

Long-Term and Late Effects Following AYA Cancer

Addressing the Needs of Adolescent and Young Adults with Cancer
IOM / NCPF Workshop
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Memorial Sloan-Kettering
Cancer Center

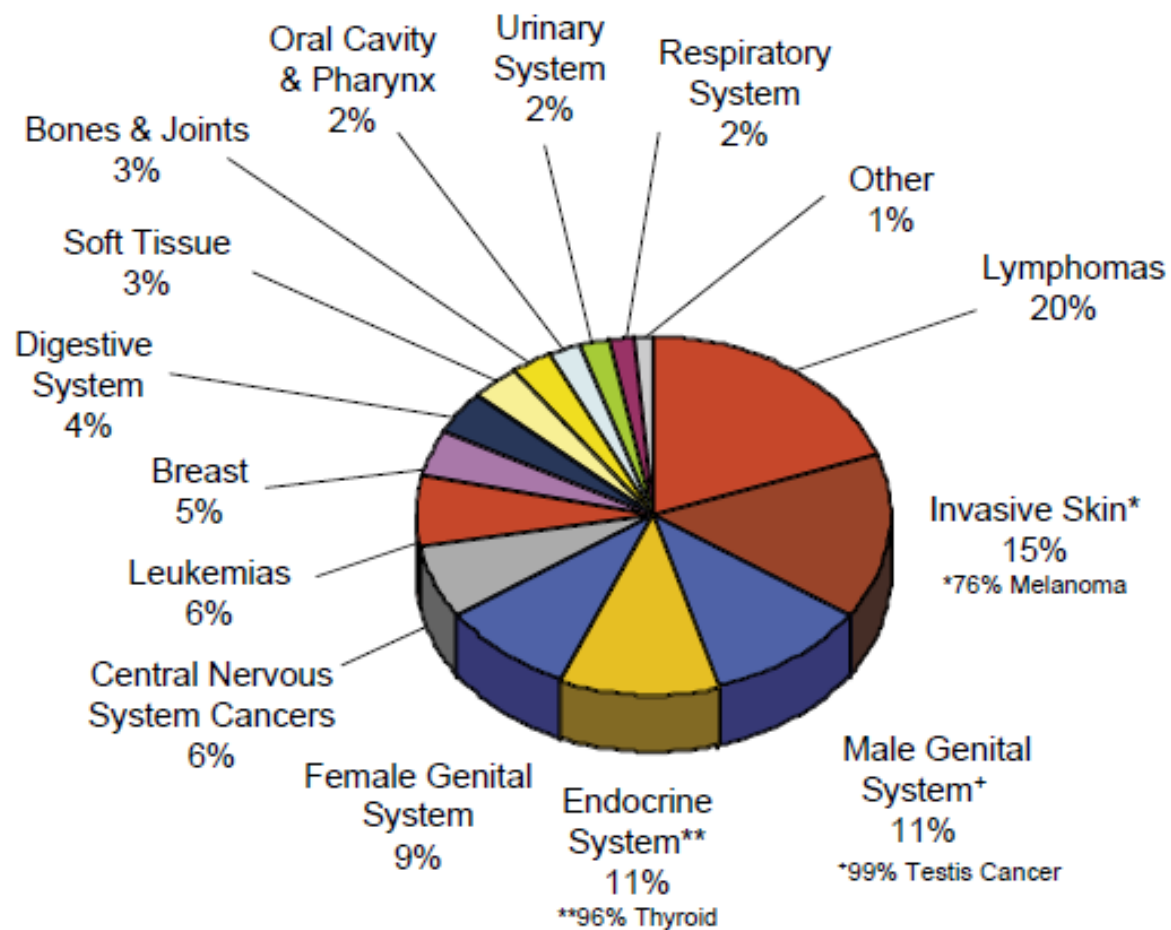
Terminology

- Long-term and late effects
- Excess risk: relative, absolute, attributable
- Are all comorbidities = late effects?
- Chronic health conditions
 - Physical
 - Psychosocial



Late Effects Following AYA Cancer

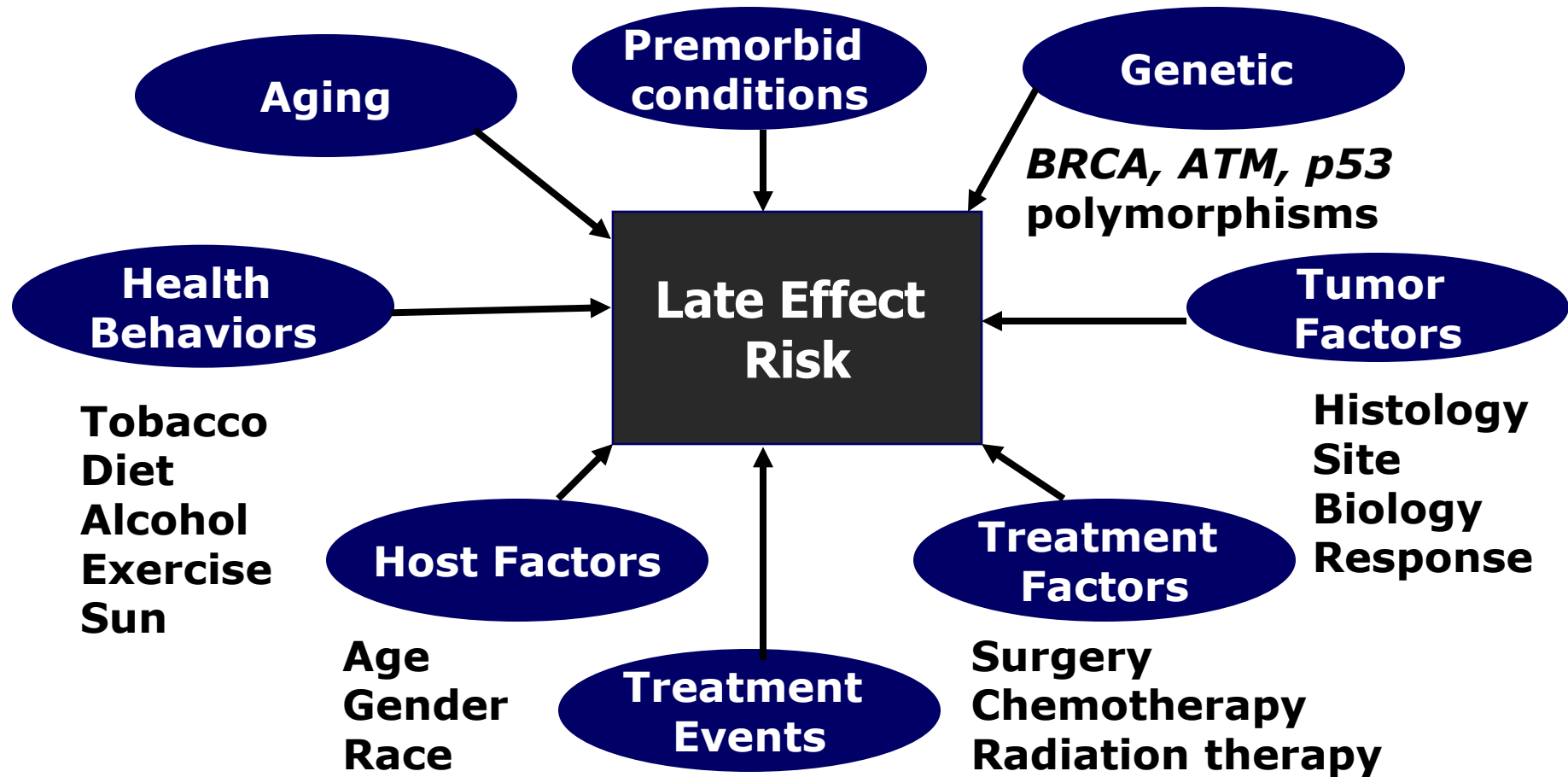
AYA Cancer and Late Effects



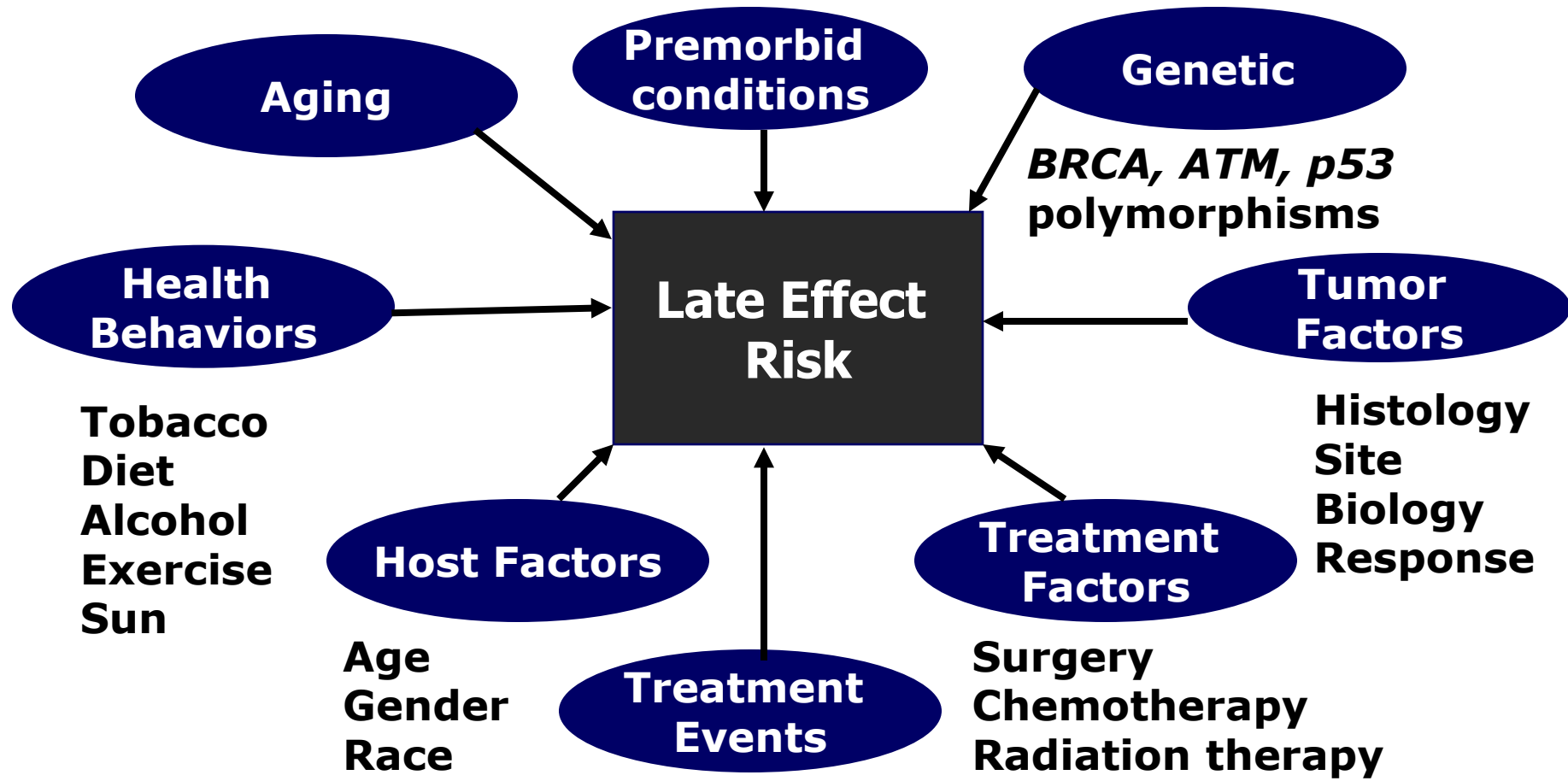
Bleyer A, et al. 2006



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"Accelerated Aging"

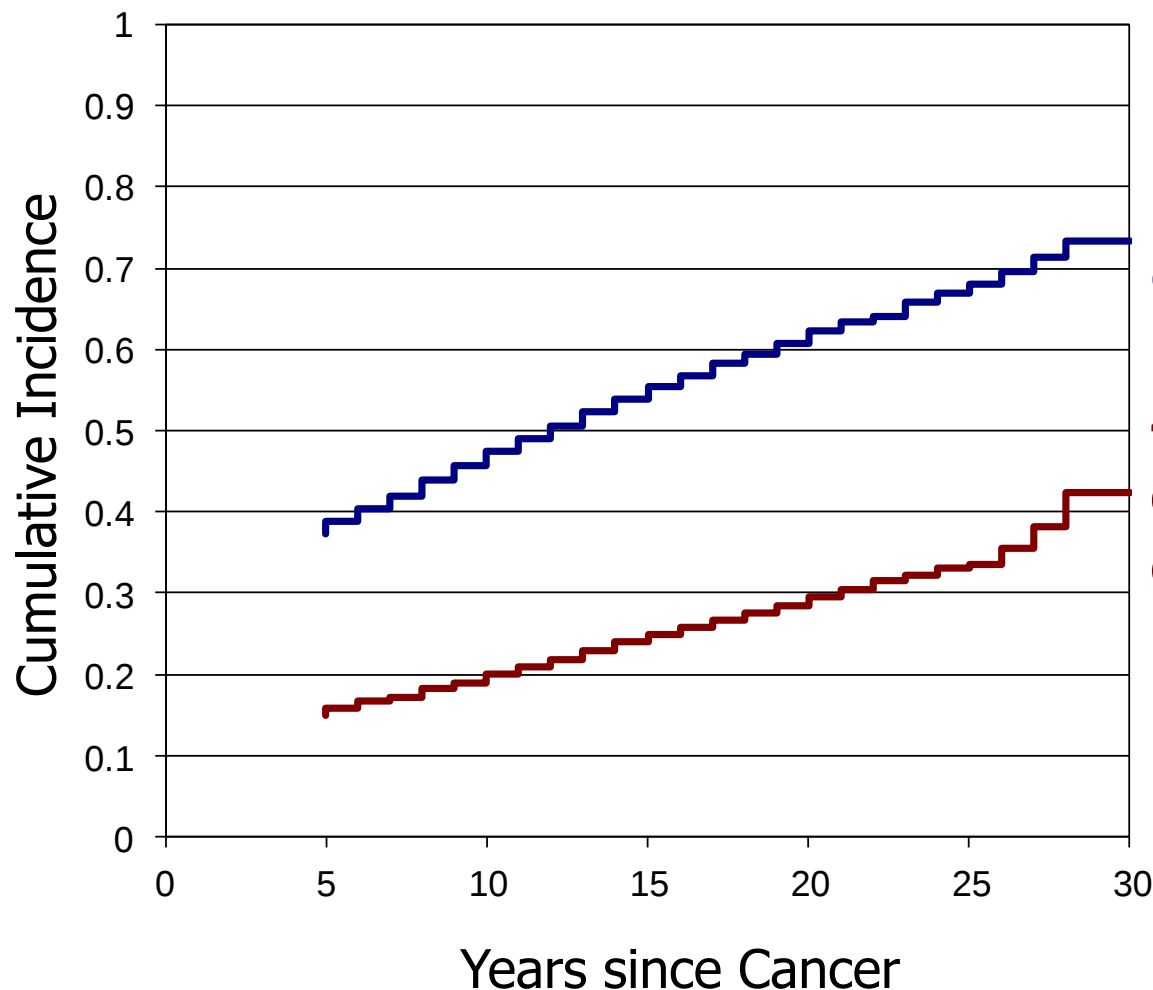


System	Exposures	Potential Late Effects
Cardiovascular	Radiation therapy Anthracyclines Cisplatin	Myocardial infarction or stroke Congestive heart failure Valvular disease Hypertension
Pulmonary	Radiation therapy Bleomycin Carmustine/Lomustine	Restrictive lung disease Pulmonary fibrosis Exercise intolerance
Renal/Urological	Radiation therapy Platinums Ifosfamide/Cyclophosphos	Renal insufficiency or failure Hemorrhagic cystitis
Endocrine	Radiation therapy Alkylating agents	Obesity Infertility and gonadal dysfunction Dyslipidemia Insulin resistance and diabetes
CNS	Radiation therapy Intrathecal chemotherapy	Learning disabilities 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

Late Effects Following AYA Cancer

Cumulative incidence of chronic physical health conditions

Childhood Cancer Survivor Study



73.4% with at least one chronic condition

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

Clinical Ascertainment of Health Outcomes Among Adults Treated for Childhood Cancer

Melissa M. Hudson

Kirsten K. Ness,

James G. Gurney

Daniel A. Mulrooney

Wassim Chemaitell

Kevin R. Krull,

Daniel M. Green

Gregory T. Armstrong

Kerri A. Nottage

Kendra E. Jones

Charles A. Sklar, MD

Deo Kumar Srivastava, PhD

Leslie L. Robison, PhD

By age 45

95.5% with a chronic health condition
80.5% with a grade 3-4 condition

Main Outcomes and Measures Age-specific cumulative prevalence of adverse outcomes by organ system.

Results Using clinical criteria, the crude prevalence of adverse health outcomes was highest for pulmonary (abnormal pulmonary function, 65.2% [95% CI, 60.4%-69.8%]).

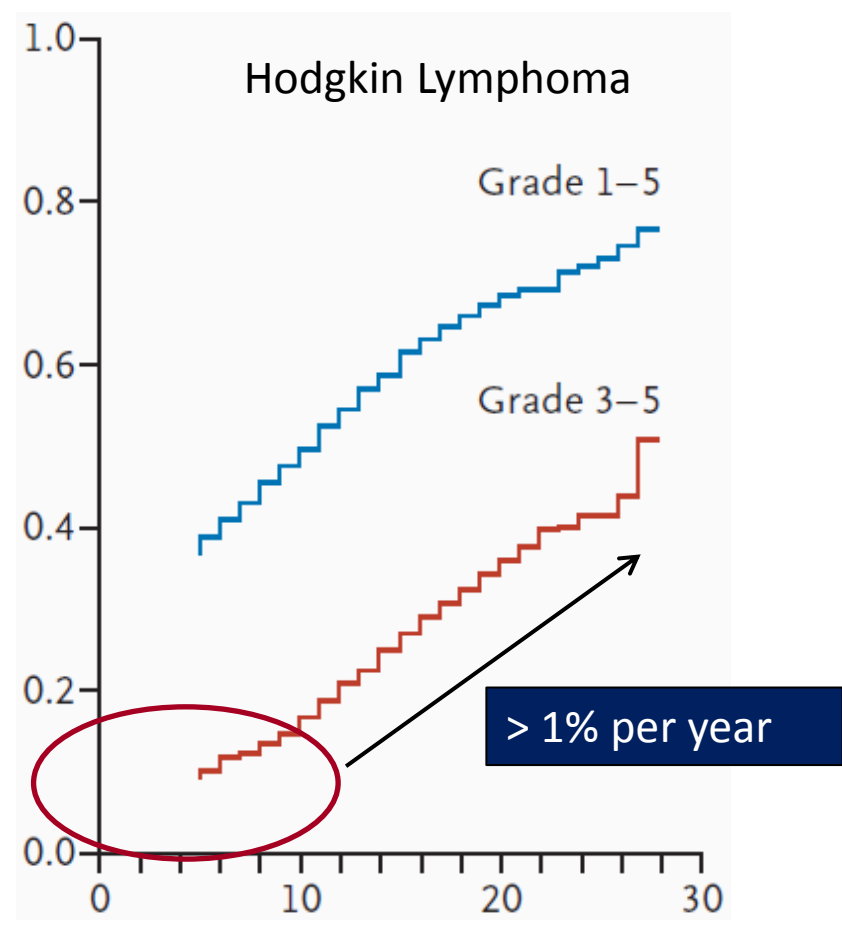
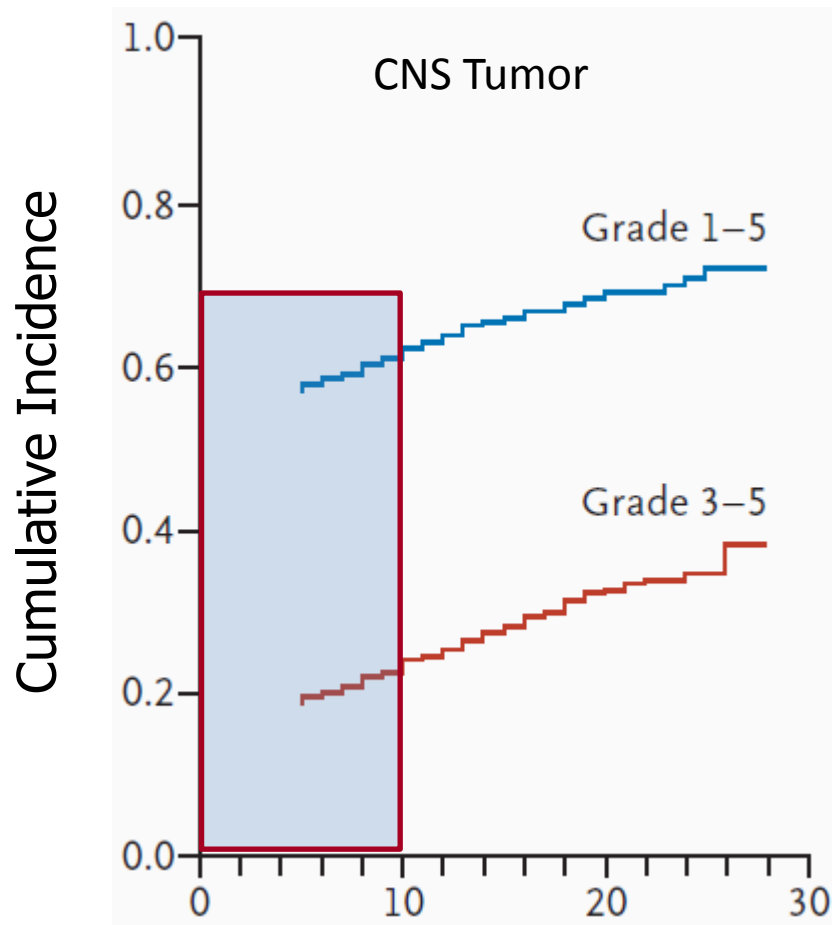
treatment-
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d the pro-
adult survi-

ascertained
median age,
diagnosis,
October

Late Effects Following AYA Cancer

Cumulative incidence of chronic physical health conditions



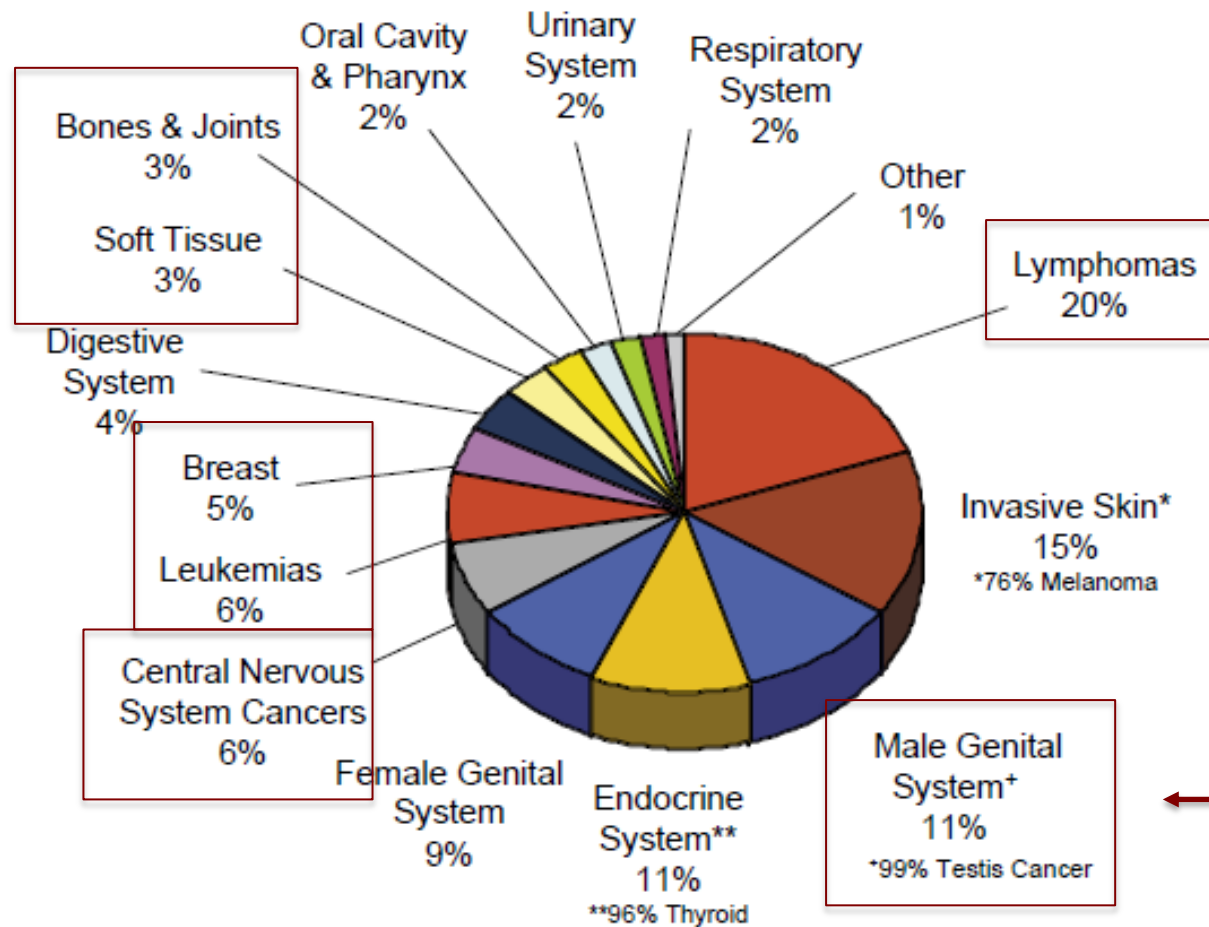
Years since Cancer

Examples in Survivors of AYA Cancer

- Cardiovascular disease and metabolic syndrome in testicular cancer survivors
- Breast cancer in AYA Hodgkin lymphoma survivors treated with chest radiation
- Infertility and gonadal dysfunction in AYA cancer survivors
- AYA allogeneic stem cell transplant recipients and multiple morbidities

Late Effects Following AYA Cancer

Cardiovascular Disease

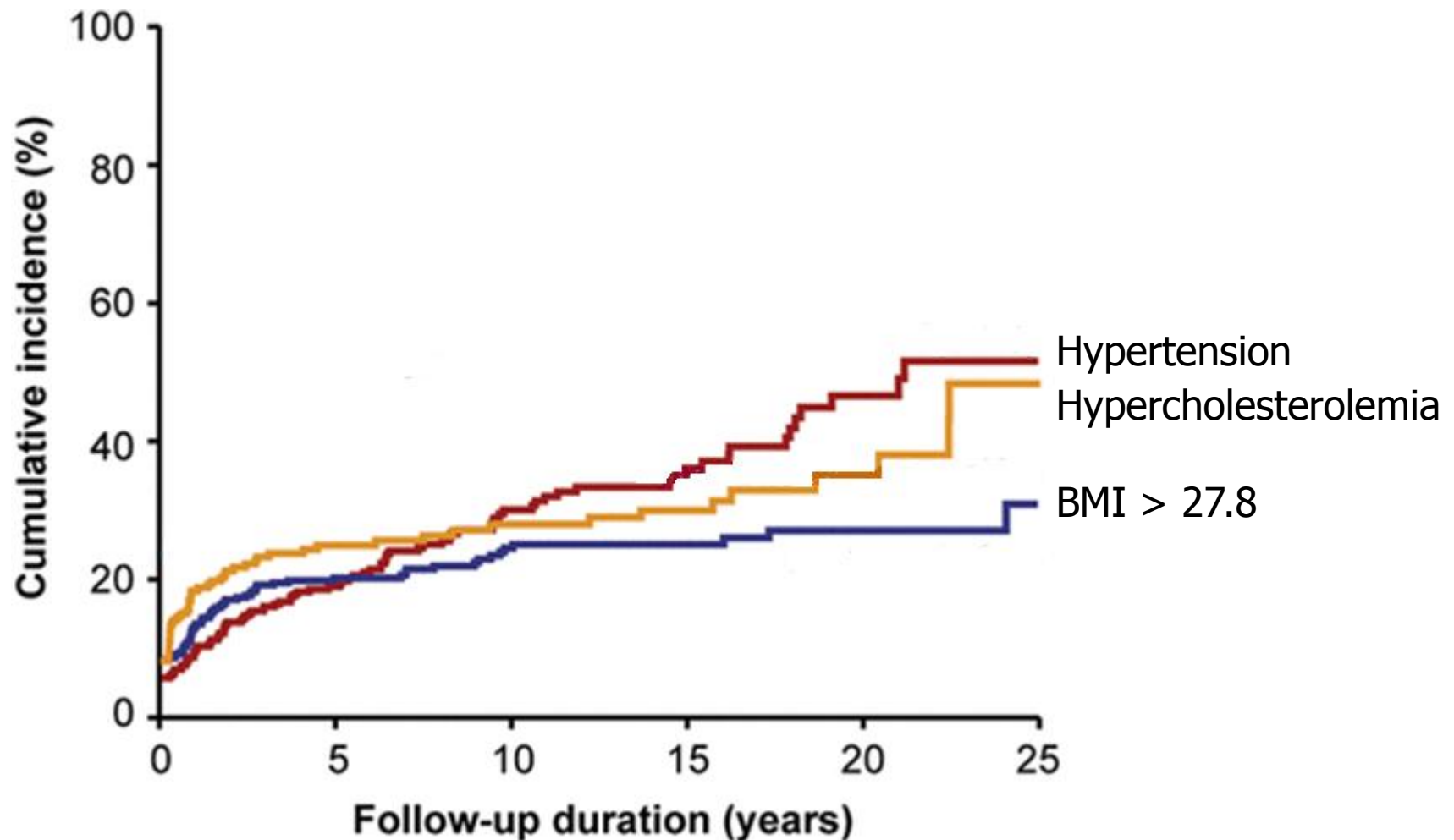


Cardiovascular Disease in Testicular Cancer Survivors

- Norway, 1962-1997 *Fossa et al. British J Cancer 2004*
 - Circulatory-deaths: **SMR = 1.2** (95% CI, 1.0-1.5)
 - No difference in SMR or AER after intro of cisplatin
- Netherlands, 1965-1995 *Van den Belt-Dusebout et al. J Clin Oncol 2007*
 - CVD in platinum w/o radiation: **HR = 1.7** (1.2-2.4)
 - Median survival post CVD = 4.7 yrs
- United Kingdom, 1982-1992 *Huddart RA et al. J Clin Oncol 2003*
 - CVD **RR = 2.6** (1.2-5.8) in chemo only vs surgery
- Norway, 1980-1994 *Haugnes HS et al. J Cancer Surviv 2008*
 - Cisplatin > 850 mg with **OR = 3.4** (1.3-8.7) compared with surgery only

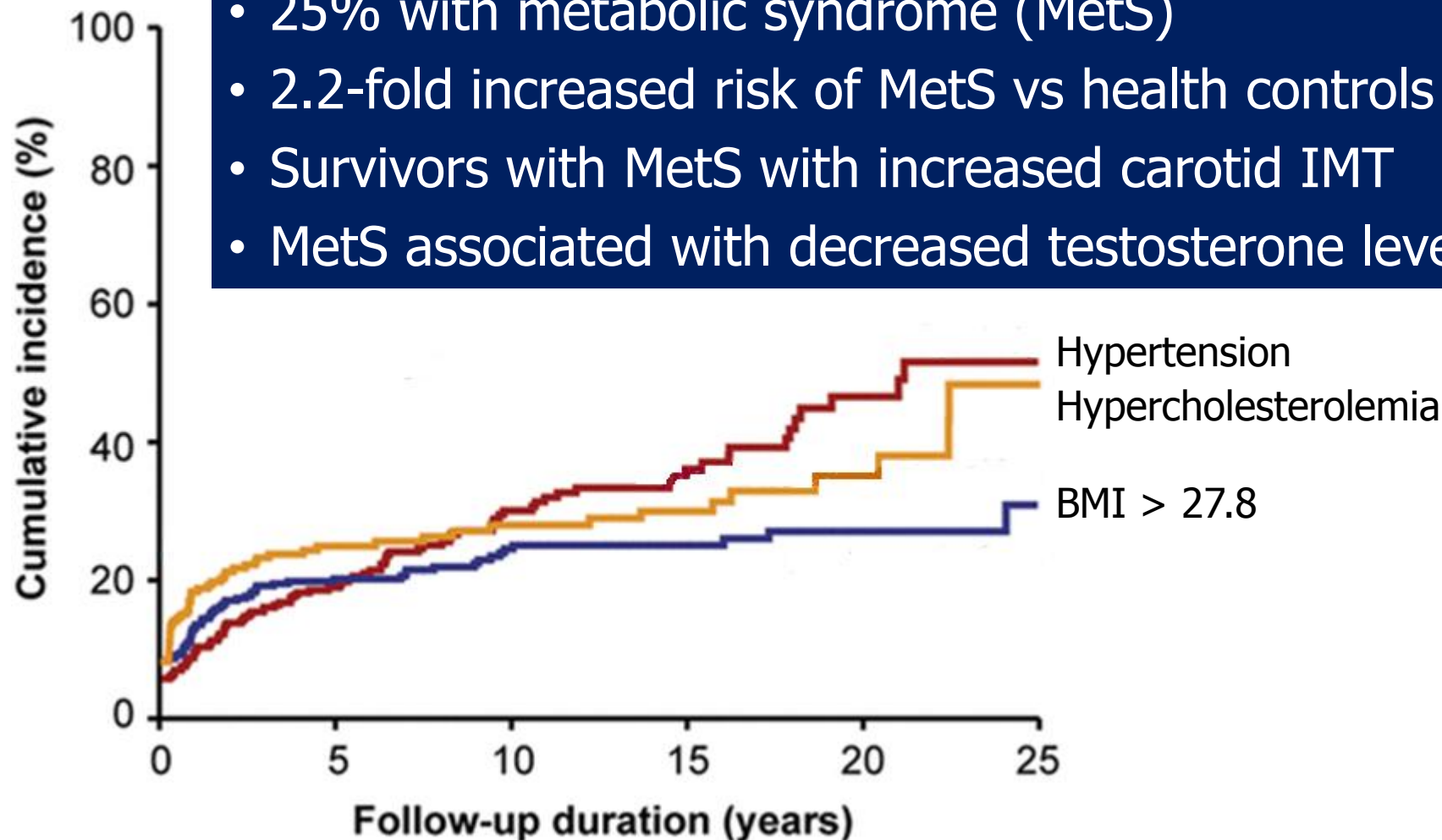
Late Effects Following AYA Cancer

Incidence of CVD Risk Factors Following Therapy



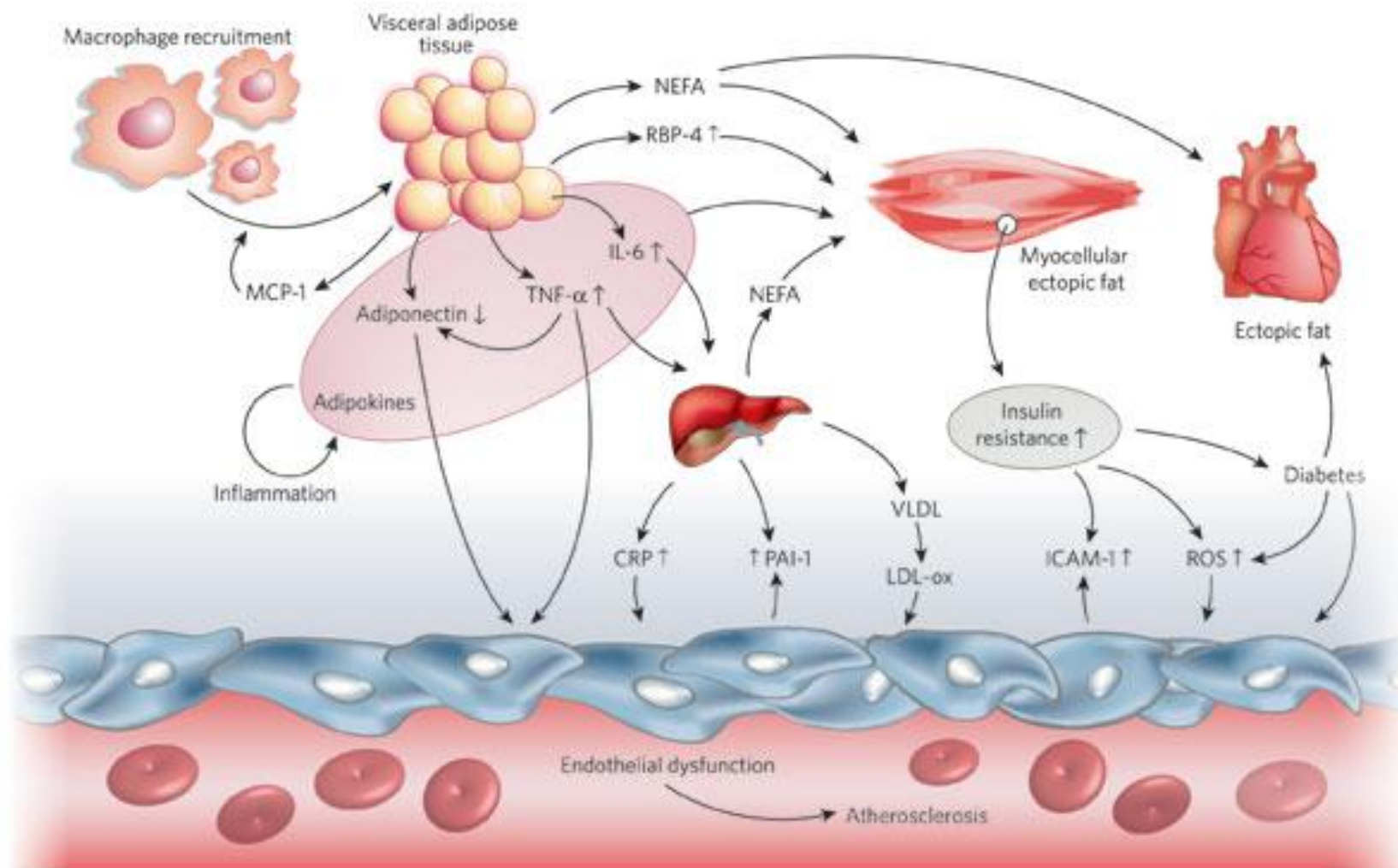
Incidence of CVD Risk Factors Following Therapy

- 25% with metabolic syndrome (MetS)
- 2.2-fold increased risk of MetS vs health controls
- Survivors with MetS with increased carotid IMT
- MetS associated with decreased testosterone level



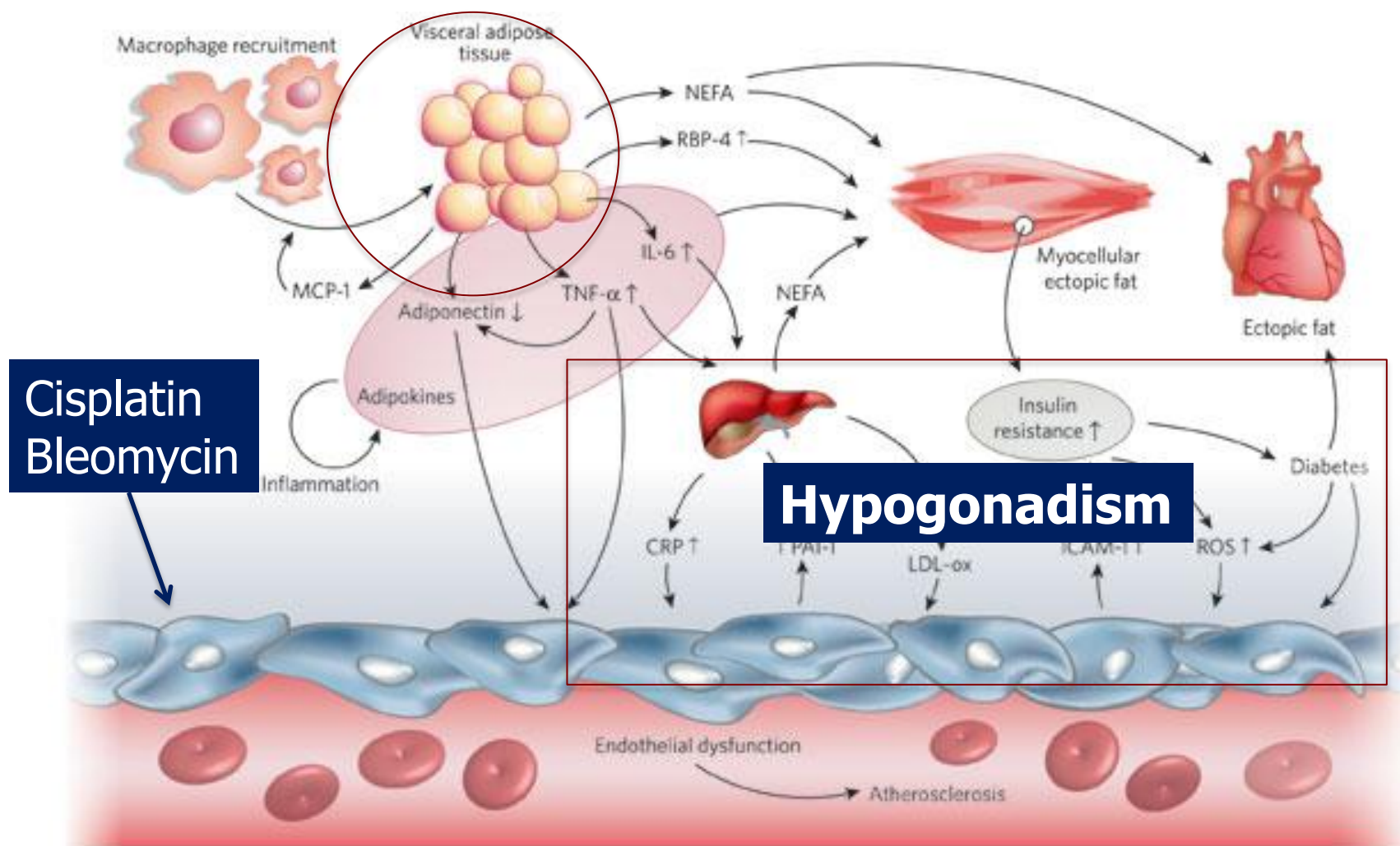
Late Effects Following AYA Cancer

Development of Cardiovascular Disease



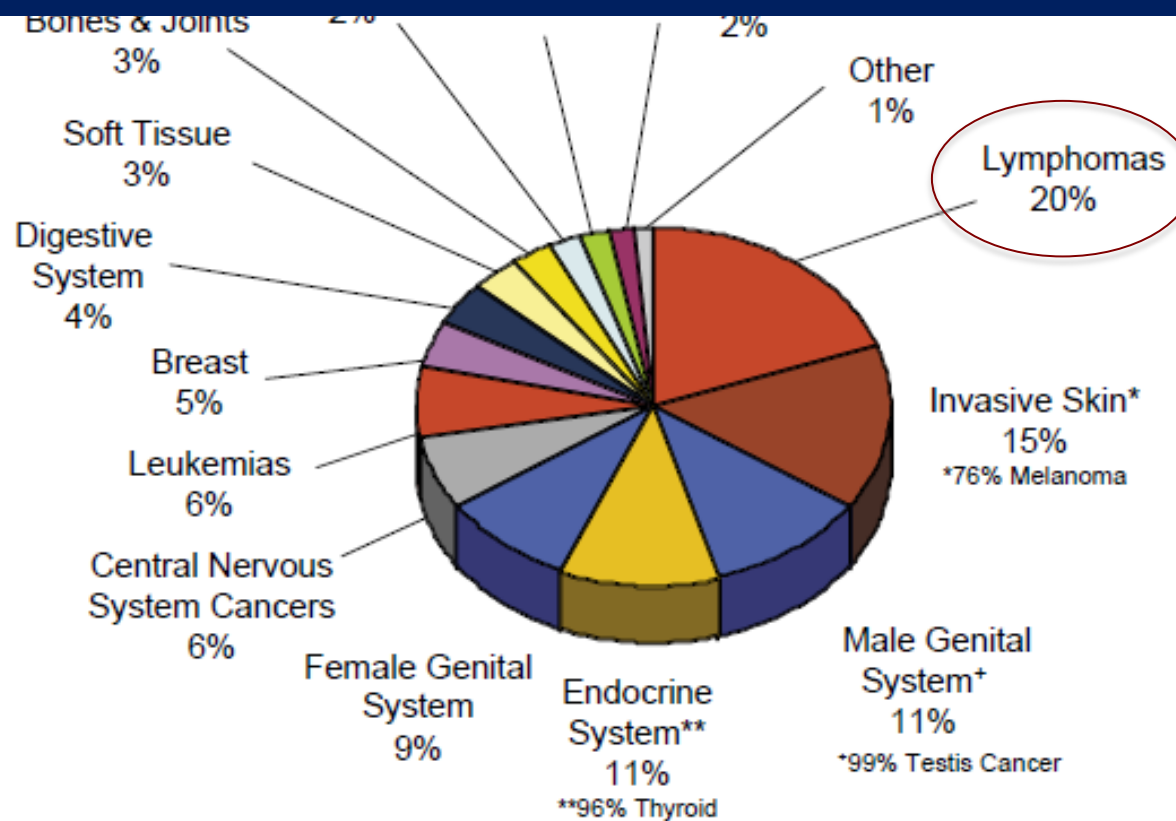
Late Effects Following AYA Cancer

Development of Cardiovascular Disease



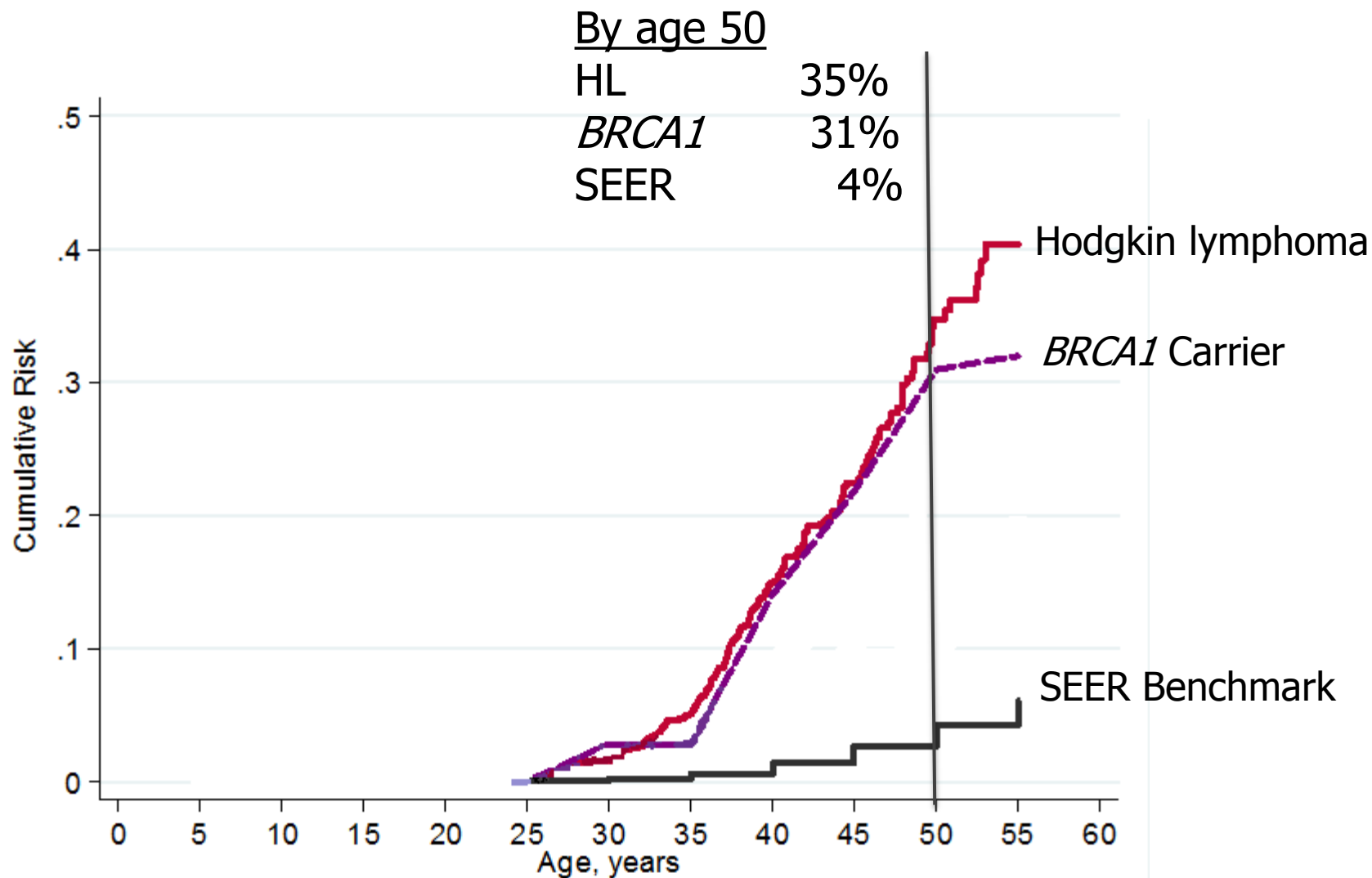
Second Primary Neoplasms

16% of all incident cancers are an SPN



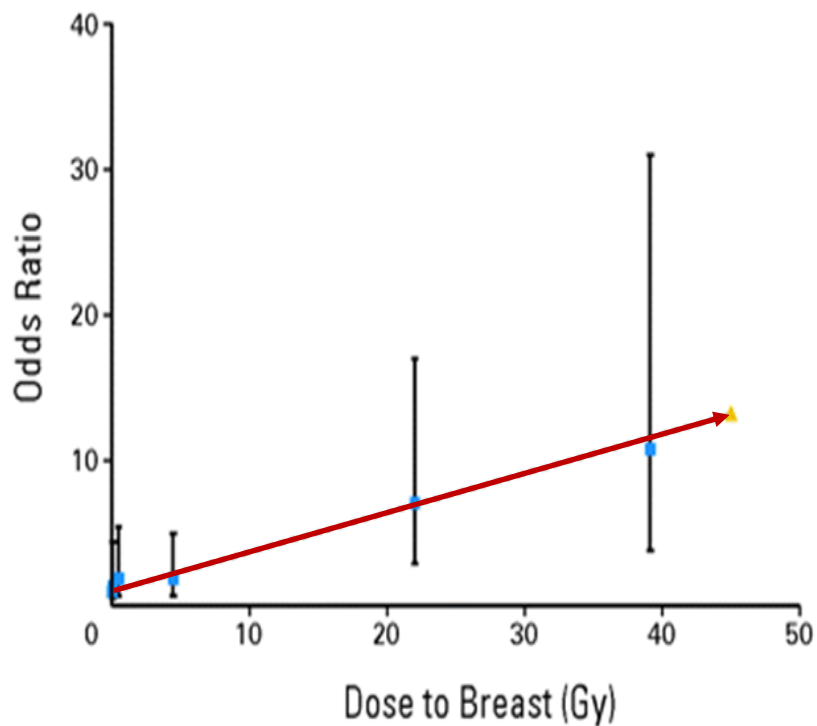
Late Effects Following AYA Cancer

Breast Cancer Following Chest Radiation

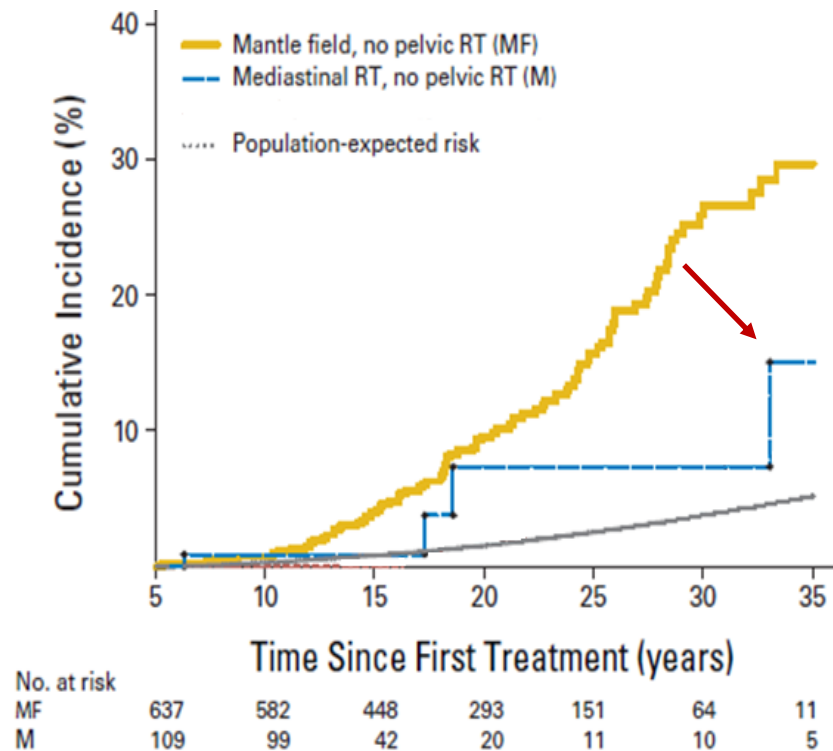


Late Effects Following AYA Cancer

Breast Cancer Risk, Dose and Volume



Inskip PD, et al. J Clin Oncol, 2009



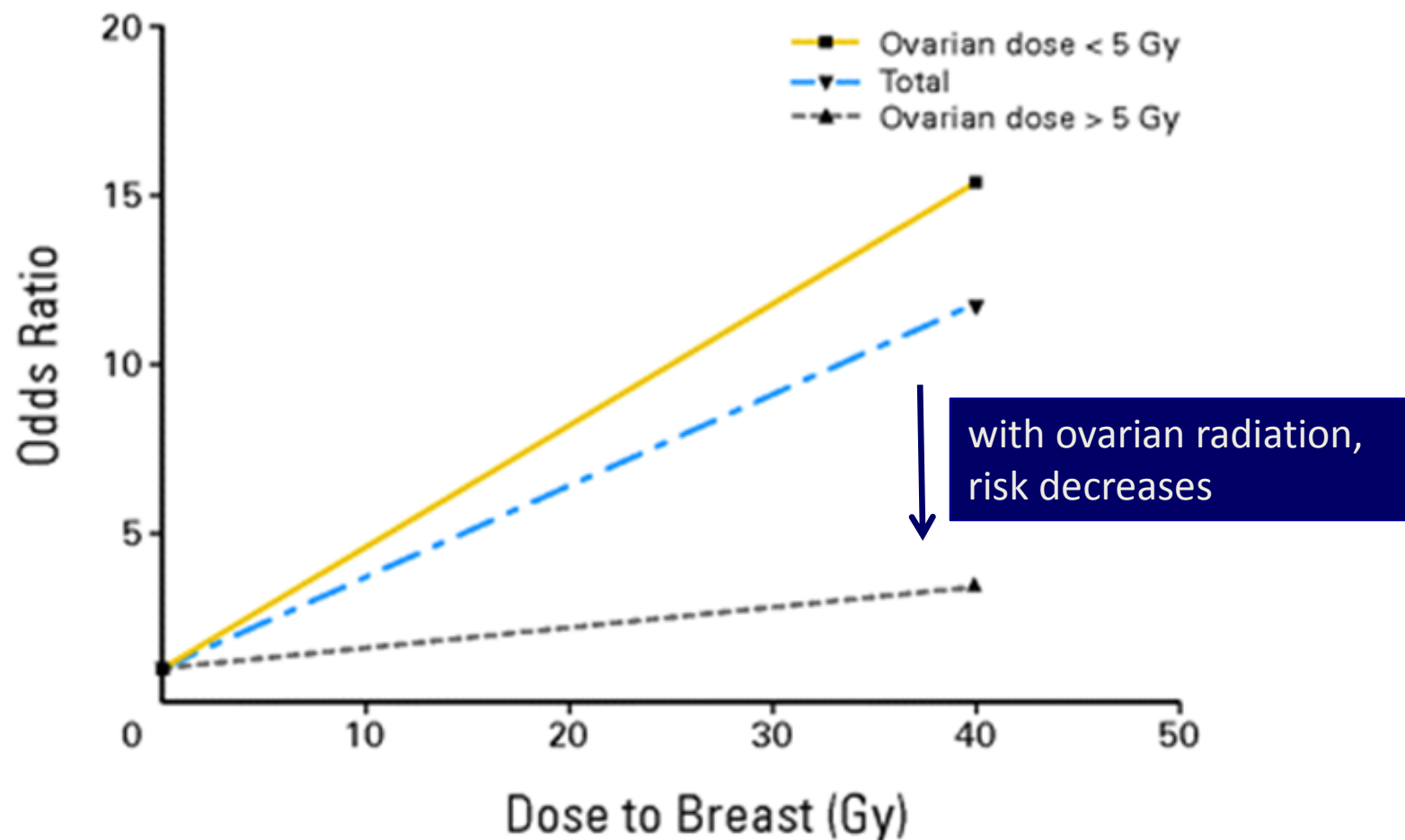
De Bruin ML, et al. J Clin Oncol, 2009



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Late Effects Following AYA Cancer

Breast Cancer Risk, Ovarian Radiation



Inskip PD, et al. J Clin Oncol, 2009



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32,591 HL patients in 16 population-based registries

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

Characteristics of Breast Cancer

- 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)



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

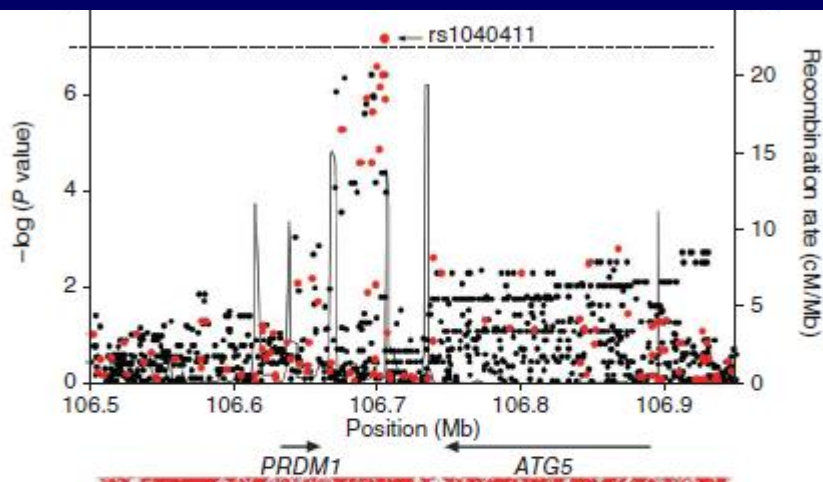
Tara O. Henderson, MD, MPH; Alison Amsterdam, MD; Smita Bhatia, MD, MPH; Melissa M. Hudson, MD; Anna T. Meadows, MD; Joseph P. Neglia, MD, MPH; Lisa R. Diller, MD; Louis S. Constine, MD; Robert A. Smith, PhD; Martin C. Mahoney, MD, PhD; Elizabeth A. Morris, MD; Leslie L. Montgomery, MD; Wendy Landier,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

Late Effects Following AYA Cancer

Radiation-Gene Interactions

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

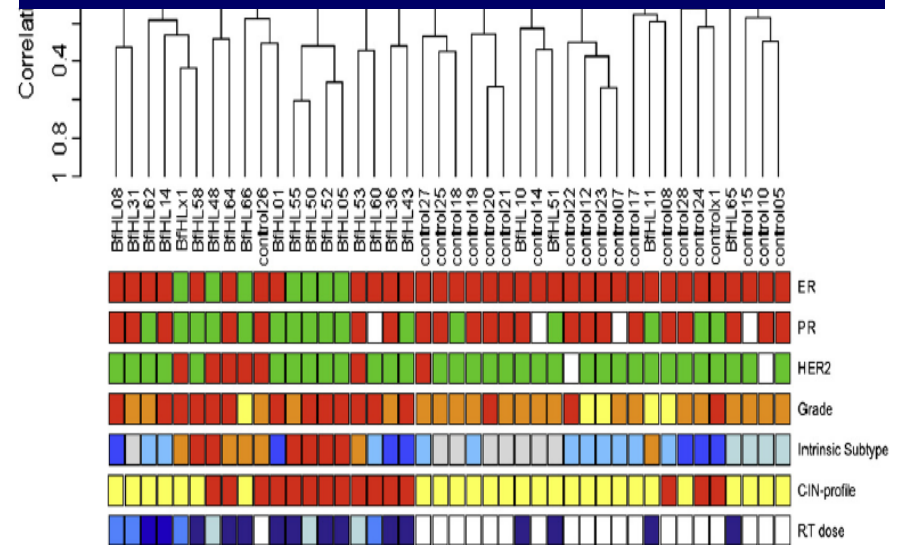


Fig. 1. Dendrogram showing unsupervised hierarchical clustering of the gene expression data with BRB array tools using 4,040 significant oligos (centered correlation and complete linkage) IHC; ER status, PR, HER2 in red = positive, green = negative. Grade I = yellow, II = orange, III = red. Tumor subtype: normal = gray, lum A = light blue, lum B = dark blue, HER2 = orange, basal = red. CIN profile: no correlation = yellow, correlation = red. Radiation dose in white (0 Gy), light (1-4 Gy), middle (~20 Gy), dark (~40 Gy) blue.

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

Breast Cancer Risk Prediction Model

Treatment-related factors

- RT dose/volume, chest
- RT dose fractionation
- RT, pelvis or abdomen
- Alkylating agent
- Age at exposure
- Interval from primary cancer diagnosis
- Primary cancer diagnosis

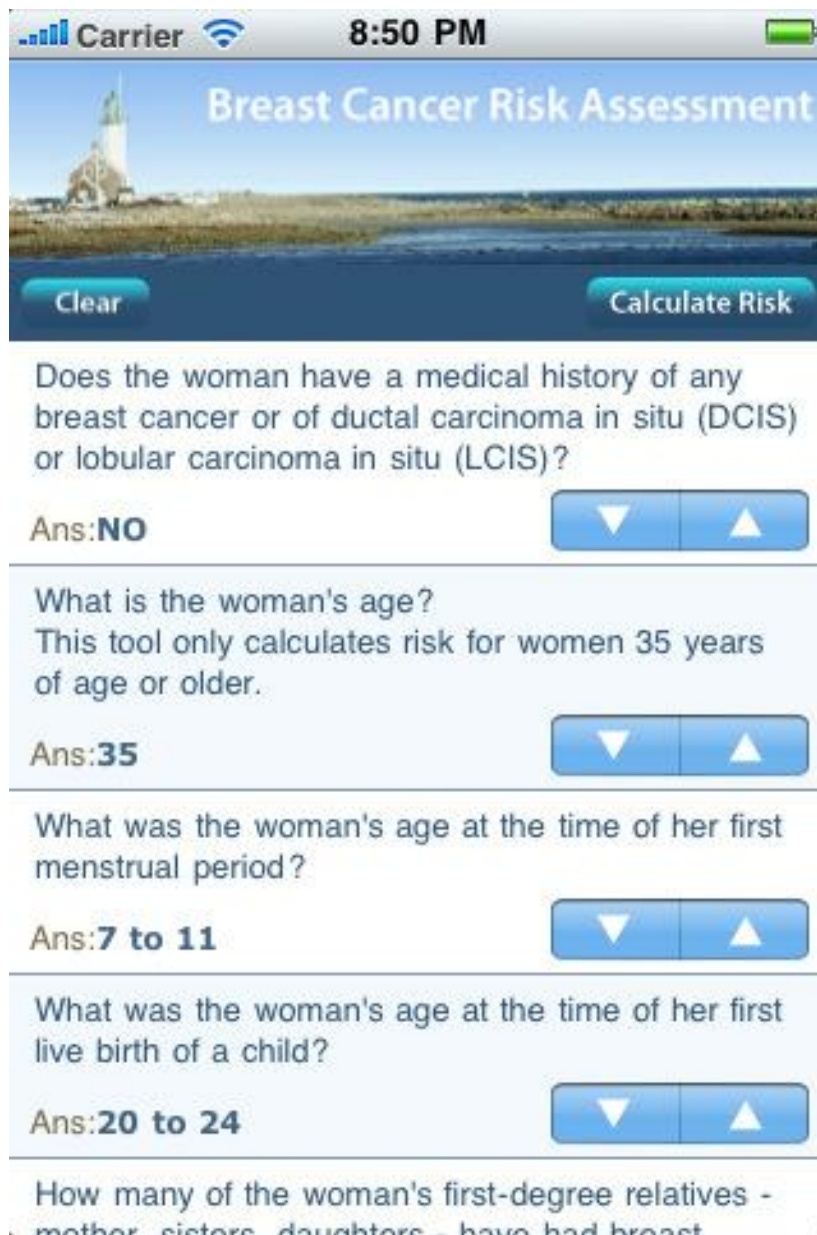
Gail model predictors

- Age
- Age at menarche
- Age at first live-birth
- # of first degree relatives with breast ca
- # previous breast bx
- Biopsy with atypical hyperplasia

Other potential risk factors

- Age at menopause
- Years of intact ovarian function after radiation
- Oral contraceptive/ HRT
- BMI at breast cancer diagnosis

Breast Cancer Risk Prediction Model



Carrier 8:50 PM

Breast Cancer Risk Assessment

Clear Calculate Risk

Does the woman have a medical history of any breast cancer or of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)?

Ans: **NO**

What is the woman's age?
This tool only calculates risk for women 35 years of age or older.

Ans: **35**

What was the woman's age at the time of her first menstrual period?

Ans: **7 to 11**

What was the woman's age at the time of her first live birth of a child?

Ans: **20 to 24**

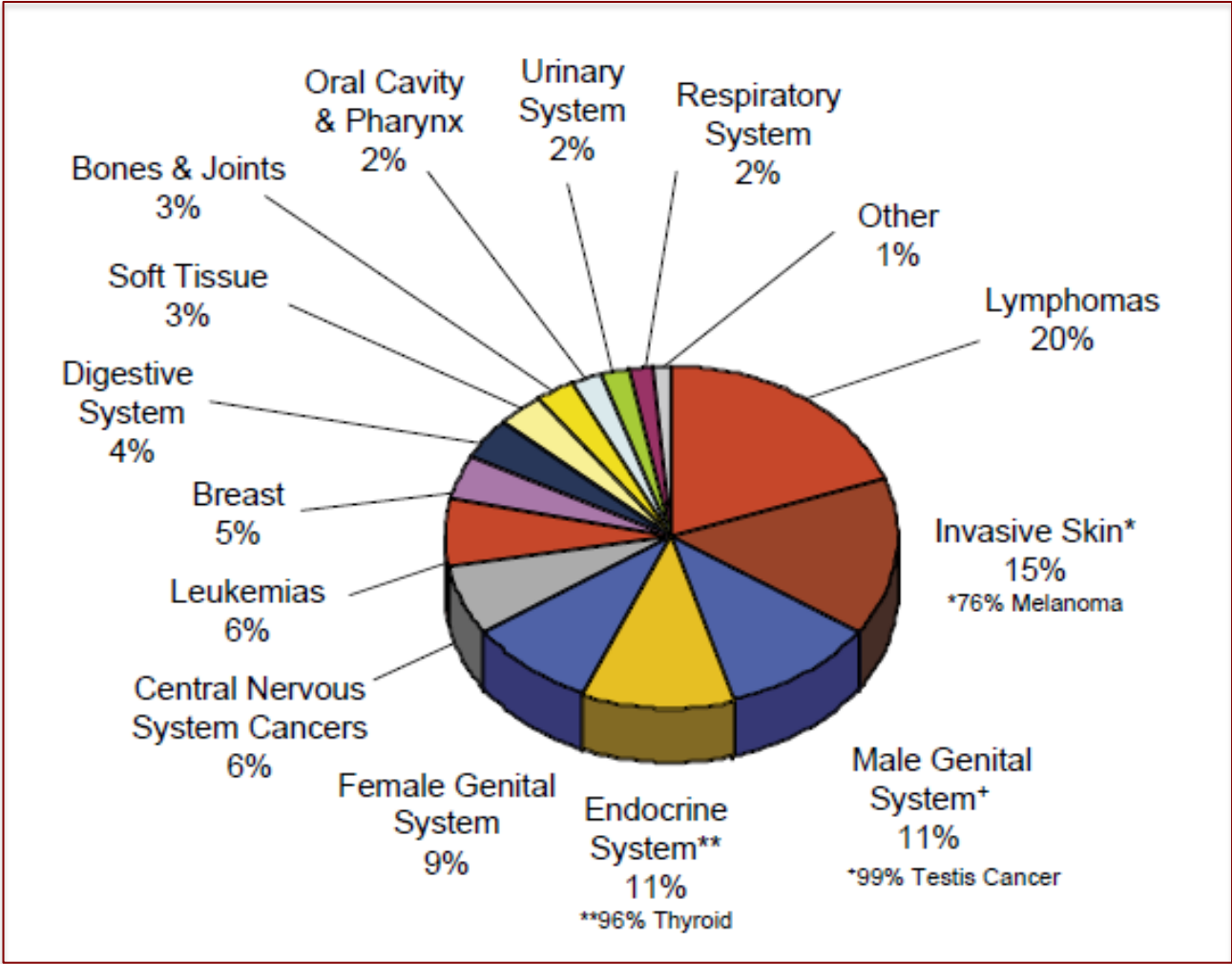
How many of the woman's first-degree relatives - mother, sisters, daughters - have had breast

R01CA136783

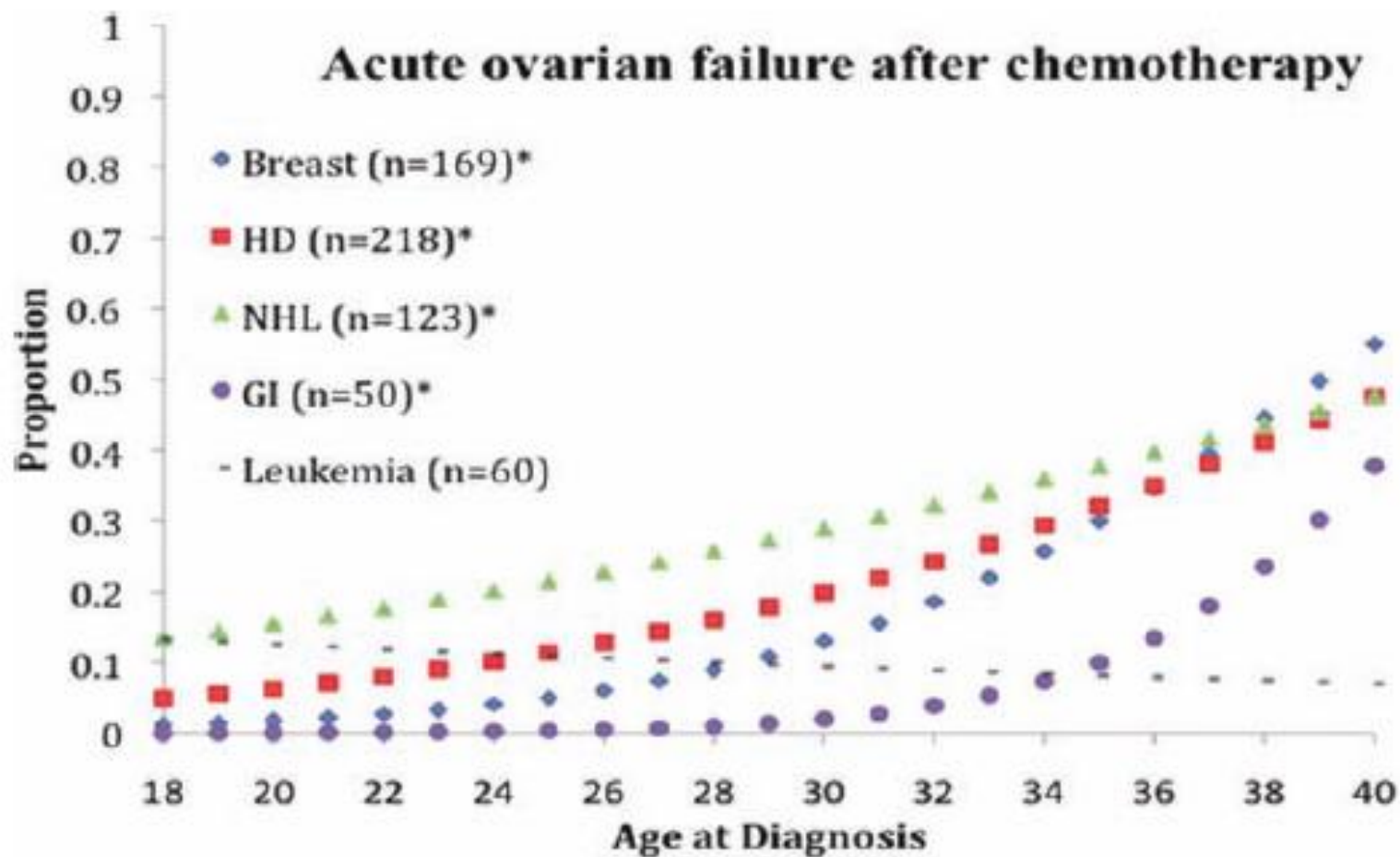
Chaya Moskowitz, PhD
Kevin Oeffinger, MD
Suzanne Wolden, MD
Greg Armstrong, MD
Tara Henderson, MD
Monica Morrow, MD
Jonine Bernstein, PhD
Colin Begg, PhD
Flora van Leeuwen, PhD
Cecile Ronckers, PhD
Helena van der Pal, MD



Infertility

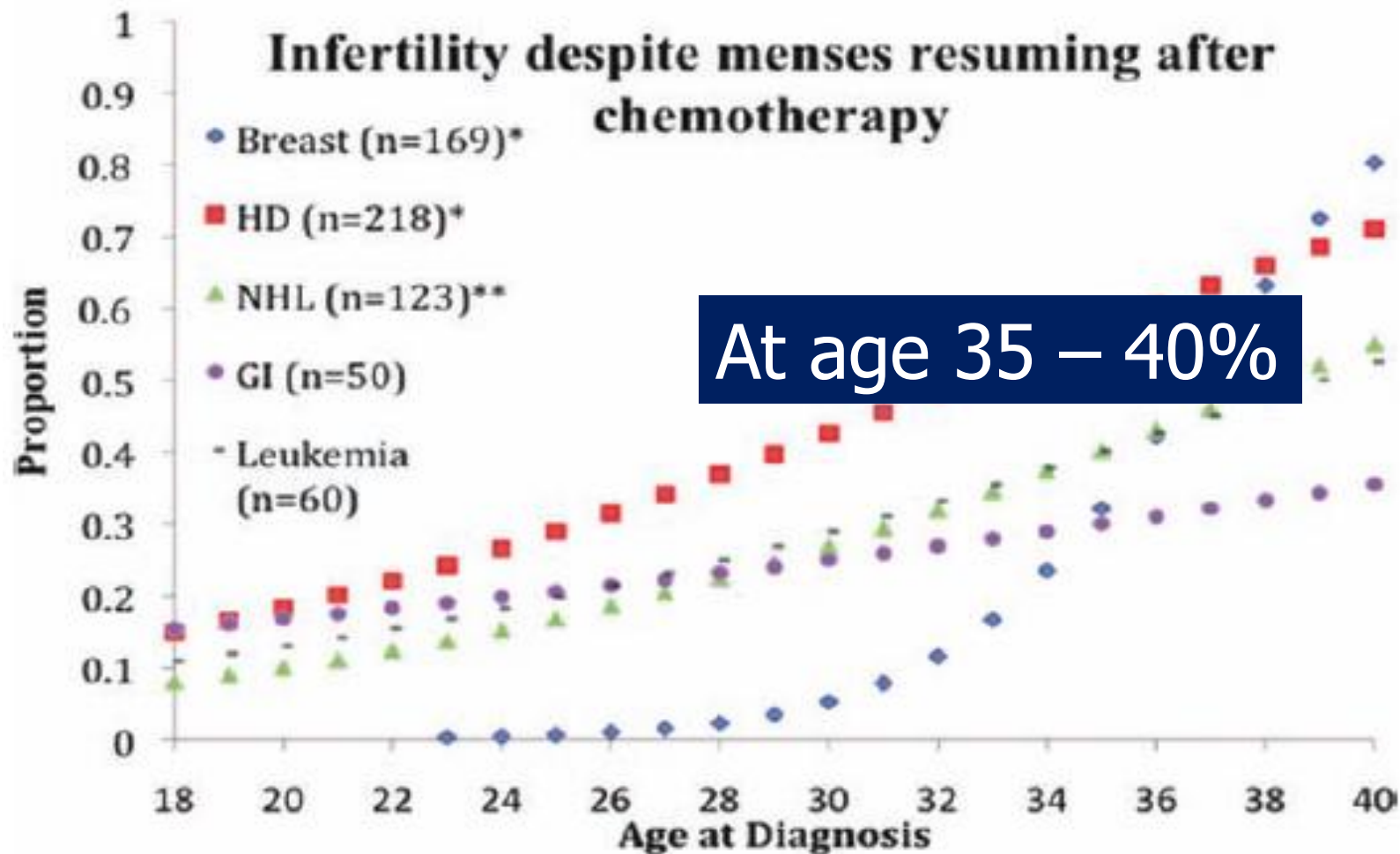


Acute Ovarian Failure in AYA Cancer Survivors



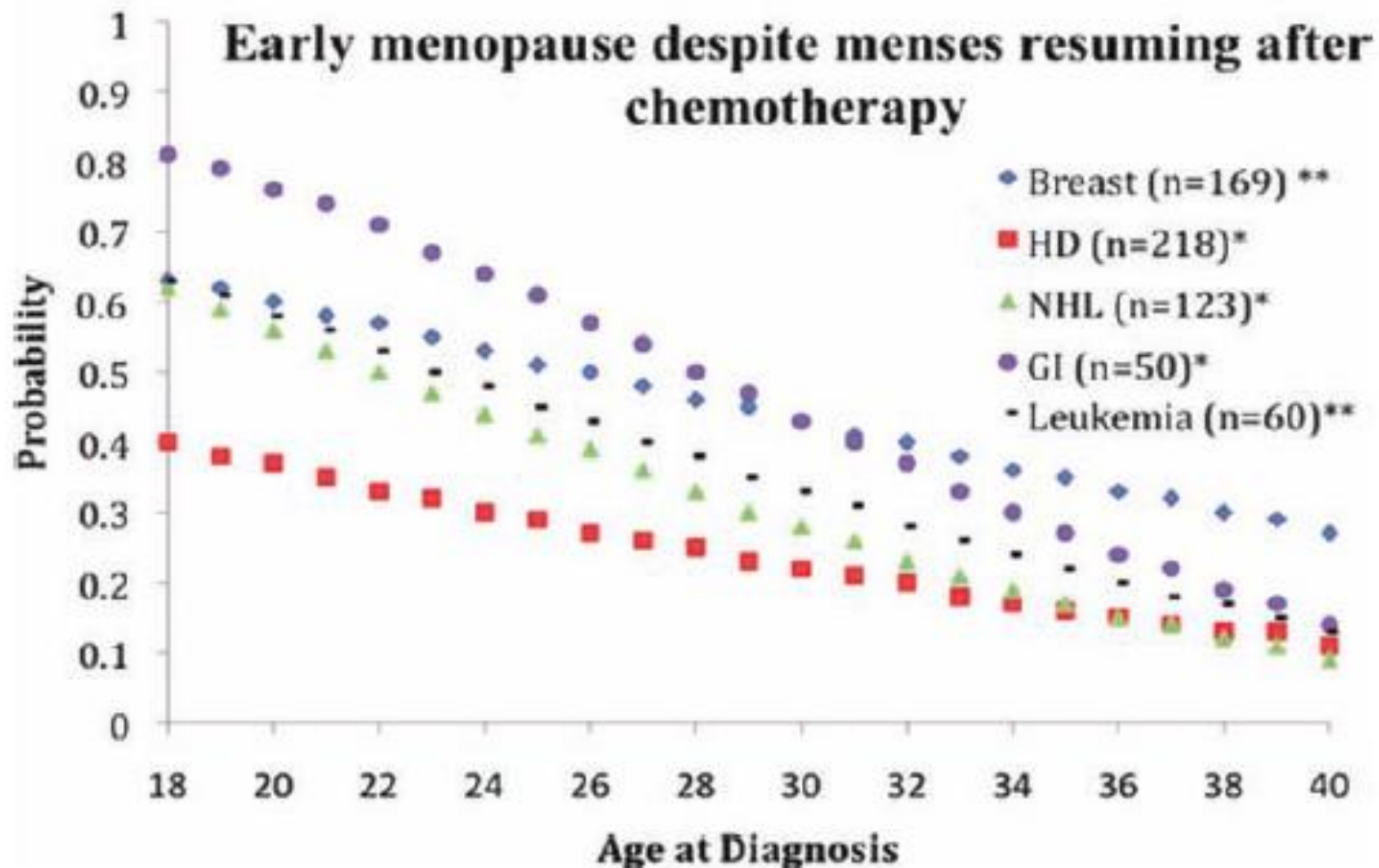
Late Effects Following AYA Cancer

Infertility in Female AYA Cancer Survivors



Late Effects Following AYA Cancer

Early Menopause in AYA Cancer Survivors



Factors Associated with Infertility

Females

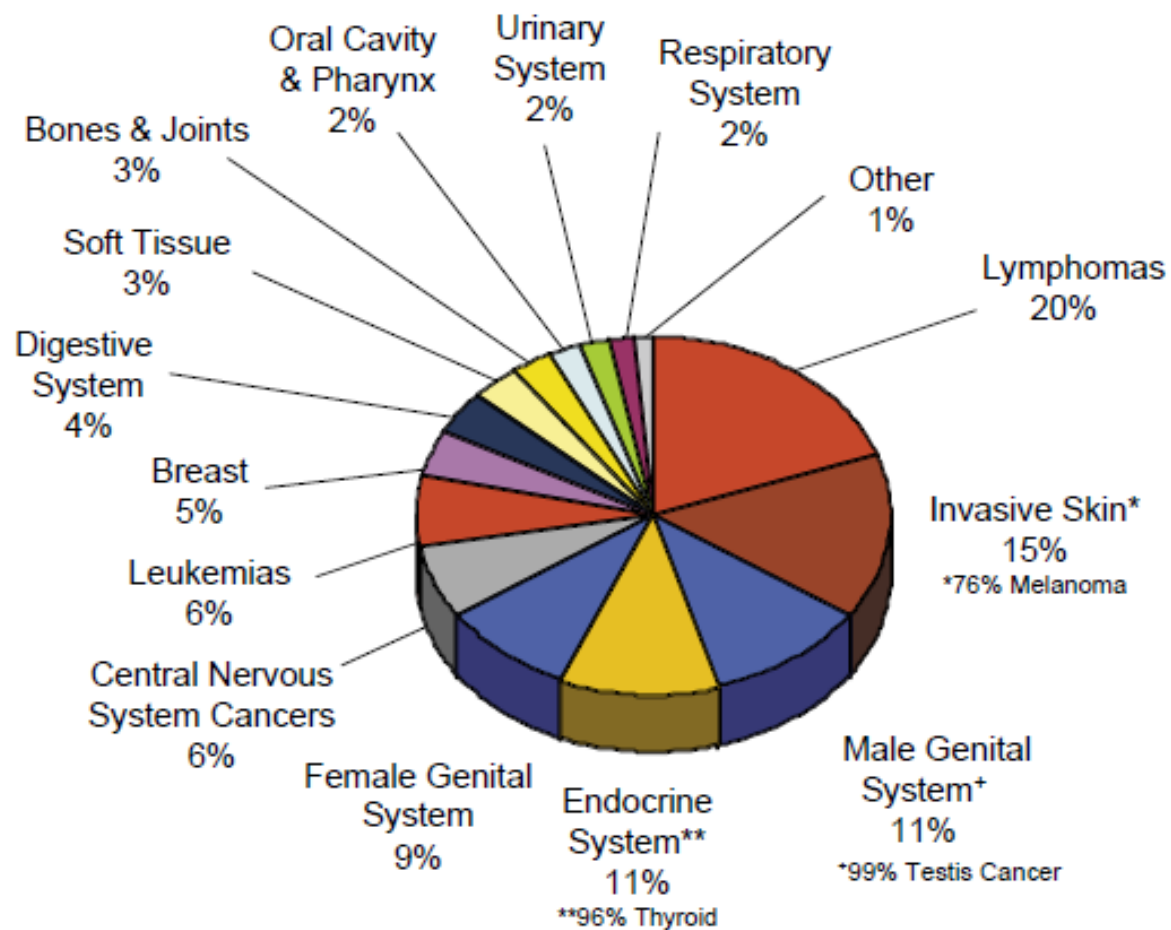
- Alkylating agents
- Radiation to the ovaries
- Stem cell transplant

Males

- Alkylating agents
- Radiation to the testes
- Stem cell transplant

Late Effects Following AYA Cancer

Multiple Chronic Conditions and AYA Cancer Survivors



Multiple Chronic Conditions post Allogeneic SCT

Prior therapy

Preconditioning
chemotherapy

TBI

GVHD

- Gonadal dysfunction
- SMN
- Endocrinopathies
- Osteoporosis
- Osteonecrosis
- Renal insufficiency
- Pulmonary complications
- Cataracts
- Gait and balance disturbances
- Hypertension
- Metabolic obesity (thin/fat)
- Insulin resistance / diabetes
- Dyslipidemia / fatty liver
- Coronary artery disease

Maximizing the Cure – Minimizing the Cost





Lorene (mom)

HL, Stage IIB
1975, Age 20
46 Gy Mantle
36 Gy Para-aortic

Thyroid CA, Age 51
2-v CABG, Age 53
Breast CA, Age 55
Multiple BCC
Asplenic
Diabetes
Fatty liver
Dyslipidemia
Restrictive lung dis
Musculoskeletal

Lauren

HL, Stage IIB
2002, Age 15
21 Gy IFRT
21 Gy Para-aortic
BEACOPP

MDS/AML, Age 15.5
Allo BMT
Bu/Meph/Flu

Ovarian failure
AVN, hips
Hypothyroidism
Insulin resistance
Dyslipidemia
Iron overload



Lorene (mom)

HL, Stage IIB
1975, Age 20
46 Gy Mantle
36 Gy Para-aortic

Lauren

HL, Stage IIIB
2002, Age 15
21 Gy IFRT
21 Gy Para-aortic
BEACOPP

The remains an urgency
to understand, predict,
prevent and manage
late effects
in AYA cancer survivors

Restrictive lung dis
Musculoskeletal

Dyslipidemia
Iron overload

Future Directions

- Better estimates across cancers and exposures
- Mechanisms
- Gene*Exposure*Lifestyles
- Risk prediction / risk stratification
- Interventions