The Spectrum of Late Effects of Radiation Fibrosis

Moving from Risk to Risk Reduction

1st Annual Cancer Rehabilitation Symposium
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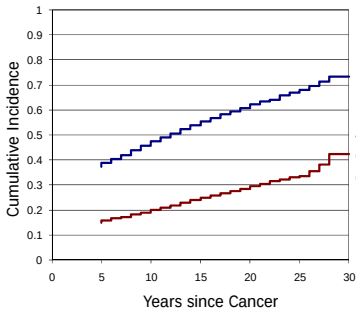
Kevin C. Oeffinger, MD
Director, Adult Long-Term Follow-Up Program
Member, Departments of Medicine and Pediatrics

Outline

- Moving from risk to risk reduction
- Two models for research and clinical care of post radiation sequelae
  - Breast cancer (younger age at exposure)
  - Coronary artery disease (any age at exposure)
- Future directions

❖ Remember: radiation is critically important in curing the primary cancer

Cumulative incidence of chronic physical health conditions among 10,397 young adult survivors of childhood cancer
Childhood Cancer Survivor Study



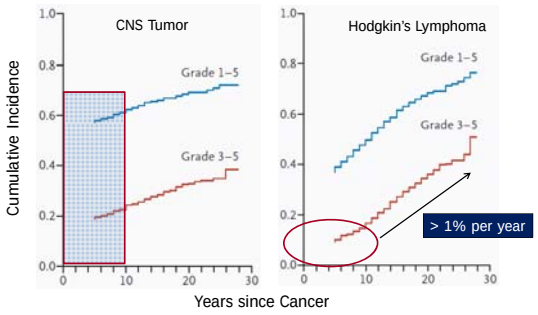
73.4% with at least one chronic condition

42.4% with a severe or life-threatening condition or death

Oeffinger KC, et al. N Engl J Med, 2006

Cumulative incidence of chronic physical health conditions among 10,397 young adult survivors of childhood cancer

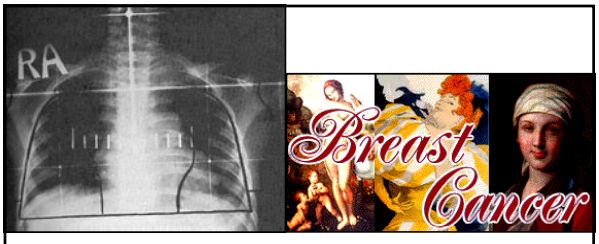
Childhood Cancer Survivor Study



Oeffinger KC, et al. N Engl J Med, 2006

Morbidity following Adult Cancer

- To date, some studies looking at specific outcomes (SMN, cardiac) in specific cancer populations (Hodgkin lymphoma, testicular cancer)
- No overall estimates of morbidity
- U-shaped curve by age?
  - Younger age: developing organs
  - Mid-age: interaction of therapy with comorbid health conditions
  - Older age: senescent organs

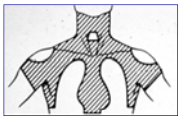


Breast Cancer After Treatment of Hodgkin's Disease

*Steven L. Hancock, Margaret A. Tucker, Richard T. Hoppe**

Journal of the National Cancer Institute, Vol. 85, No. 1, January 6, 1993

Mantle Field



Hodgkin's lymphoma
2500 – 4500 cGy

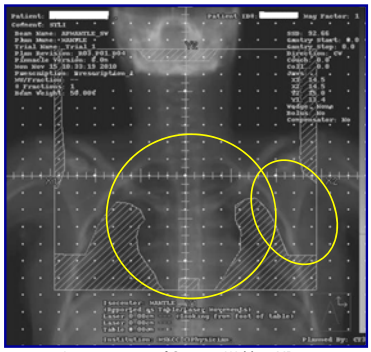


Image courtesy of Suzanne Wolden, MD

Involved Field, Mediastinum

- Hodgkin's lymphoma
- Non-Hodgkin
- Neuroblastoma

1500 – 3500 cGy

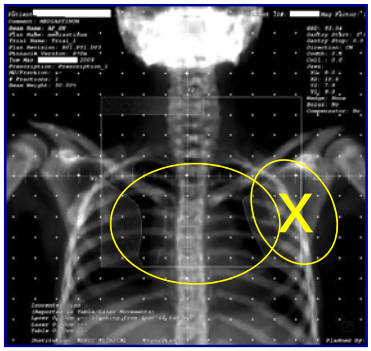
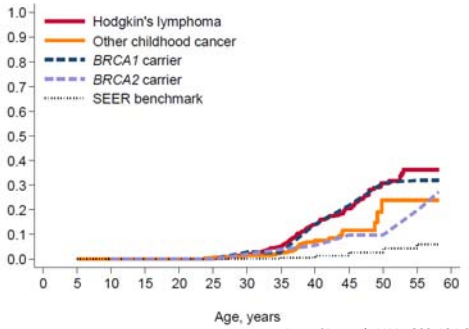


Image courtesy of Suzanne Wolden, MD

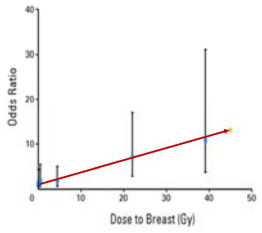
Cumulative incidence of breast cancer among women treated for a childhood cancer with chest radiation and BRCA mutation carriers

Childhood Cancer Survivor Study and WECARE Study

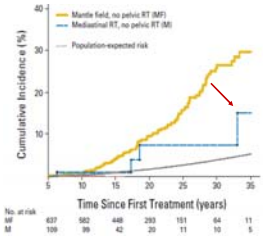


Begg CB, et al. JAMA 299:194-201, 2008
Moskowitz CS, unpublished, 2013

Breast cancer risk, dose and volume



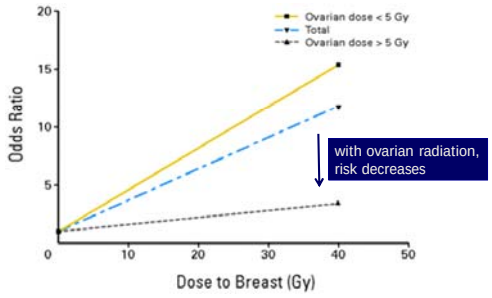
Inskip PD, et al. J Clin Oncol, 2009



De Bruin ML, et al. J Clin Oncol, 2009

Breast cancer risk decreases with concurrent radiation to the ovary

Childhood Cancer Survivor Study



Inskip PD, et al. J Clin Oncol, 2009

Younger age at radiation exposure is associated with increased risk of breast cancer

32,591 HL patients in 16 population-based registries

Age at HL	RR	AER
< 21 yrs	14.2	18.6
21-30	3.7	12.9
31-40	1.2	2.6

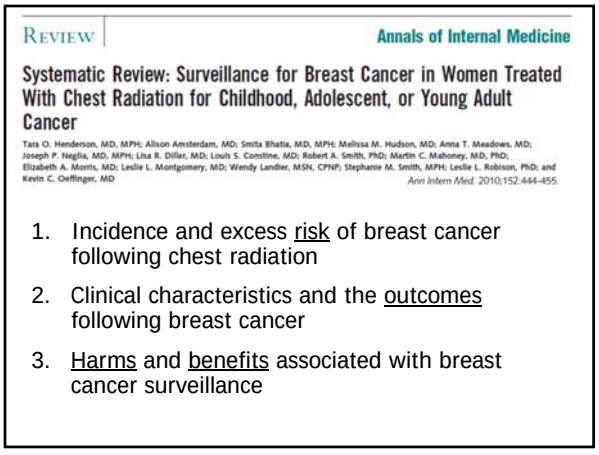
Dores GM, et al. J Clin Oncol, 2002

Characteristics of Breast Tumors

- Median age is young
- Interval from radiation to breast cancer is often short (10-20 yrs)
- Upper outer quadrant (inner quadrant)
- Updated CCSS data
  - 26% bilateral: 12% synchronous, 14% asynchronous
  - 55% w/ bilateral mastectomy at time of 1st diagnosis

Outcomes of Breast Cancer

- 5-yr survival strongly associated with stage at diagnosis (women with early stage disease have good outcomes)
- Limitations in therapy
  - Further radiation?
  - Anthracyclines (doxorubicin)


REVIEW | Annals of Internal Medicine

Systematic Review: Surveillance for Breast Cancer in Women Treated With Chest Radiation for Childhood, Adolescent, or Young Adult Cancer

Tara O. Henderson, MD, MPH; Alison Amsterdam, MD; Smita Bhatia, MD, MPH; Melissa M. Hudson, MD; Anna T. Meadows, MD; Joseph P. Neglia, MD, MPH; Lisa R. Diller, MD; Louis S. Constine, MD; Robert A. Smith, PhD; Martin C. Mahoney, MD, PhD; Elizabeth A. Morris, MD; Leslie L. Montgomery, MD; Wendy Landier, MSN, CPNP; Stephanie M. Smith, MPH; Leslie L. Robison, PhD; and Kevin C. Oeffinger, MD

Ann Intern Med. 2010;152:444-455.

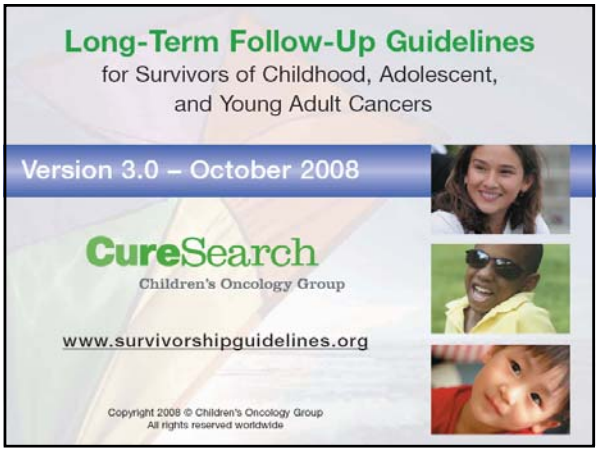
1. Incidence and excess risk of breast cancer following chest radiation
2. Clinical characteristics and the outcomes following breast cancer
3. Harms and benefits associated with breast cancer surveillance

Children's Oncology Group

www.survivorshipguidelines.org

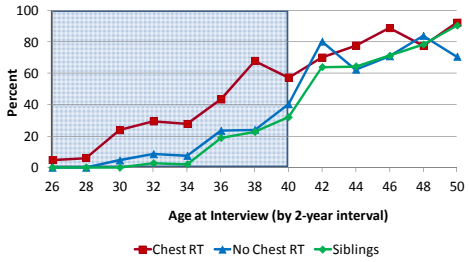
American Cancer Society

Annual mammogram and breast MRI
Starting at the age of 25 or 8 yrs after the RT



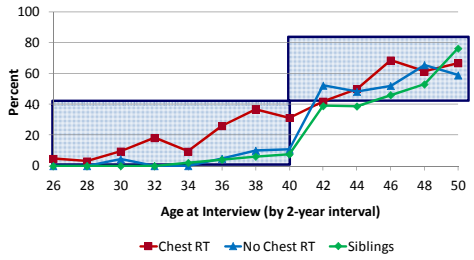
International Harmonization of Guidelines

Proportion of women with at least ONE screening mammogram within the preceding TWO years
Childhood Cancer Survivor Study

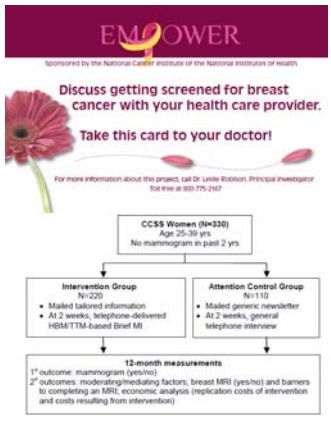


Oeffinger KC, et al. JAMA , 2009

Proportion of women with at least TWO screening mammogram within the preceding FOUR years
Childhood Cancer Survivor Study



Oeffinger KC, et al. JAMA , 2009



R01 CA134722

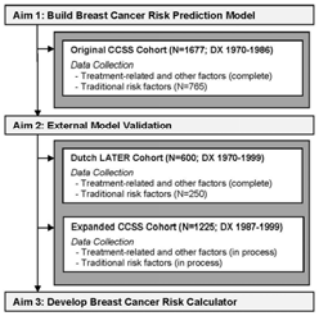
Research Team
Kevin Oeffinger
Greg Armstrong
Aaron McDonald
Jennifer Ford
Chaya Moskowitz
Al Marcus
Elena Elkin
Melissa Hudson
Tara Henderson
Lisa Diller

Co-Investigators
St. Jude / CCSS
University of Colorado
Dana-Farber
U Chicago

Predicting Risk

Chaya Moskowitz, PhD

Breast Cancer Risk Prediction Model



Research Team

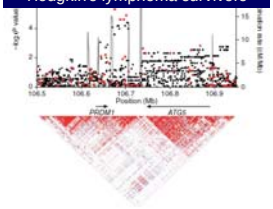
Chaya Moskowitz, PhD
Kevin Oeffinger, MD
Suzanne Wolden, MD
Greg Armstrong, MD
Monica Morrow, MD
Jonine Bernstein, PhD
Colin Begg, PhD
Flora van Leeuwen, PhD
Cecile Ronckers, PhD

Consultants

Mitchell Gail, MD, PhD
Peter Inskip, PhD
Lois Travis, MD, ScD
Michael Kattan, PhD
Robert Smith, PhD

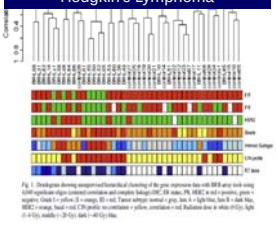
Gene-Radiation Interaction

Identified two variants at chromosome 6q21 associated with radiation-induced SMN in Hodgkin's lymphoma survivors

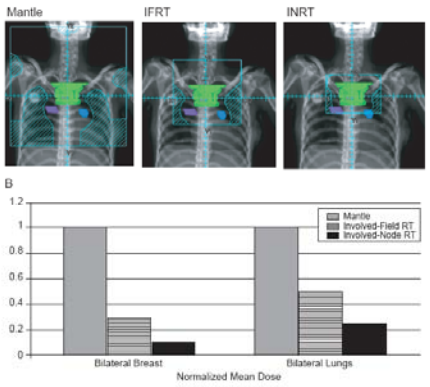


Best T, et al. Nature Med, 2011

Identified a genetic profile for breast cancer following Hodgkin's Lymphoma

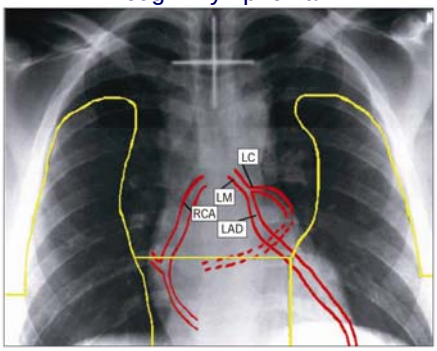


Broeks A, et al. Int J Rad Onc Biol Phys, 2010



Hodgson DC, et al. Semin Radiat Oncol 2007

24 Gy Irradiation to 11 year-old with Hodgkin lymphoma

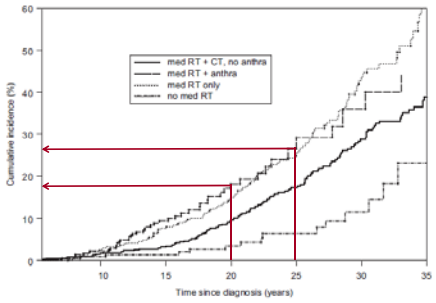


Courtesy of Constine LS.

Mantle/Mediastinal RT

- 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 CVD in 1474 survivors of Hodgkin lymphoma diagnosed prior to age 41 (1965-1995)*



*Death from any cause as competing risk

Aleman BM, et al. Blood 2007

NATIONAL CHOLESTEROL EDUCATION PROGRAM
Third Report of the Expert Panel on
Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

The risk assessment tool below uses recent data from the Framingham Heart Study to estimate 10-year risk for "hard" coronary heart disease outcomes (myocardial infarction and coronary death). This tool is designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes. Use the calculator below to estimate 10-year risk.

Age:	____ years
Gender:	○ Female ○ Male
Total Cholesterol:	____ mg/dL
HDL Cholesterol:	____ mg/dL
Smoker:	○ No ○ Yes
Systolic Blood Pressure:	____ mm/Hg
Currently on any medication to treat high blood pressure.	○ No ○ Yes

Calculate 10-Year Risk

40-year-old female Hodgkin lymphoma survivor

20 yrs from treatment with 30 Gy mediastinal RT
+ non-anthracycline chemotherapy

Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

The risk assessment tool below uses recent data from the Framingham Heart Study to estimate 10-year risk for "hard" coronary heart disease outcomes (myocardial infarction and coronary death). This tool is designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes. Use the calculator below to estimate 10-year risk.

Age:	40 years
Gender:	◉ Female ○ Male
Total Cholesterol:	232 mg/dL
HDL Cholesterol:	38 mg/dL
Smoker:	○ No ○ Yes
Systolic Blood Pressure:	105 mm/Hg
Currently on any medication to treat high blood pressure.	◉ No ○ Yes

Calculate 10-Year Risk

40-year-old female Hodgkin lymphoma survivor
20 yrs from treatment with 30 Gy mediastinal RT
+ non-anthracycline chemotherapy

NATIONAL CHOLESTEROL EDUCATION PROGRAM
Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Risk score results:

Age:	40
Gender:	female
Total Cholesterol:	232 mg/dL
HDL Cholesterol:	38 mg/dL
Smoker:	No
Systolic Blood Pressure:	105 mm/Hg
On medication for HBP:	No
Risk Score*	Less than 1%

10-15% 10-year risk

* The risk score shown was derived on the basis of an equation. Other NCEP materials, such as ATP III print products, use a point-based system to calculate a risk score that approximates the equation-based one.

To interpret the risk score and for specific information about CHD risk assessment as part of detection, evaluation, and treatment of high blood cholesterol, see ATP III Executive Summary and ATP III At-a-Glance.

NATIONAL CHOLESTEROL EDUCATION PROGRAM
Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

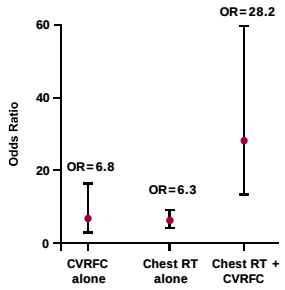
Risk score results:

Age:	40
Gender:	male
Total Cholesterol:	232 mg/dL
HDL Cholesterol:	38 mg/dL
Smoker:	No
Systolic Blood Pressure:	125 mm/Hg
On medication for HBP:	No
Risk Score*	3%

* The risk score shown was derived on the basis of an equation. Other NCEP materials, such as ATP III print products, use a point-based system to calculate a risk score that approximates the equation-based one.

To interpret the risk score and for specific information about CHD risk assessment as part of detection, evaluation, and treatment of high blood cholesterol, see ATP III Executive Summary and ATP III At-a-Glance.

Risk of Coronary Artery Disease
Interaction between Chest RT and CVD Risk Factors
Childhood Cancer Survivor Study



Armstrong G, et al. ASCO 2011

CAD post Chest Radiation

- Risk is modified by traditional risk factors
  - Tobacco avoidance/cessation
  - Evaluation for HTN and insulin resistance
  - Aggressive management of dyslipidemia with LDL target < 100
  - ASA 81 mg/day
  - Physical activity, low fat diet
- Detection of pre-obstructive disease?

Screening for CAD in HL survivors

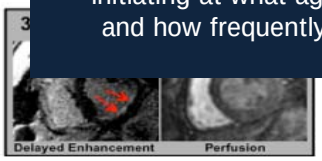
- Stress echo or radionucleotide perfusion
  - 294 asymptomatic HL survivors[1]
  - 21% with abnormal testing
  - False negative rates:
    - 41% - stress echo
    - 35% - nuclear scintigraphy
    - 62% - stress EKG
- CT coronary angiogram[2]
  - Role? Radiation exposure?

[1]Heidenreich PA, et al. J Clin Oncol, 2007
[2]Rademaker J, et al. Am J Roentgenol, 2008
and Kupeli S, et al. J Clin Oncol, 2010

Novel Tools to Screen for CAD in HL

- Calciu
  - Risk
- CMR ti onal cardiac

Many questions remain:
who to screen
with what test
initiating at what age
and how frequently



Future Directions

- Risk estimates are established; being refined as population ages
- High risk groups (partially) identified
- Early work showing genetic predictors and potential pathways in small studies
- No studies with ample power to investigate the interaction of treatment, genetic factors, lifestyle behaviors, and comorbid conditions
- Era of large collaborations

Future Directions (2)

- Study of harms / benefits of surveillance with limitations of small samples
- Development of risk prediction models
- Use of models in assessing / determining surveillance strategies
- Testing of patient or clinician education aids and knowledge translation/transfer incorporating risk prediction

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Charles Sklar, MD
Talya Salz, PhD
Elena Elkin, PhD
Suzanne Wolden, MD
Elizabeth Morris, MD
Joanne Chou, MPH
Nidha Mubdi, MPH

CCSS Investigators
Greg Armstrong, MD
Lisa Diller, MD
Melissa Hudson, MD
Tara Henderson, MD
Wendy Leisenring, PhD
Leslie Robison, PhD

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