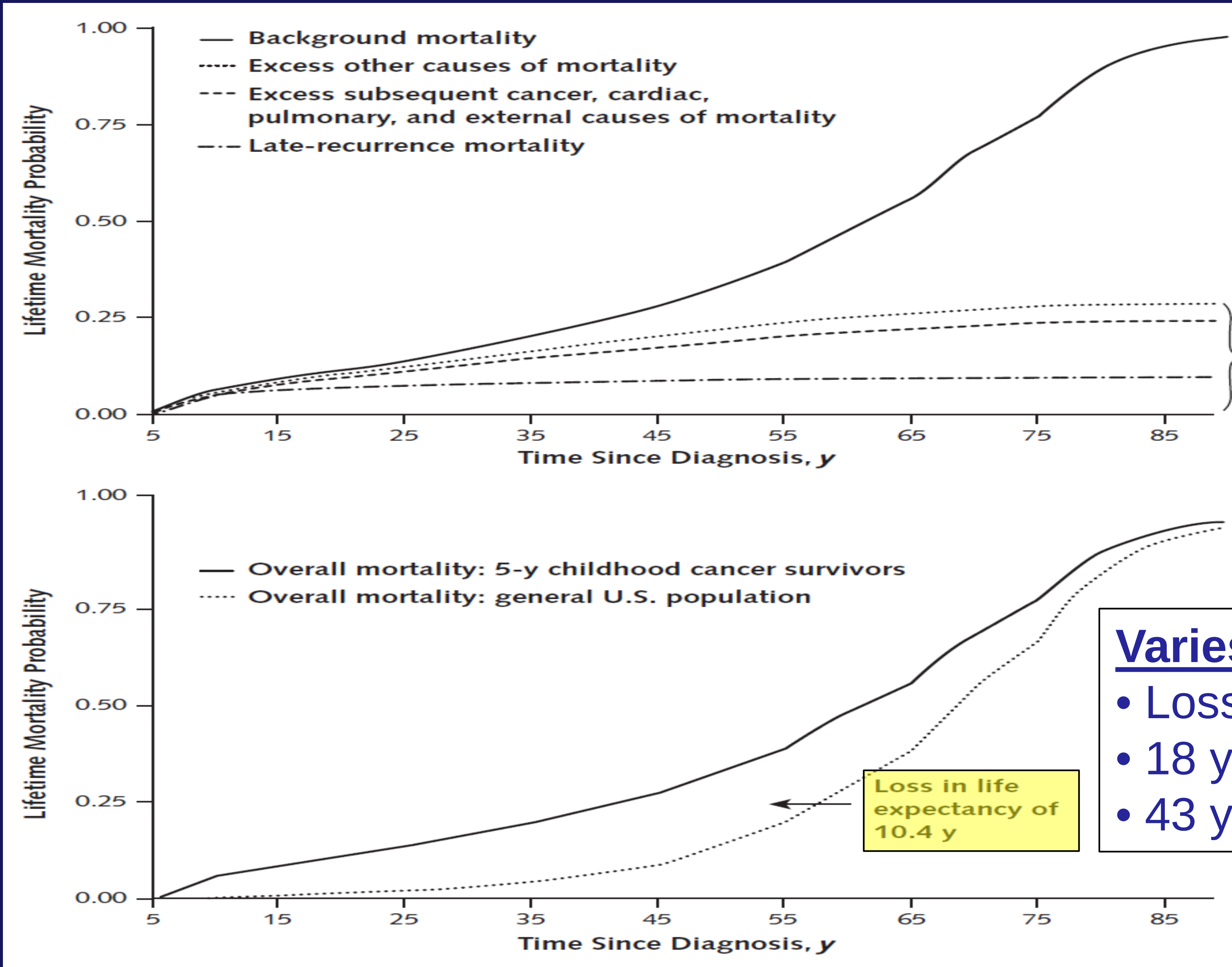
Diller, et al., JCO 2009

NCI CCSS: Cumulative incidence of cardiac disorders among 14,358 childhood cancer survivors by average cardiac radiation dose



Mulrooney, et al., BMJ 2009

CCSS Survivor Lifetime Cause-Specific Mortality



Varies by Disease

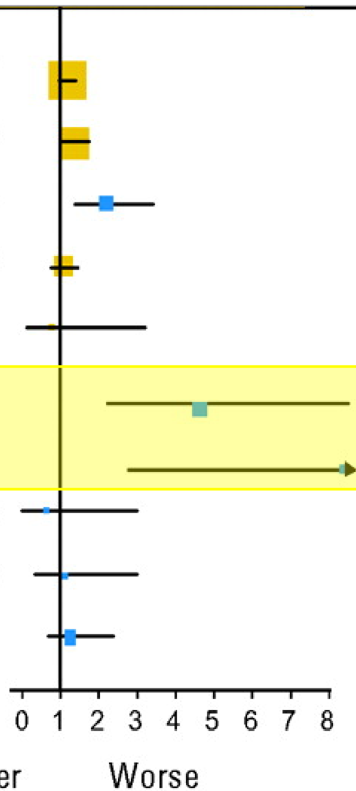
- Loss to 28%
- 18 y lost life
- 43 yo expectancy

Yeh, et al., Ann Intern Med 2010

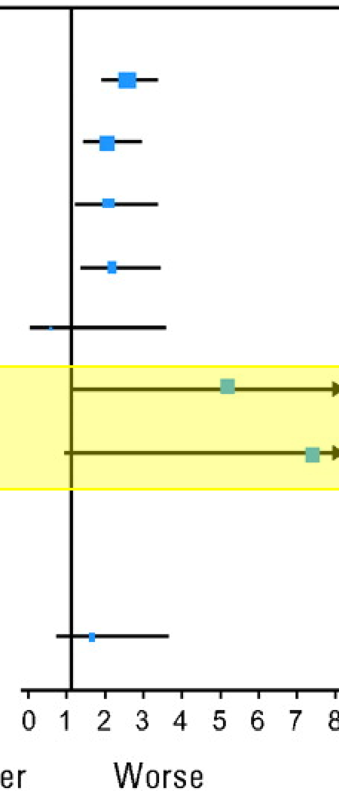
4,122 5-yr Childhood Cancer Survivors with 86,453 pt-yrs of Follow-up from France and UK, 27-year average F/U

Cause of Deaths	Chemotherapy Observed/Expected* No	Chemotherapy Observed/Expected* Yes	RR (95% CI)	Radiotherapy Observed/Expected* No	Radiotherapy Observed/Expected* Yes	RR (95% CI)
Overall	231/36	371/37	1.2 (1.0 to 1.4)	72/18	530/55	2.6 (2.0 to 3.4)
Others than 1st†	114/33	171/35	1.4 (1.1 to 1.8)	42/51	243/17	2.1 (1.5 to 2.9)
Second cancer	45/8	90/4	2.2 (1.4 to 3.5)	21/3	114/9	2.1 (1.3 to 3.4)
Others than cancer‡	60/27	76/33	1.1 (0.8 to 1.5)	20/15	116/44	2.2 (1.4 to 3.5)
Infectious	6/1	3/1	0.8 (0.2 to 3.2)	3/1	6/2	0.6 (0.1 to 3.6)
All cardiovascular	9/4	23/1	4.1 (1.6 to 10.4)	2/1	30/4	5.0 (1.2 to 21.4)
Cardiac	3/2	18/1	7.9 (2.3 to 31.3)	1/1	20/3	7.4 (1.0 to 56.5)
Respiratory	8/1	7/0.3	0.8 (0.3 to 2.5)	0/0.3	15/1	NC
Ill-defined	6/2	9/3	1.1 (0.4 to 3.0)	0/1	15/3	NC
External	19/14	30/21	1.3 (0.7 to 2.5)	8/9	41/26	1.7 (0.8 to 3.6)

Chemotherapy: Adjusted Relative Risk

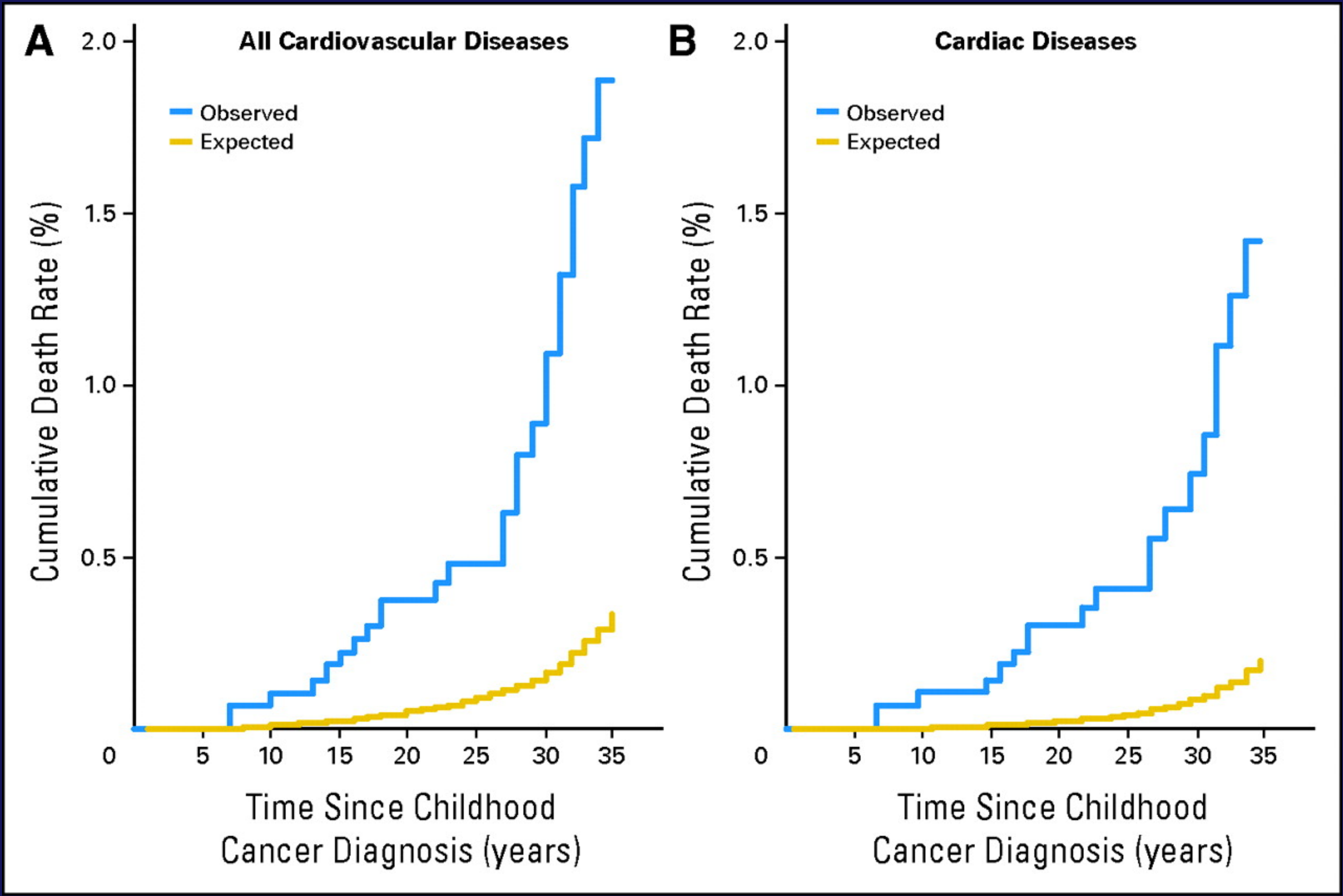


Radiotherapy: Adjusted Relative Risk



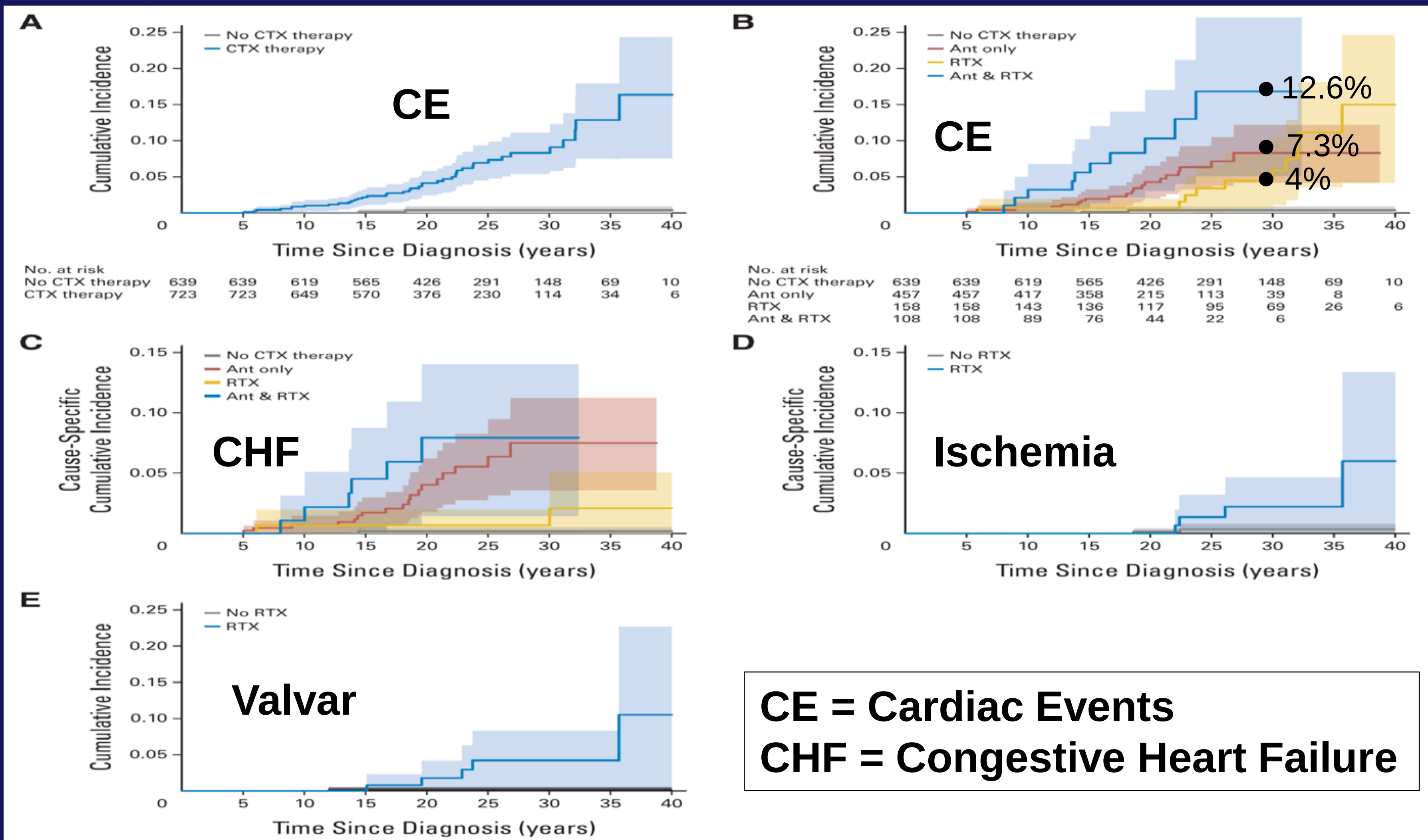
Tukenova, et al., JCO 2010

Estimates of (A) cumulative cardiovascular and (B) cardiac mortality in the French-British CCSS (86,453 pt-yrs follow up) in the general population in France and Great Britain



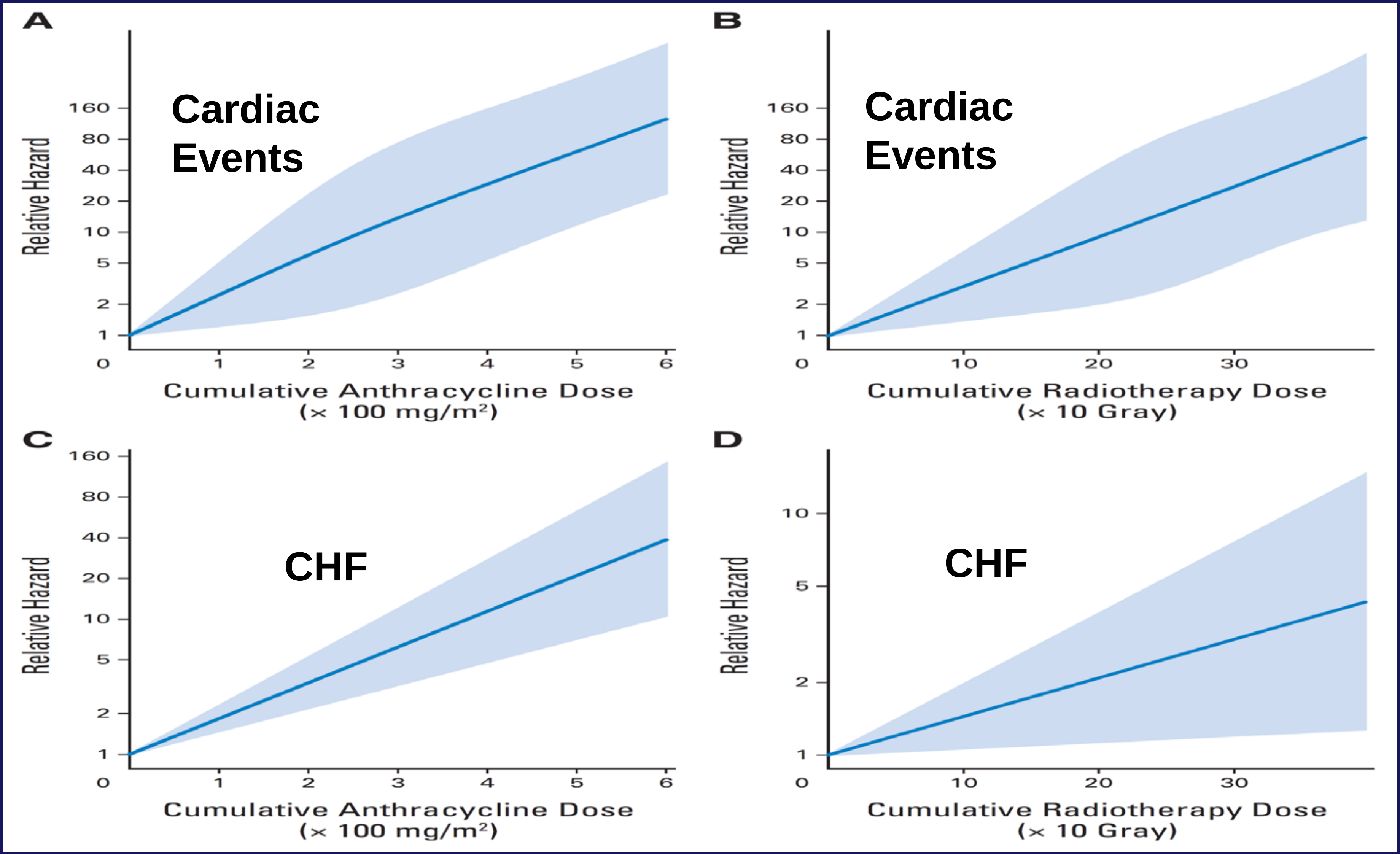
Tukenova, et al., JCO 2010

Netherlands: ↑ Symptomatic Cardiac Events at Early Age. Anthr & Rad Highest Risk. After 30 yrs, 1 in 8 Develops Severe Heart Disease



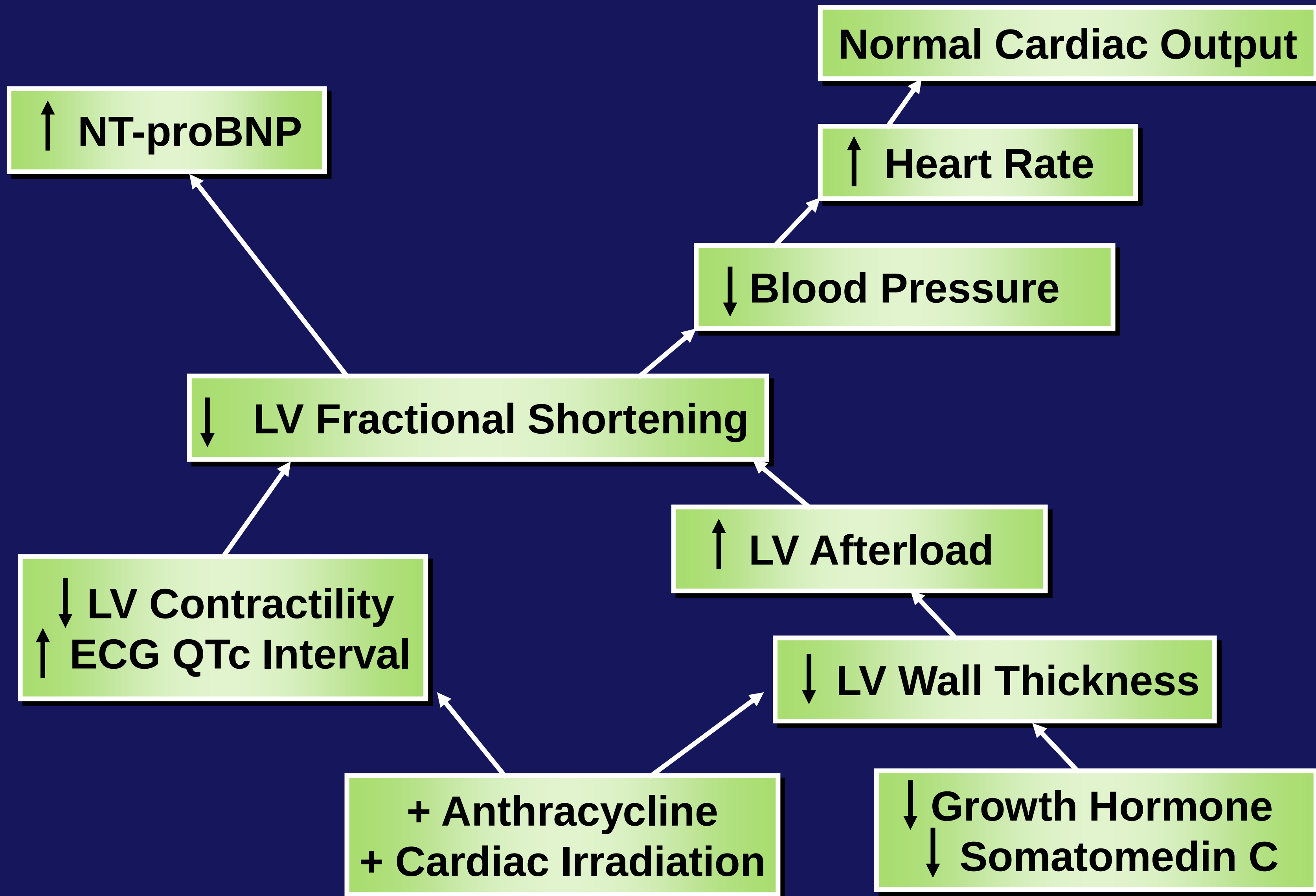
van der Pal, et al., JCO 2012

Netherlands: All Cardiac Events (A&B) and CHF (C&D) Increase with Dose



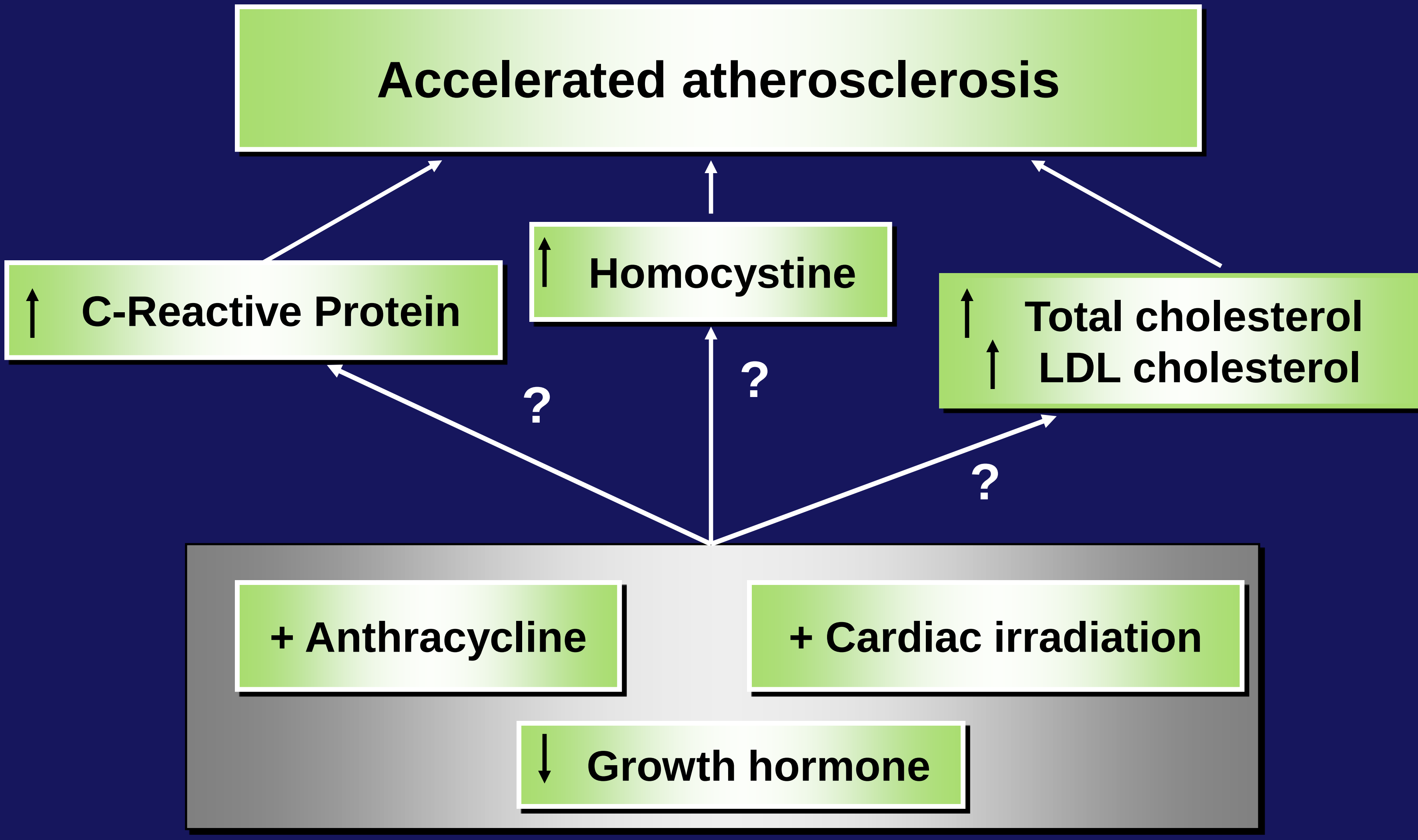
van der Pal, et al., JCO 2012

NCI CRG Study: 10-Year Survivors of Childhood Cancer Cardiomyopathy Changes



Lipshultz et al., JCO 2012

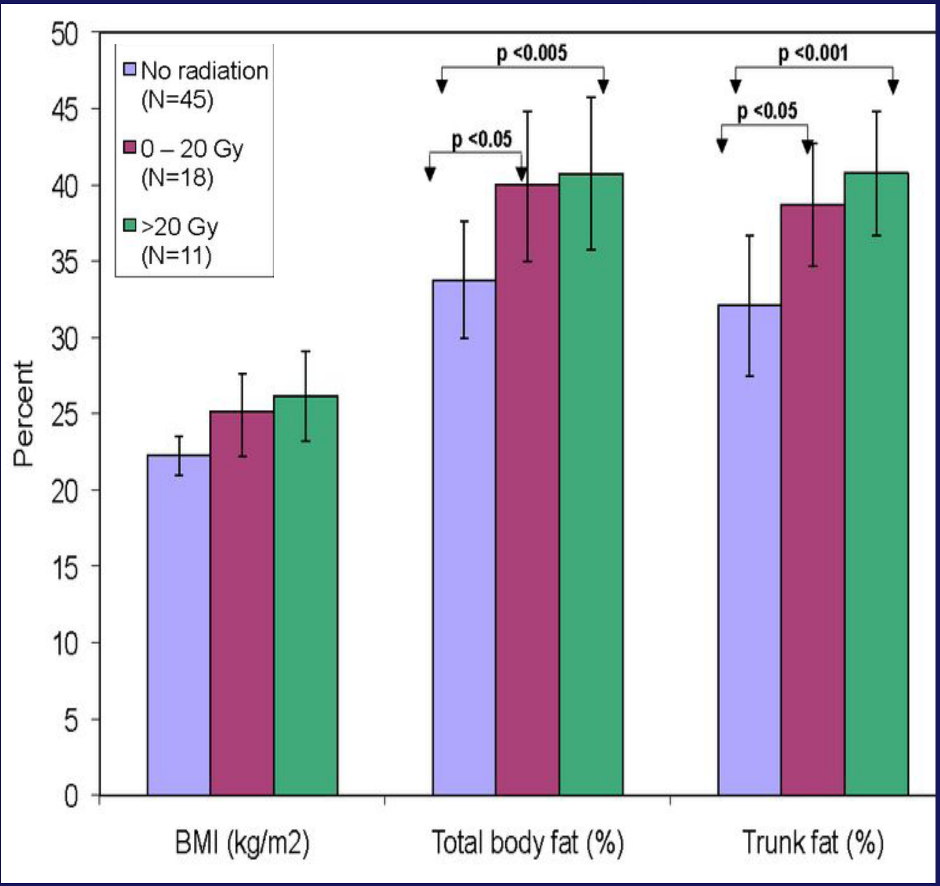
NCI CRG Study: 10-Year Survivors of Childhood Cancer Coronary Artery Disease Risk



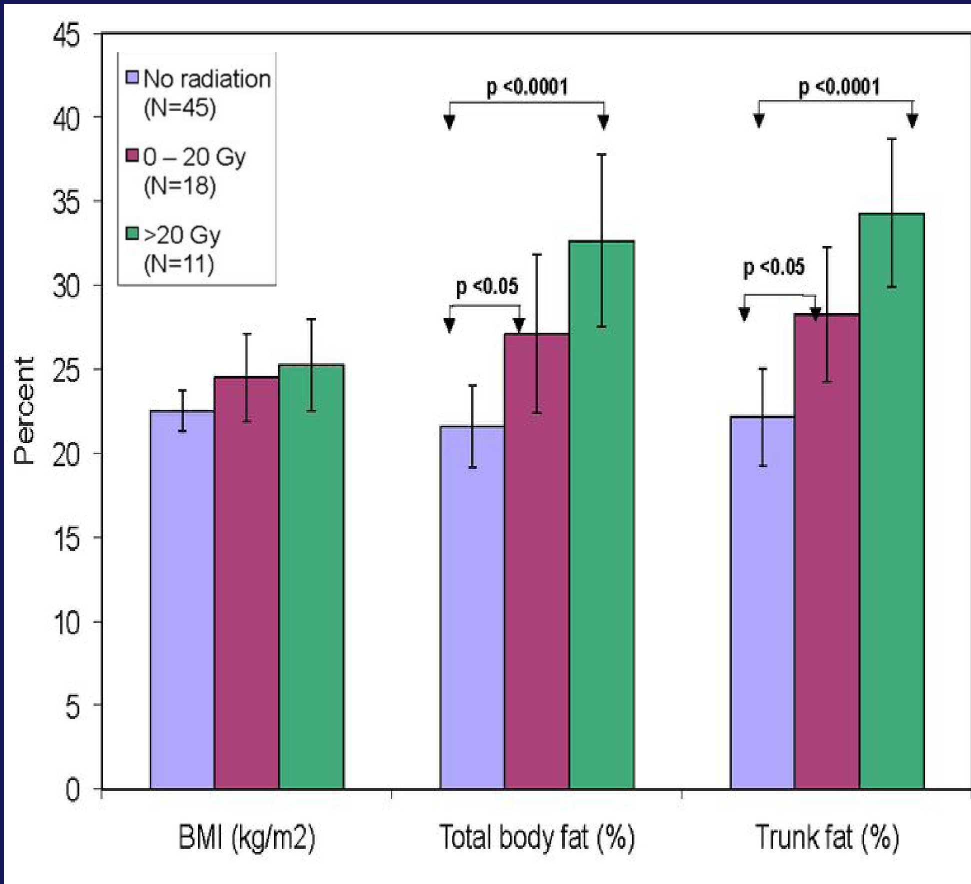
Miller TL, Lipshultz SE, et al., Cancer Epidemiol Biomarkers Prev 2010
Lipshultz, et al., JCO 2012

NCI CRG Study: Adiposity Measures Among Cancer Survivors, by Dose of Cranial Irradiation, by Gender

Females



Males



Miller TL, Mitnik G, Lipshultz SE, et al., Cancer Epidemiol Biomarkers Prev 2010

NCI CRG Study: 30-Year Risk of Cardiovascular Disease in Childhood Cancer Survivors

Framingham Heart Study's calculator (FHC) predicts 30-yr risk of CVD (myocardial infarction (MI), stroke, or coronary death) in those over 20-yrs old.

Mean (Range) FHC Risk Estimate for Survivors by Age-Group and Sex			
20-29 yr old females	20-29 yr old males	30-39 yr old females	30-39 yr old males
2.1% (1-9%)	3.3% (1-12%)	2.9% (1-5%)	15.6% (5-35%)

- Survivors had a 52% increased risk vs. siblings.
- Among survivors from the Long-Term Survivors Study (LTSS), median age of 56 yrs and 48 yrs since dx, 17% reported coronary artery disease and 4% reported cerebral vascular disease.
- Among survivors from the Childhood Cancer Survivor Study (CCSS), 30 yrs since dx, 1.5% reported MI.

Landy DC, Lipshultz SE, et al., AHJ 2012

NCI CRG Study: Risk of Atherosclerotic Disease Coronary Artery Lesions in Childhood Cancer Survivors

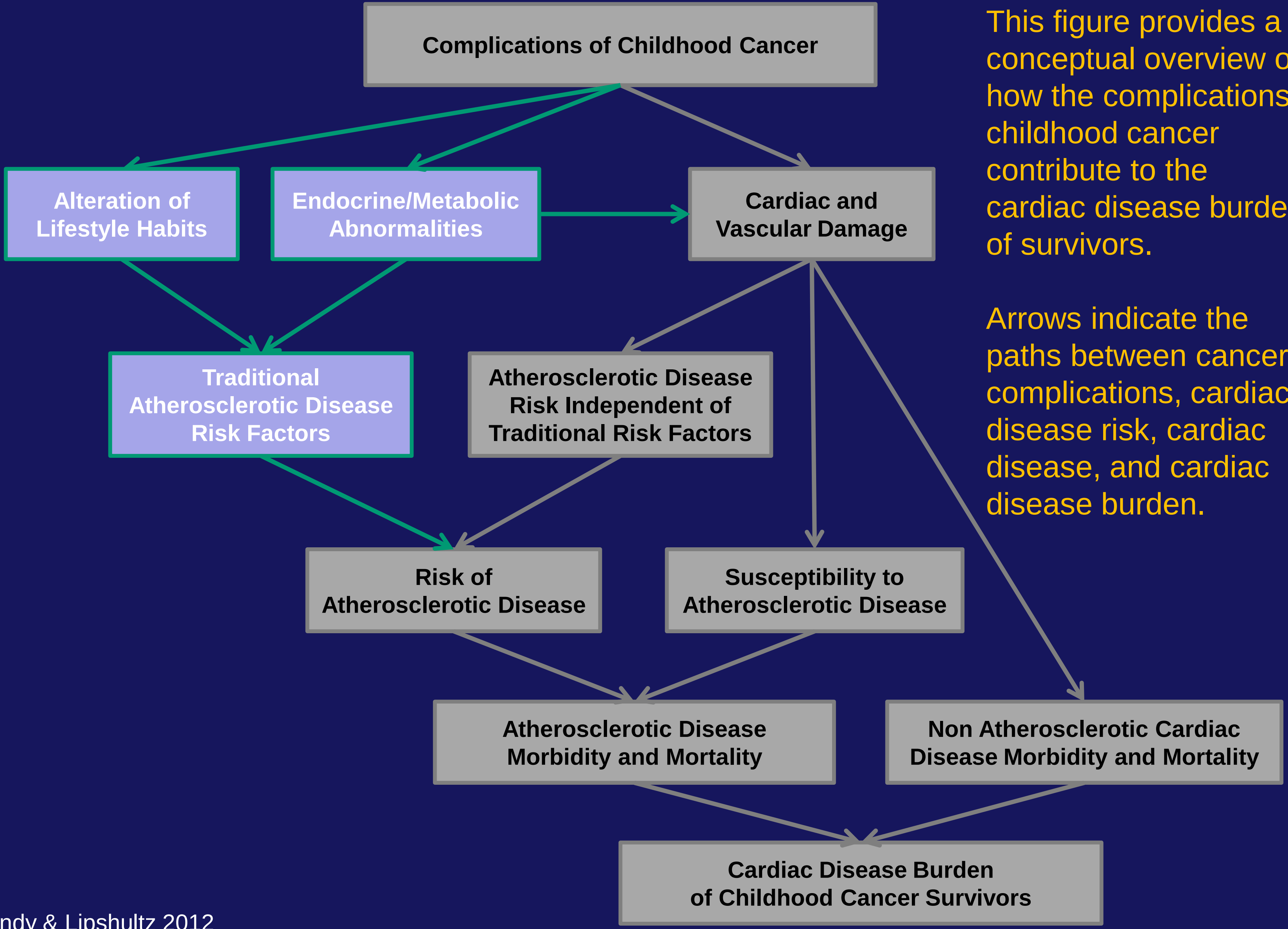
NIH Pathobiological Determinants of Atherosclerosis Study's risk scoring system (PDAY) that predicts risk of an atherosclerotic (AthD) coronary artery lesion in 15- to 34-yr olds.

Mean (Range) PDAY Risk Estimate of AthD Lesions for Survivor Subgroups			
15-24 yr old females	15-24 yr old males	25-34 yr old females	25-34 yr old males
<1% (0-8%)	3% (0-24%)	9% (3-26%)	18% (7-42%)

- Risk was increased for males.
- Risk increased by age.

Landy DC, Lipshultz SE, et al., AHJ 2012

Increased Cardiac Burden of Childhood Cancer Survivors

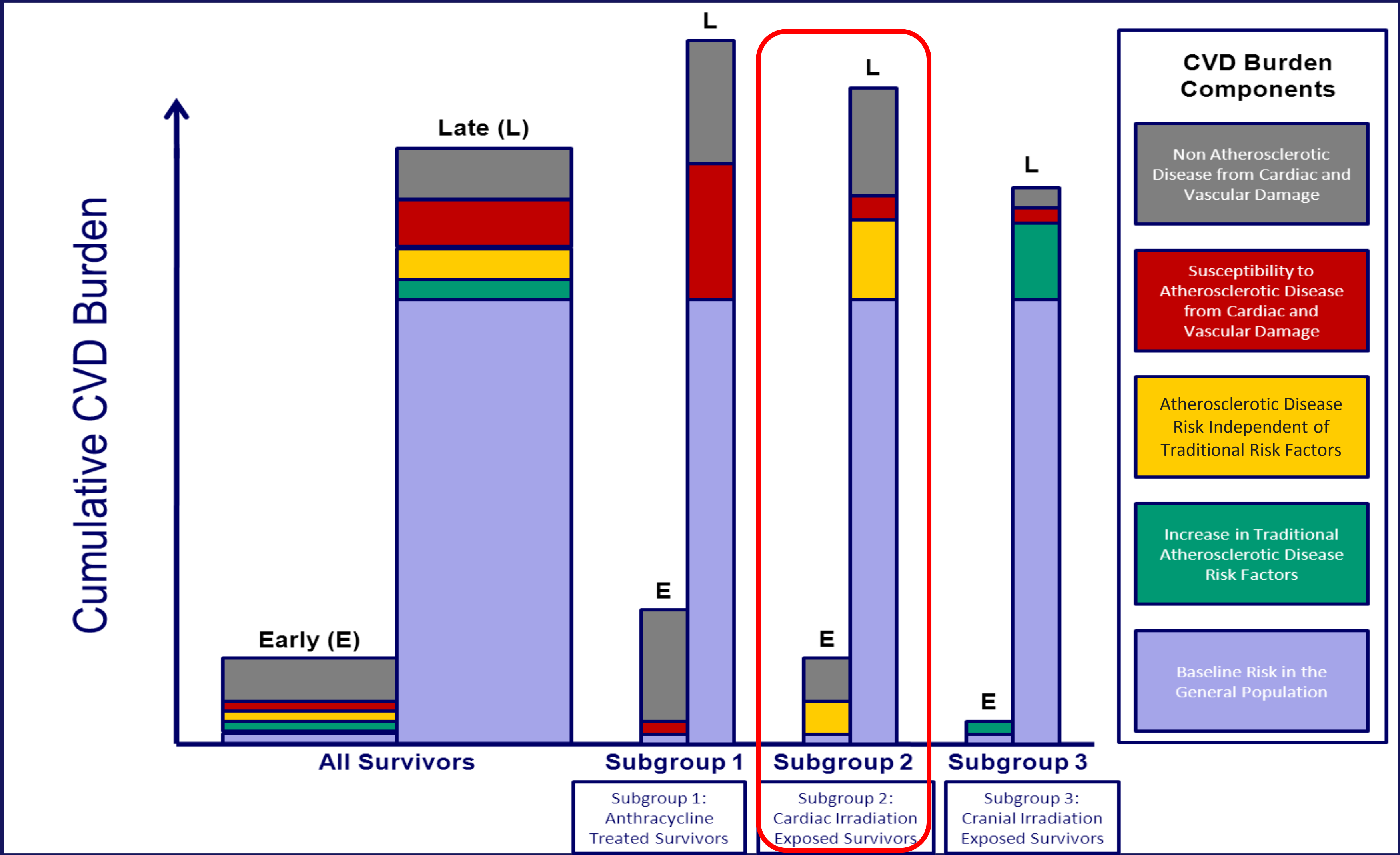


This figure provides a conceptual overview of how the complications of childhood cancer contribute to the cardiac disease burden of survivors.

Arrows indicate the paths between cancer complications, cardiac disease risk, cardiac disease, and cardiac disease burden.

Landy & Lipshultz 2012

Global CVD Risk Components



Potential CVD burden of childhood cancer survivors, both early and late in life, by simplified exposure examples. All component magnitudes are hypothetical, though theory based and survivor subgroups are assumed to have a single uncomplicated therapy exposure.

Landy & Lipshultz 2012

Identical Twins at 26 Years of Age

The twin on the right was treated for childhood ALL at 4 years old.

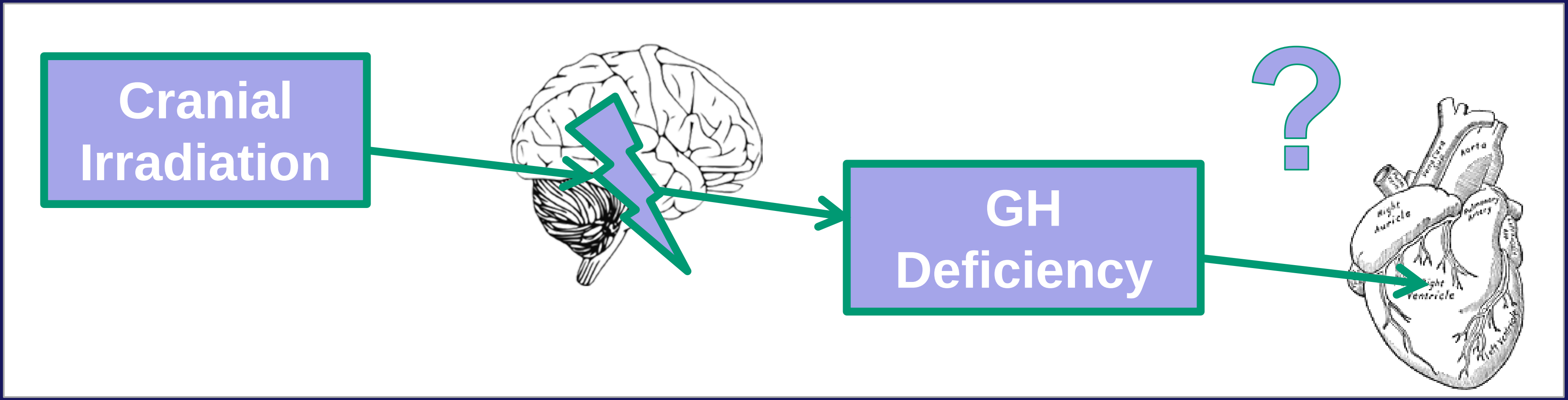
Diller, et al., NEJM 2011

Adult Patient Treated During Childhood for Medulloblastoma (Right) Alongside His Father (Left). The Short Stature Results from GH Deficit, As Well As Spinal Irradiation

Vinchon, et al., Childs Nerv Syst 2011

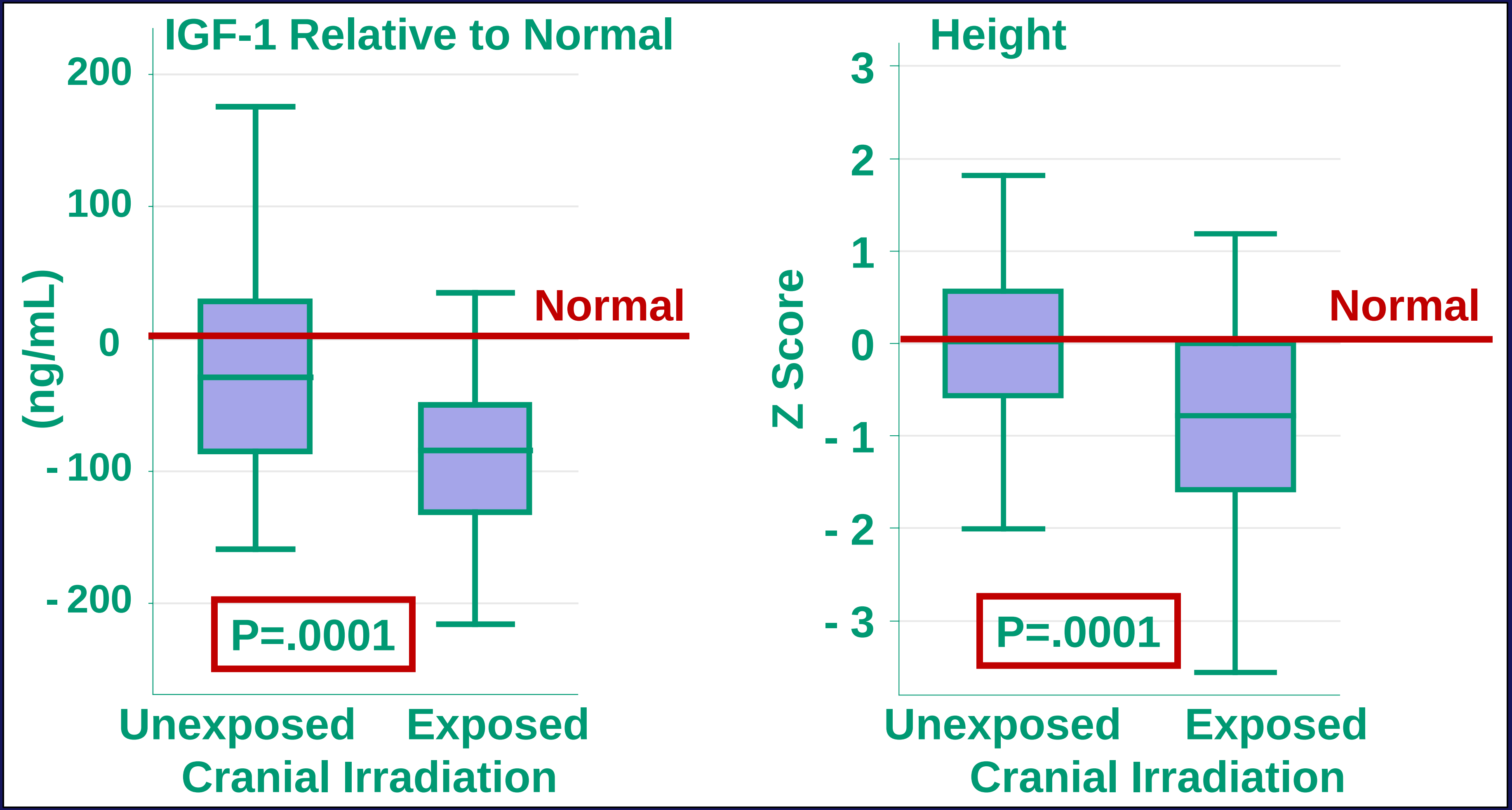
Cranial Irradiation Can Damage the Hypothalamic-Pituitary Axis

- Growth hormone (GH) deficiency
    - An early complication of cranial irradiation
    - Occurs after exposure to even low radiation doses
- GH deficiency from other etiologies
    - Results in reduced LV mass
    - GH replacement can increase LV mass



Landy, Lipshultz, Pediatr Cardiol 2012

Cranial Irradiation Was Associated With ↓IGF-1 and ↓Height



Landy, Lipshultz, et al., Circulation 2010

Landy, Lipshultz, et al., Ped Cardiology 2012

LV mass & dimension significantly ↓ in cranial radiation (CR) exposed anth-treated survivors even after adjusting for other known anthracycline cardiotoxicity risk factors:

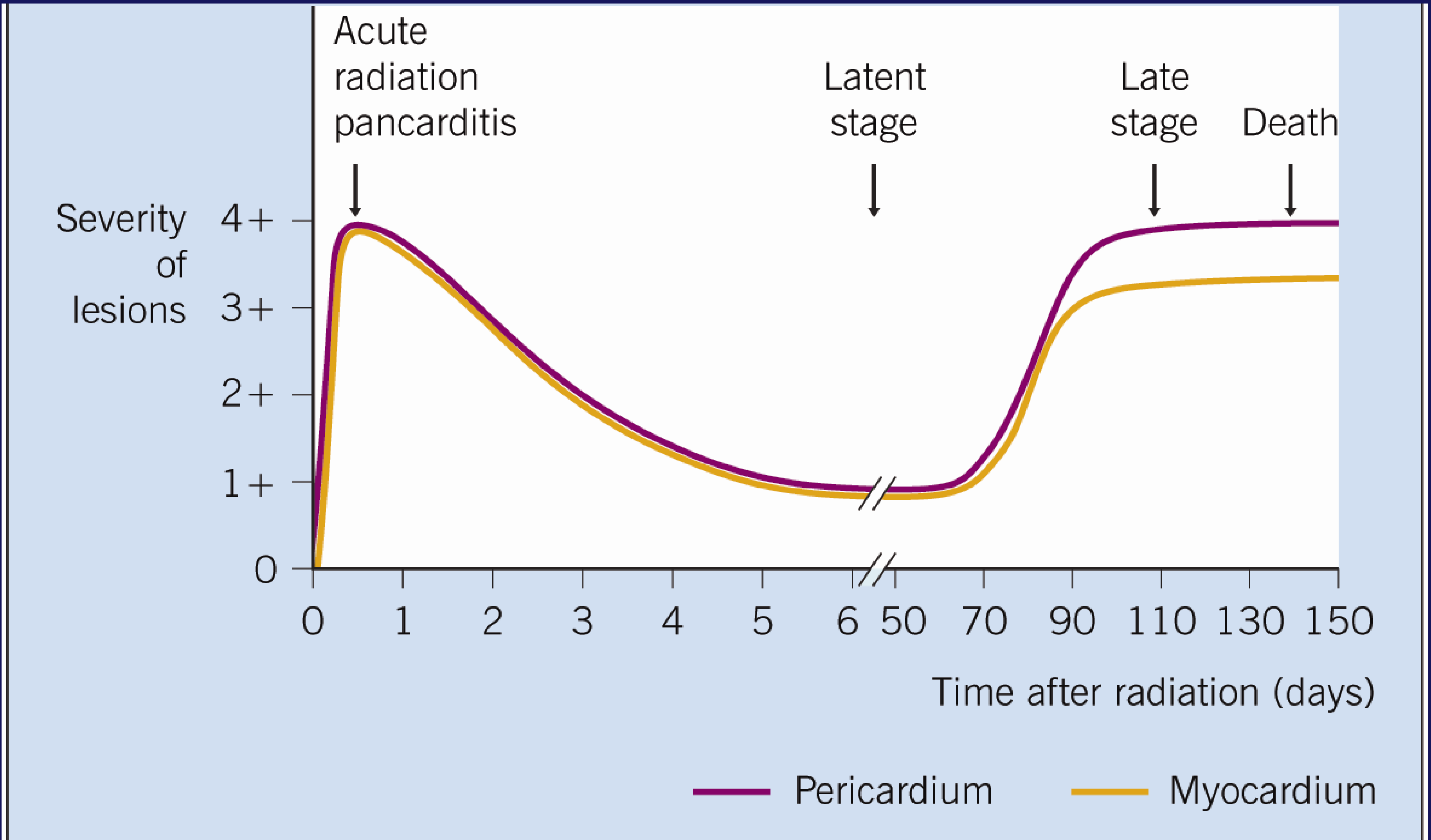
gender, cardiac irradiation, anthracycline dose, age at diagnosis, and time from diagnosis

LV parameter	Adj. difference in % change from normal (CR exposed minus CR unexposed)	P
Mass	-12.0%	<.01
Wall thickness	-2.5%	.39
Dimension	-3.6%	.03
Afterload	+1.8%	.77
F. shortening	-0.7%	.74

Landy, Lipshultz, et al., Circulation 2010

Landy, Lipshultz, et al., Ped Cardiology 2012

Development of Radiation Heart Disease in White Rabbits as Observed by Light Microscopy After a Single Dose of 20 GY



Adams, Lipshultz, Cardiology 2005

Summary of Pre-Clinical Studies into Basic Mechanisms of Radiation Induced Heart Disease (RIHD): Main Observation or Study Outcome References

- Reduced myocardial capillary density, focal loss of endothelial alkaline phosphatase, and increased expression of vonWillebrand factor indicate vascular injury in rat models of RIHD.

- Coronary artery disease has been observed after localized heart irradiation in hypertensive rats or rats on a high-fat diet.

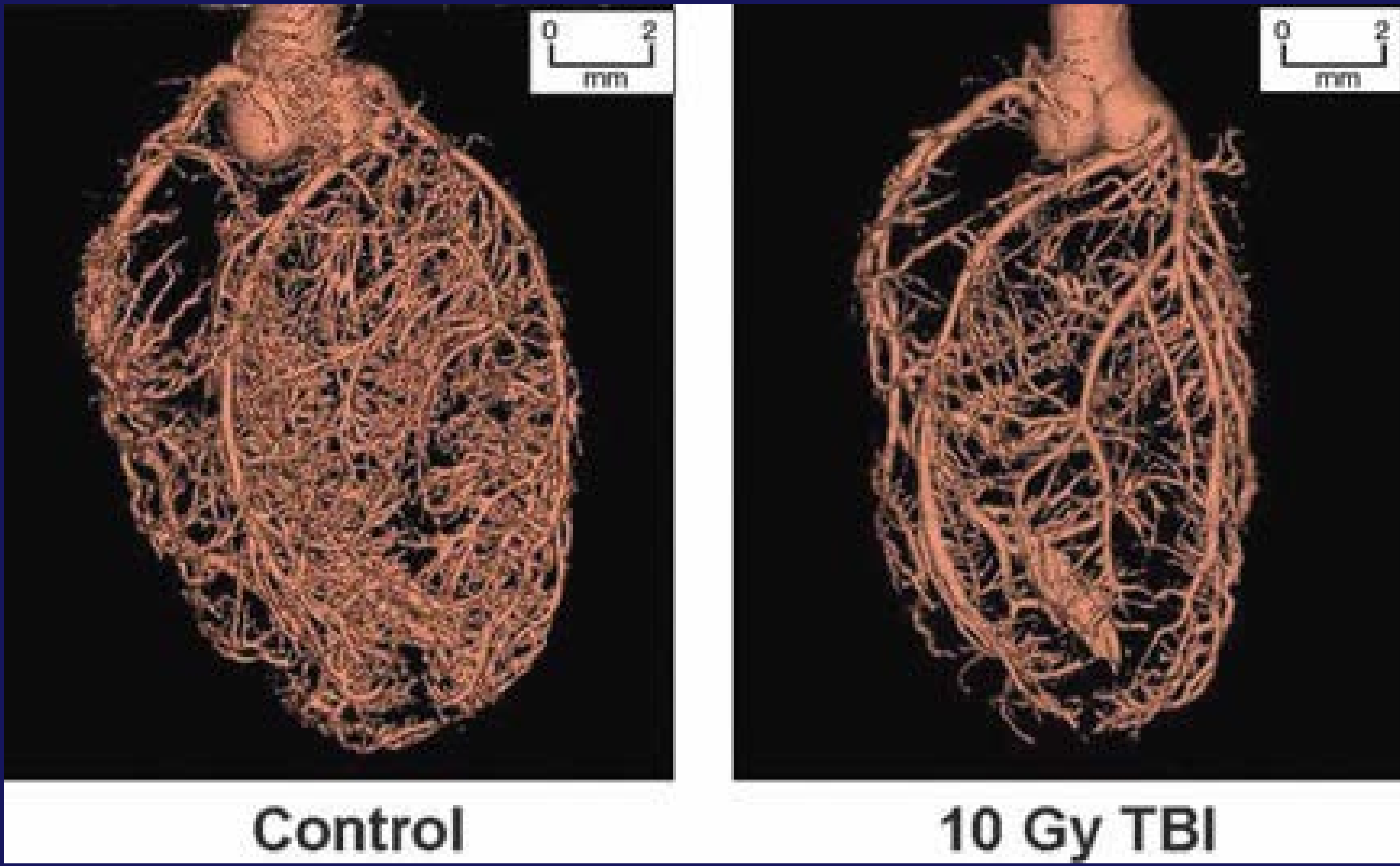
- Increased myocardial levels of TGF-β1, Ang II, and aldosterone have been found after localized heart irradiation in rats.

- ACE inhibitor captopril reduced myocardial fibrosis and prevented left ventricular capillary density loss after localized heart irradiation in rats.

- Mast cell-deficient rats showed reduced radiation-induced myocardial inflammation and degeneration, but increased myocardial fibrosis when compared to mast cell-competent rats.

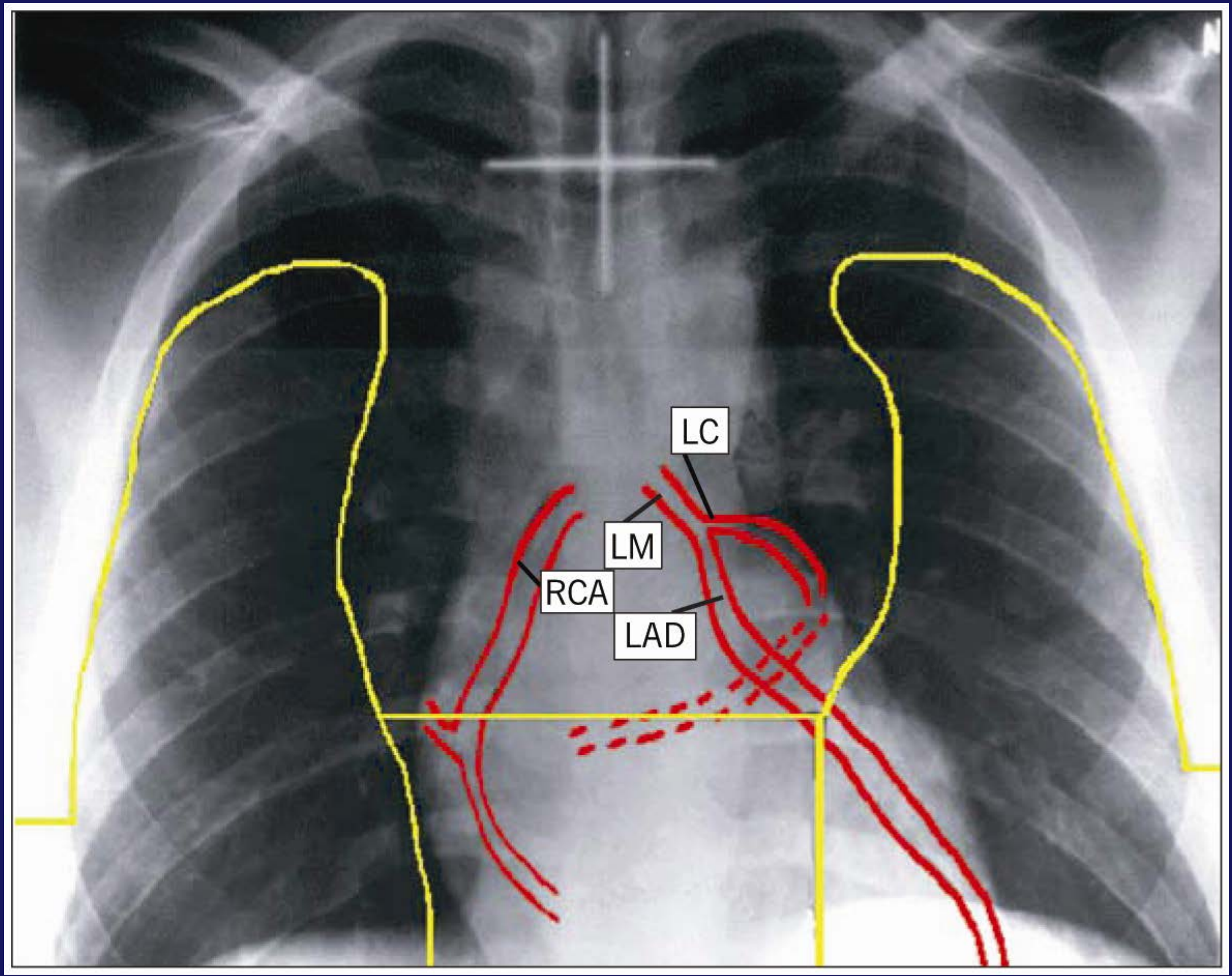
M. Boerma and M. Hauer-Jensen, Cardiology Research and Practice 2011

↓ Vascular Density After Cardiac Irradiation



Baker et al., Antioxidants & Redox Signaling 2011

30 Gy Irradiation to 15-Year-Olds with Hodgkin's Disease



Adams, Lipshultz, Cardiology 2005

Radiotherapy to the Heart During Childhood is Associated with Progressive Late Cardiac Findings 16-Years Later and Potential Future Morbidity and Mortality

- Restrictive cardiomyopathy
→ heart failure

- Valvular heart disease
→ endocarditis
- Intracardiac conduction defects → sudden death
- Coronary artery disease → heart attack
- Others

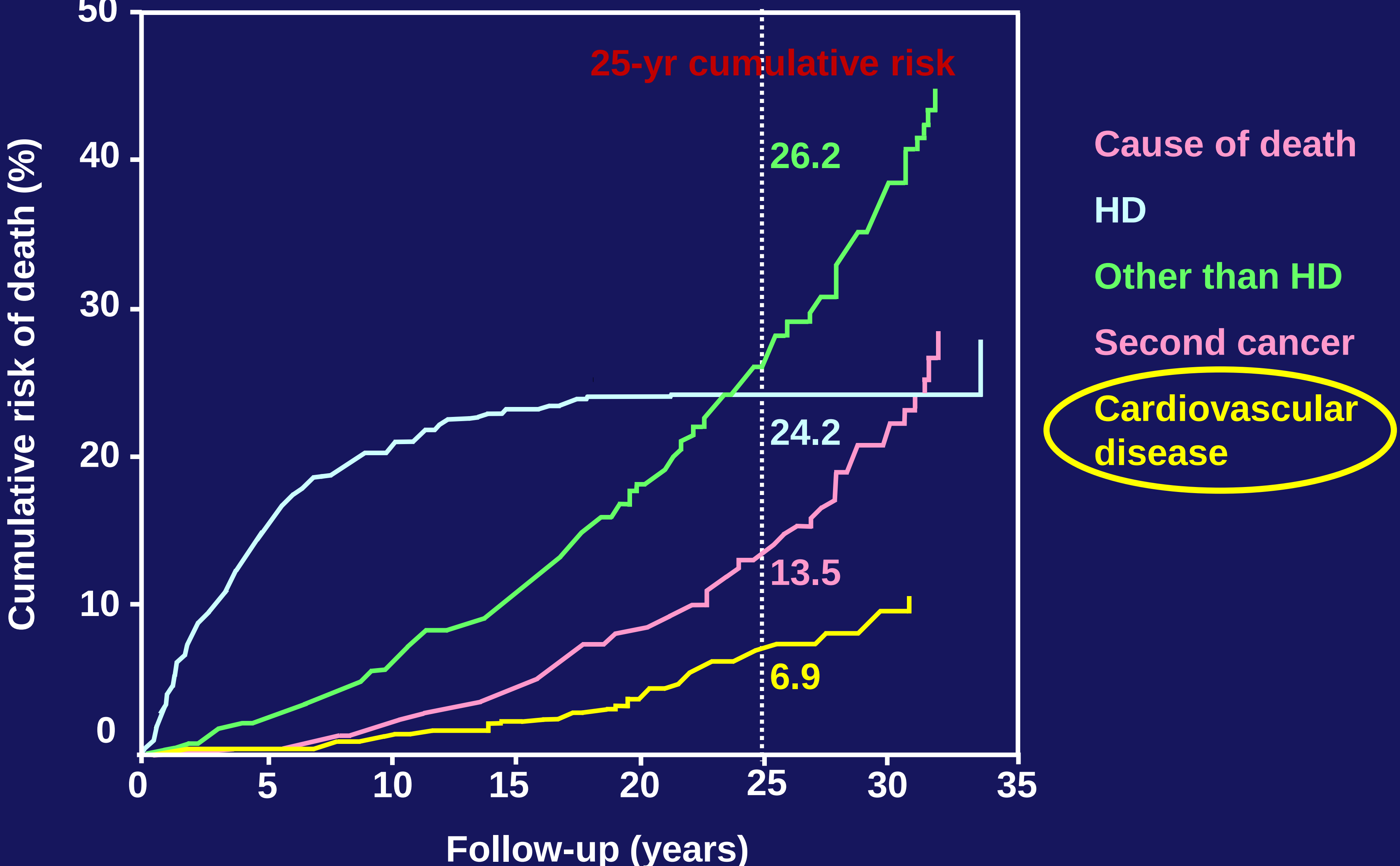
Adams, Lipshultz, et al., JCO 2004

- Progressive findings may become apparent clinically 10 or more years after radiotherapy
  - **Findings may be unsuspected but clinically significant**
  - **Serial comprehensive cardiac testing is advised**

- Unlike the loss of heart muscle cells related to anthracycline use, radiotherapy to the heart appears related to progressive fibrosis (scar tissue formation) years after therapy

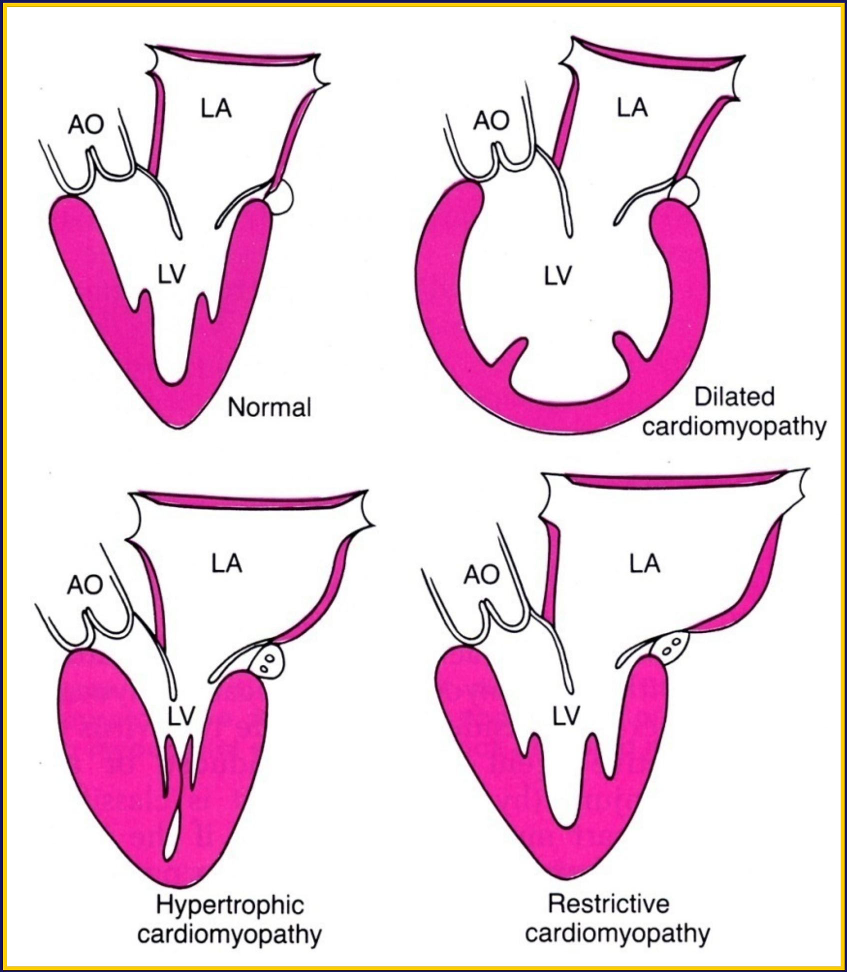
Adams, Lipshultz, et al. JCO 2004

Competing Mortality Over Time



Aleman, JCO 2003

Picture of Restrictive Cardiomyopathy



- **12% with an abnormal measurement of LV systolic function**

Restrictive cardiomyopathy

↓

Diastolic dysfunction

Adams, Lipshultz et. al., J Clin Oncol 2004

Fibrotic Heart Valve Defects

Valve Defect	Obs %	Expected %	P-value*
Mitral stenosis	**2**	**–**	**–**
Mitral regurgitation **(Grade ≥ Mild)**	**21**	**9.7**	**0.022**
Aortic stenosis	**6**	**–**	**–**
Aortic regurgitation **(Grade ≥ Mild)**	**19**	**0.0**	**<0.001**
Significant left-sided valve defect	36	**–**	**–**

Adams, Lipshultz et. al., J Clin Oncol 2004

Progressive Fibrotic Heart Valve Disease

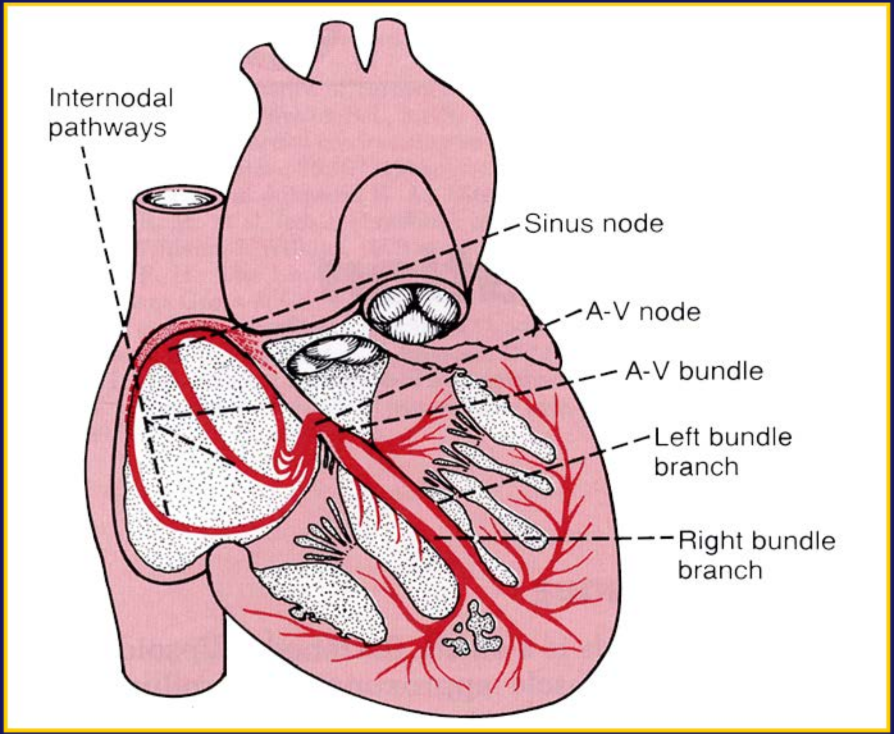
Valve Defect	Obs %	Expected %	P-Value*
Tricuspid regurgitation (Grade ≥ Mild)	25.6	14.4	0.06*
Pulmonary regurgitation (Any)	2.6	–	–
Signif. right-sided defect	23		–
Any significant defect	42.6	– –	–
Any valve defect	68		

*** Comparison values from Framingham Heart Study. *Am J Cardiol* 1999.**

Number of patients screened to find one patient needed antibiotics for valvular heart disease (SBE prophylaxis): <10 years since irradiation: 13 patients and >20 years since irradiation: 1.6 patients.

Heidenreich, et. al., JACC 2003
Adams, Lipshultz et. al., J Clin Oncol 2004

Scarring of the Electrical System in the Heart Conduction Defect/Arrhythmia in 74.5%



- **59.6% conduction delay in anterior right bundle**
- **4% right bundle branch block**
- **8.5% prolonged corrected QT interval**

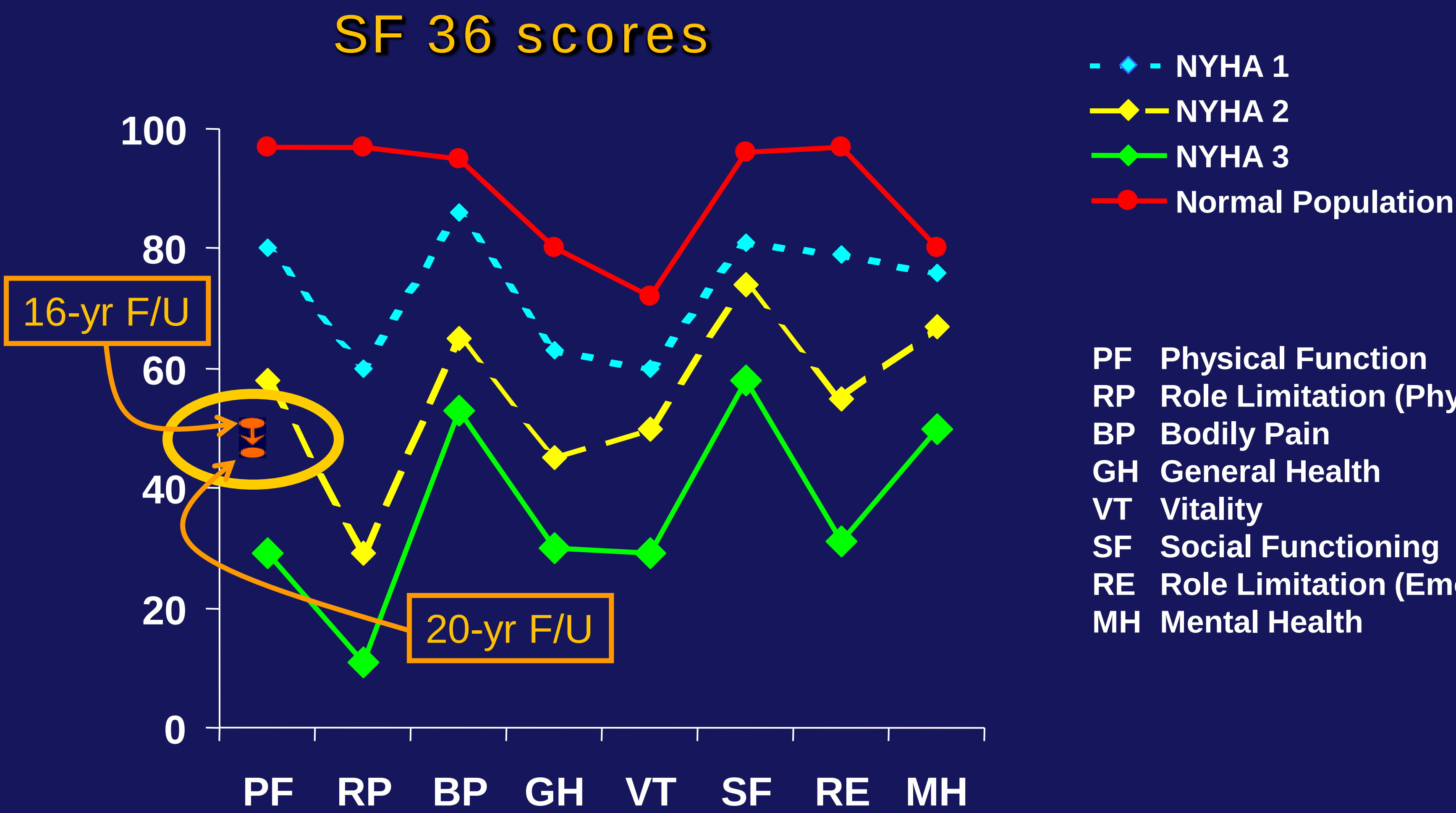
Adams, Lipshultz, JCO 2004

Decreased Quality of Life and Physical Functioning

- **All Rated Overall Health as Good or Better**
- **However on the General Health Survey:**
  - 67% fatigue (half ≥ moderate problem)
  - 40% short of breath (1/3 ≥ moderate problem)
  - 10% significant problem with dizziness
  - 25% chest pain

Adams, Lipshultz et al., JCO 2004

QoL: Radiation Effects Are Similar to CHF



PF Physical Function
RP Role Limitation (Physical)
BP Bodily Pain
GH General Health
VT Vitality
SF Social Functioning
RE Role Limitation (Emotional)
MH Mental Health

Juenger et al., Heart 2002
Adams, Lipshultz, JCO 2006

Multiple Populations with Increased CHD Risk After Chest Irradiation

- Childhood Cancer Survivors
  - Particularly HD survivors treated with > 35-40 Gy
  - Significant increased relative incidence at > 15 Gy
- Increased risk demonstrated in non-cancer populations at doses as low as 2.5 Gy
  - Peptic Ulcer Disease
    - RR of mortality = 1.5
  - Atomic bomb survivors
    - Less than 40 yrs at time of bombing
    - Risk first appeared after 40 years of follow-up

Adams, Lipshultz et. al., AHA Epi Meeting, 2011

Summary of Risk Factors

- Younger age at exposure
- Cumulative radiation dose
- Treatment with other cardiotoxic therapies
- Length of follow-up since therapy
    - Approx 15 year lag time

Sievert = Biological effects of radiation

Gray = Absorbed radiation dose

Adams, Lipshultz et. al., AHA Epi Meeting, 2011

Radiation Exposure Dose-Response: Clear as Mud

Figuring out the true relationships between dose and response is — to say the least — complicated. This infographic shows a sampling of the many points along the dose spectrum where a researcher or agency detects a biological response or threshold, or where a person receives a dose from a medical test or procedure. As you'll see, effects asserted at theses points are not necessarily consistent with each other.

V Brown, Miller-McCune, 2012

Official Radiation Exposure Limits

OFFICIAL EXPOSURE LIMITS

The variety of exposure limits established by regulatory agencies and advisory bodies.

0.10 Dose (*in millisieverts*)
- Annual effective dose equivalent limit to any individual based on emissions in "ambient air"
- Environmental Protection Agency Code of Federal Regulations

1.0
- Annual regulatory limit for exposure to the public
- Nuclear Regulatory Commission
- Recommended annual limit for exposure to the public
- International Commission on Radiological Protection *Publication 103*

5.0
- Annual limit for exposure by ingestion
- Food and Drug Administration
- Annual dose that fetuses can take without harm
- Nuclear Regulatory Commission

20.0
- Recommended annual occupational limit (averaged over 5 years, with no more than 50 millisieverts in any one year)
- International Commission on Radiological Protection Publication 103 (General recommendations)

50.0
- Annual whole-body (internal and external) occupational limit
- Nuclear Regulatory Commission

300.0
- First formal annual standard for humans, set in 1928
- Alexander M. Vaiserman, Institute of Gerontology, Kiev, *Dose Response*, 2010

500.0
- Annual occupational limit for any single organ
- Nuclear Regulatory Commission

750.0
- EPA guideline for maximum dose to emergency workers volunteering for lifesaving work
- Oak Ridge National Laboratory
- Alexander M.Vaiserman, Institute of Gerontology, *Dose Response*, Ukraine 2010

V Brown, Miller-McCune, 2012

Study Population: The Hempelmann Cohort

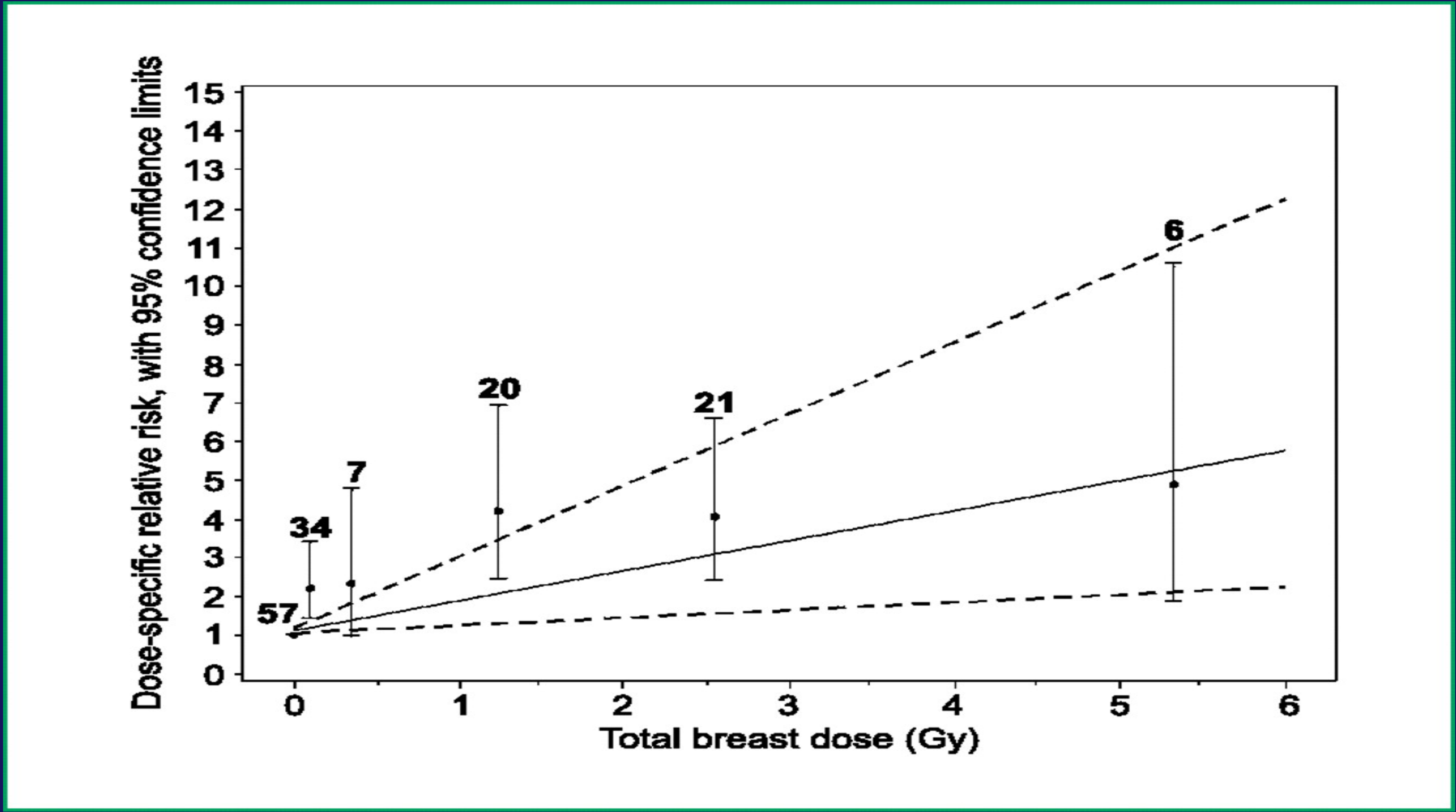
- Individuals treated with chest RT for an enlarged thymus in the Rochester NY area & siblings*
  - 2567 Treated Individuals
  - 4833 Untreated Siblings (born before 1964)

- Treated between 1926 and 1957
  - Median age at treatment: 5 weeks
  - 90% treated prior to 6 months of age
  - Mean thymus radiation dose 1.36 Gy
- Surveyed previously in 1953, 1959, 1963, 1969, 1975, 1985-87

*Eligible if successful follow-up of ≥ 5 years

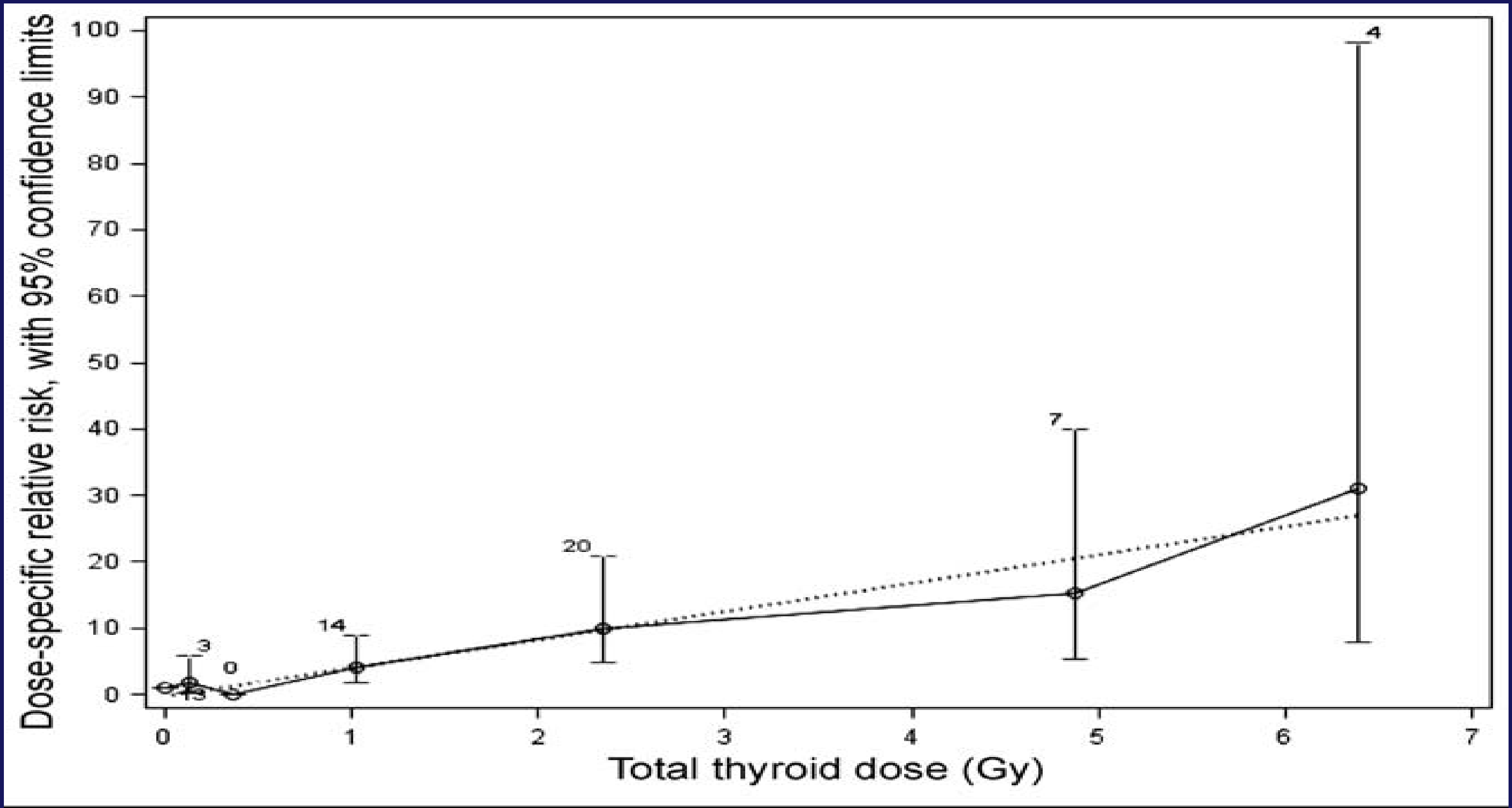
Adams, Lipshultz et. al., AHA Epi Meeting, 2011

Radiation Dose Response for Breast Cancer Incidence Among 3,449 Women in the Rochester, NY Thymus Irradiation Cohort, with Known Thymus Irradiation Doses – 57.5 yr median f/u 159,459 person-yrs f/u



Adams, Liphsultz et al. Cancer Epidemiol Biomarkers Prev 2010

Radiation Dose Response for the Incidence of Thyroid Cancer Among 7,490 Subjects in the Rochester, NY Thymus Irradiation Cohort, with Known Thyroid Radiation Dose – 57.5 yr median f/u 334,347 person-yrs f/u



Adams, Liphsultz et al. Radiation Research 2011

Person-Years After Age 15 & Event Rate by Dose Group

	# Persons	Person-years	Mean Cardiac Dose (std) (Gy)	Median Cardiac Dose (Gy)	MI Cases	MI Rate*	CHD Cases	CHD Rate*
Non-irradiated siblings	4755	141,592	--	--	130	9.2	206	14.6
Total irradiated	2608	86,898	1.45 (1.28)	1.41	83	9.6	144	16.6
0.17-0.99 Gy	1036	29,922	0.40 (0.23)	0.25	17	5.7	22	7.4
1.00-1.99 Gy	906	29,853	1.58 (0.24)	1.56	33	11.1	51	17.1
2.00-2.99 Gy	321	12,962	2.44 (0.27)	2.46	20	15.4	33	25.6
3.00-20.99 Gy	223	9,164	4.44 (1.55)	4.00	8	8.7	29	32.0
Dose unknown	122	4,997			5	10.0	9	18.1

*** Rates per 10,000 person years**

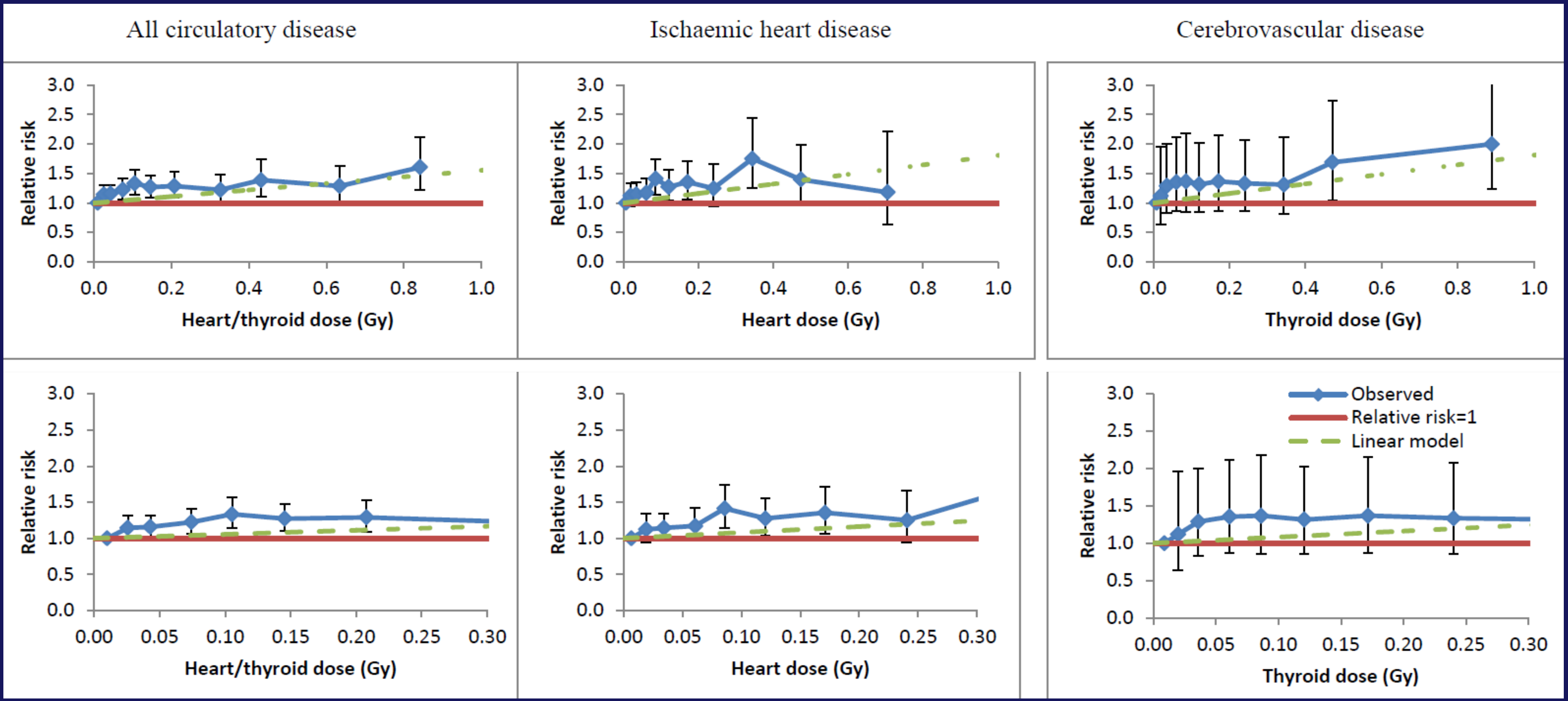
Adams, Lipshultz et. al., AHA Epi Meeting, 2011

Increased Circulatory Disease Mortality With Low and Moderate Doses of Ionizing Radiation

- >800K patients with cardiac radiation dosimetry and >18M pt-yrs of follow-up.
- Estimated excess population risks for all circulatory disease mortality in 9 developed nations ranged from 2.5%/Sv in France to 8.5%/Sv for Russia.
- Radiation-related mortality is about twice that currently estimated based on estimates for cancer end points alone (which range from 4.2% to 5.6%).
- Cardiac mortality is worse when radiation exposure occurs during childhood.

MP Little…Lipshultz SE. Envir Health Perspect 2012

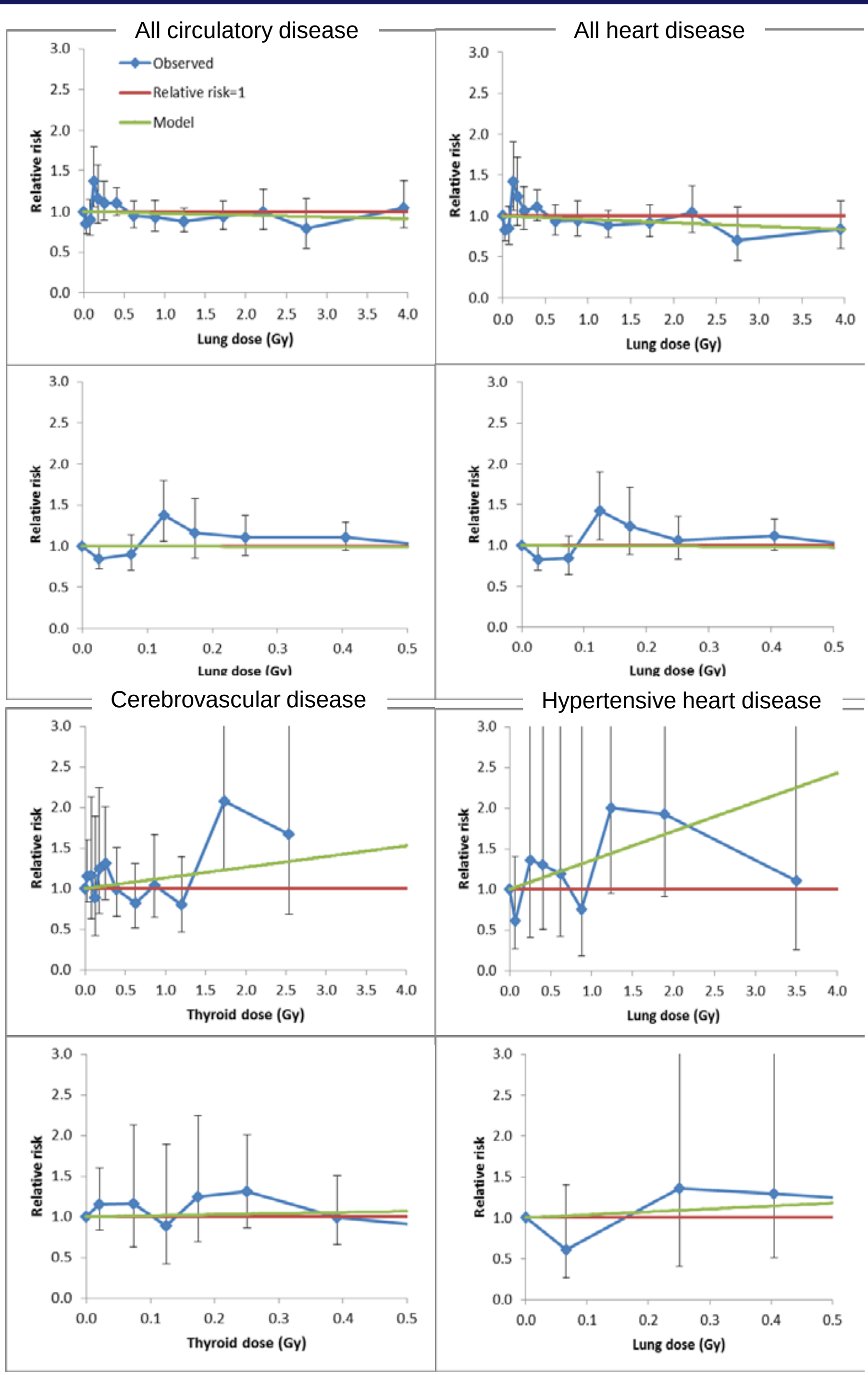
Low-dose Ionizing Radiation Exposure, under 100 mGy, is Associated with Increased Circulatory Diseases, more so than at Higher Doses



*Lower panel in each graph is low dose (<0.5 Gy) part of upper graph.

- 100,369 US Radiologic Technologists. Made worse with cigarette smoking, diabetes and obesity.

Little MP…Lipshultz SE. Int J Epi 2014



Excess Cardiovascular Disease Risks at Low Radiation Doses <0.5 Gy.

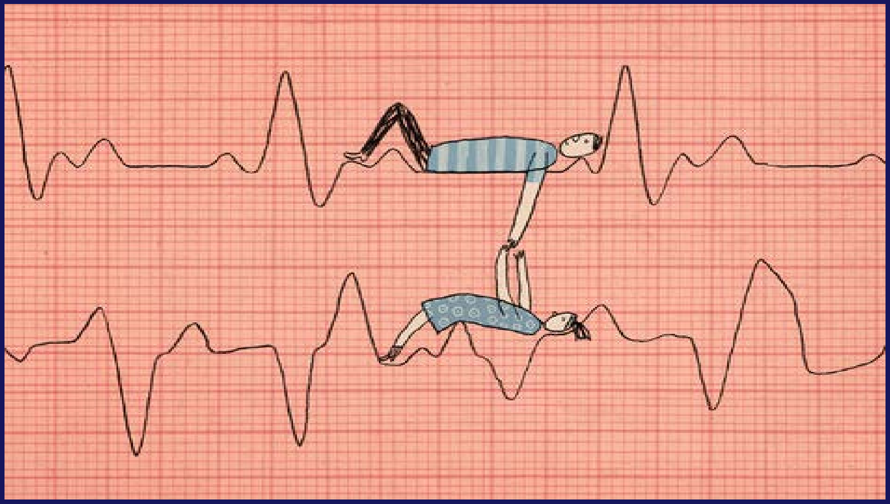
13,568 Massachusetts Tuberculosis Workers

Little MP…Lipshultz SE. Eur J Epi 2014

Conclusions

- Cardiotoxicity associated with cancer therapeutics can be pervasive, persistent, and progressive but missed clinically
- If you don't look, you don't know
- Tailored follow-up and therapies are needed and may be unique
- Genetic, environmental, and temporal factors interact to cause toxicity and identify high risk groups for safer treatment options and targeted interventions
- Validated surrogate cardiac endpoints are lacking
- Survivor cardiac monitoring delays heart failure and improves QOL
- Cardiovascular-related health burden will increase as this expanding population ages

"In Matters of the Heart, We're in This Together."



Questions and Answers

U.S. Department of Health and Human Services
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