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Transitioning Survivors of Childhood Cancer to Adult Endocrine Providers

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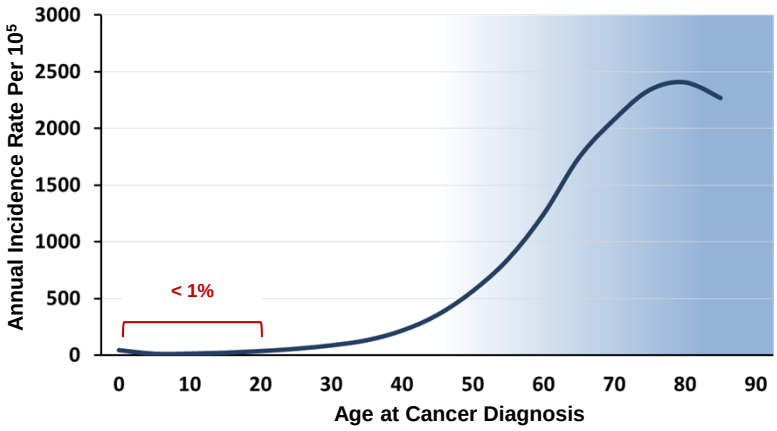
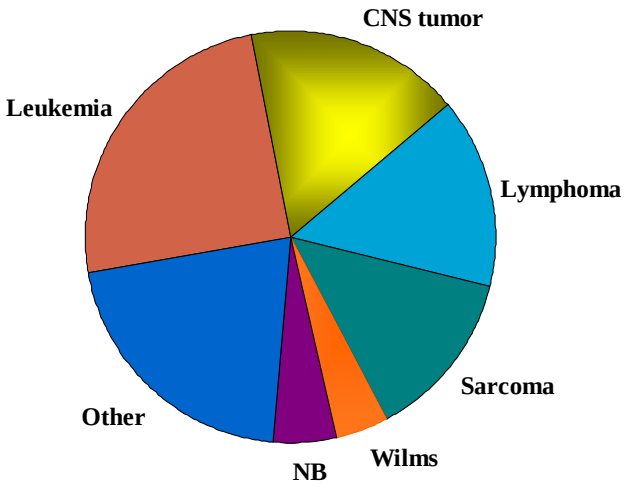
Age-specific Cancer Incidence



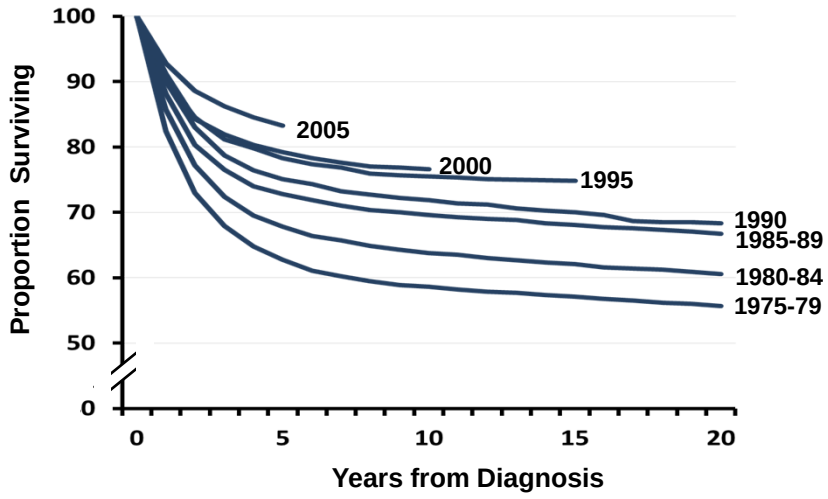
Data Source: SEER 2010

Robison and Hudson, Nature Rev Cancer, 2014;14: 61

Common Childhood Cancers



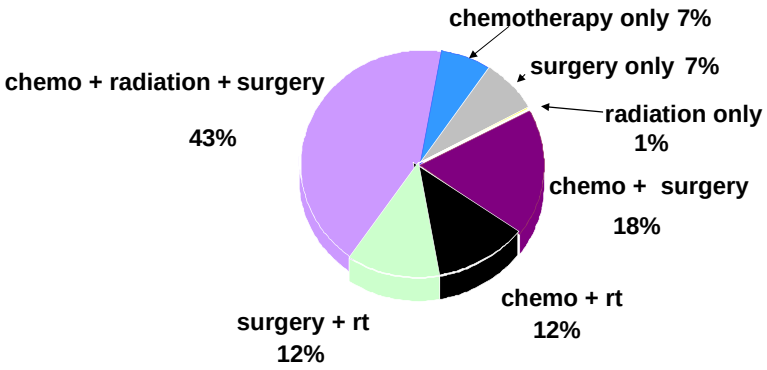
Survival of Childhood Cancers Ages 0-19 years



Data Source: SEER 2010

Robison and Hudson, Nature Rev Cancer, 2014;14: 61

Childhood Cancer Survivors: Treatment
CCSS (n = 14,000)



Childhood Cancers: Survivorship Statistics

- Currently more than 380,000 survivors living in US
- 1 in 530 in the US between ages 20 and 39 yrs is a childhood cancer survivor
- Number of survivors in US will approach 500,000 by 2020

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What are the long-term consequences of exposing children and adolescents to radiation therapy and multi-agent chemotherapy?

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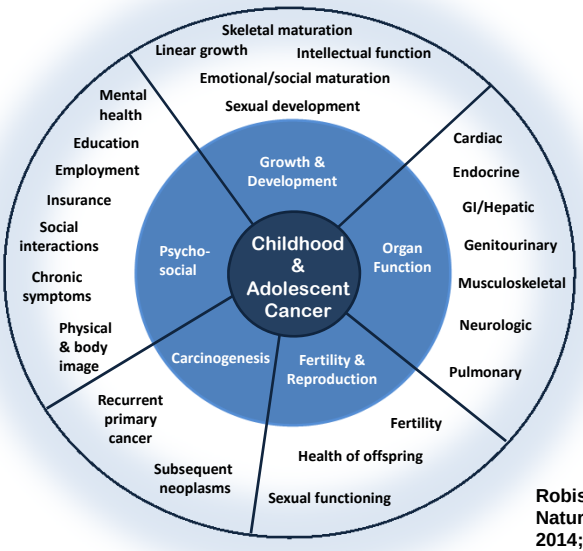
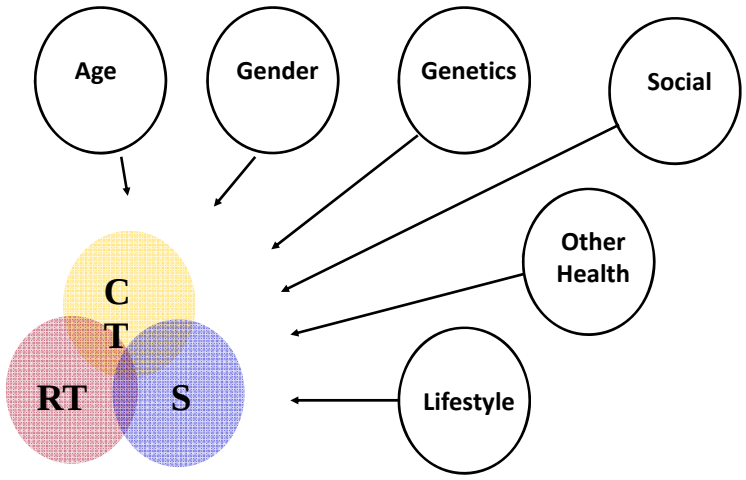
Spectrum of Health-related and Quality of Life Outcomes



Robison and Hudson, Nature Rev Cancer, 2014;14: 61

Factors to be Considered in Risk of Late Effects



Radiation-induced abnormalities are, in general, both *dose* and *time* dependent

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CCSS CHILDHOOD CANCER SURVIVOR STUDY

An NCI-Funded Resource

Childhood Cancer Survivor Study

- Retrospective Cohort Initiated 1994
- 5-Year Survival
- Leukemia, Lymphoma, CNS, Bone, Wilms, NBL, Soft-tissue sarcoma
- Diagnosis 1970-1986
- < 21 Yrs. At Diagnosis
- Detailed Treatment Data
- Biological Samples
- Wide Range of Outcomes

20,720 Eligible

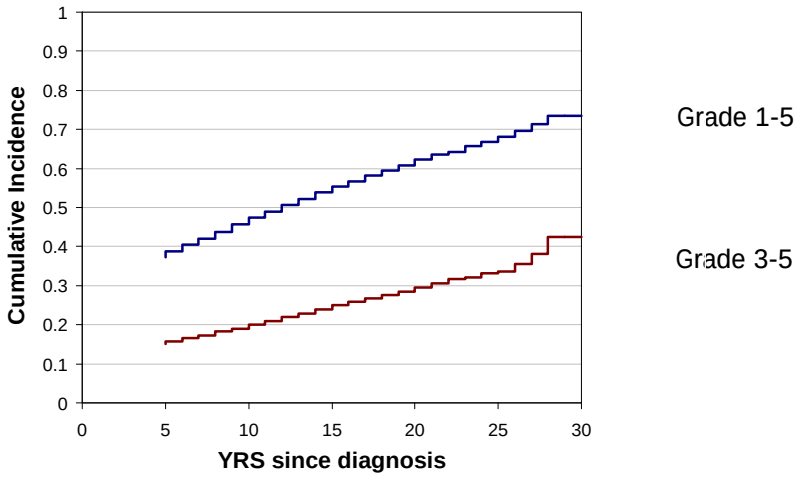
↓ Lost *(n=3017)*

17,703 Contacted

↓ Refusal *(n=3189)*

14,372 Participants

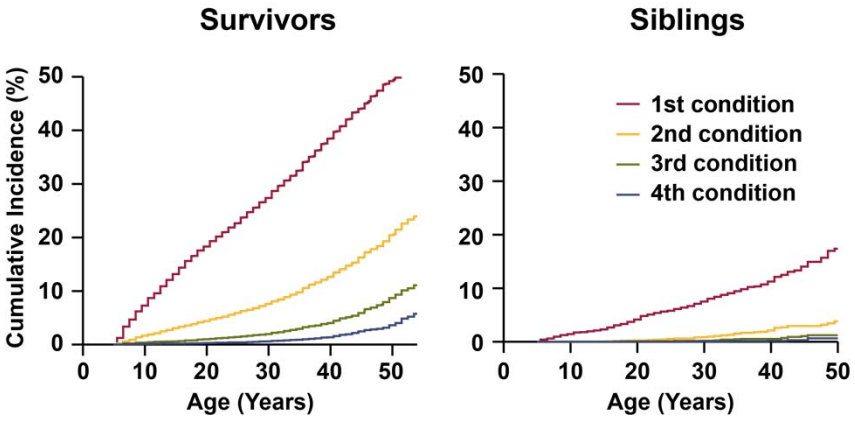
Cumulative Incidence of Chronic Health Conditions in Survivors, by Grade (n = 10,397)



CCSS CHILDHOOD CANCER SURVIVOR STUDY

Oeffinger KC, et al. N Engl J Med 355:1572-82, 2006

Multiple Chronic Health Conditions in Survivors, Grade 3-5



CCSS
CHILDHOOD CANCER SURVIVOR STUDY

Armstrong G, et al. J Clin Oncol 32: 1218-1227, 2014

Endocrine and Metabolic Complications

- Among most prevalent late effects in survivors of childhood cancer
- Most often seen in survivors treated with:
  - Radiation to head, neck, or pelvis (eg, brain tumors, Hodgkin lymphoma, TBI stem cell transplant)
  - High-dose alkylating agents (Hodgkin lymphoma, stem cell transplant)

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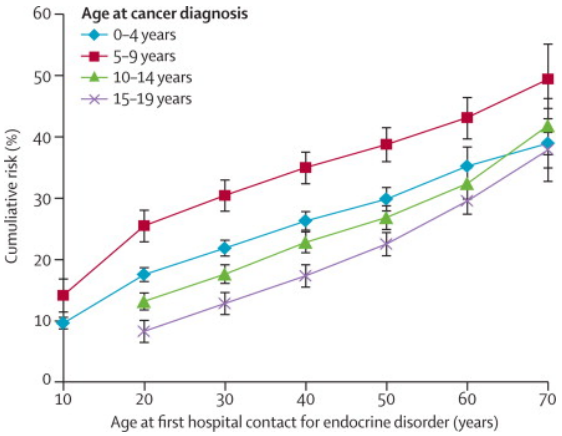
ALiCCS: Cumulative risk for a first hospital contact for an endocrine disorder (n=31,723)



- **Relative risk of endocrine diagnosis was 4.8 (4.6-5.0 95%CI) in survivors compared to controls.**
- **The prevalence of endocrine disease by the age of 60 years was 43% in individuals diagnosed with cancer when they were 5-9 years old.**

de Fine Licht S. et al. Lancet, 2014;383:1981

Endocrine Complications

- Hypothalamic-Pituitary Dysfunction
  - GH deficiency
  - Early puberty
  - LH/FSH, TSH, ACTH deficiencies
  - Hyperprolactinemia
  - Obesity
- Thyroid abnormalities
  - Primary hypothyroidism
  - Hyperthyroidism
  - Thyroid neoplasms
  - Hyperparathyroidism?
- Gonadal dysfunction
  - Males
    - Infertility
    - Leydig cell failure
  - Females
    - Acute ovarian failure
    - Premature menopause
- Bone disease
  - Osteoporosis
  - Osteonecrosis
  - Rickets
- Metabolic abnormalities
  - Insulin insufficiency
  - Insulin resistance/metabolic syndrome/DM

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Hypothalamic-Pituitary Abnormalities

GH deficiency

LH/FSH,TSH, ACTH deficiency

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Threshold Dose of RT for Clinical Neuroendocrine Dysfunction

Disorder	*Radiation Dose (Gy)*
GH deficiency	≥ 18
LH/FSH deficiency	> 30
TSH deficiency	> 30
ACTH deficiency	> 30
Hyperprolactinemia	> 40-50

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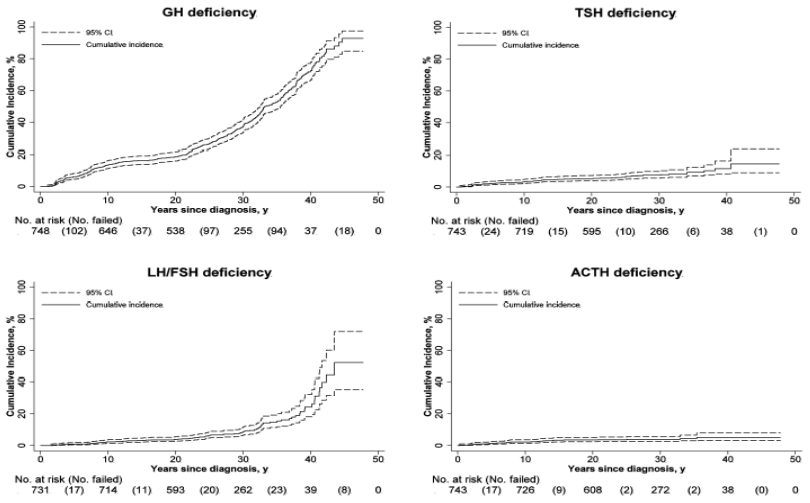
Cumulative Incidence of Hypothalamic-Pituitary Deficits in Survivors Treated with Cranial Radiation: SJLife Cohort (N=748)



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Chemaitilly W et al. J Clin Oncol 2015; 33:492

Evolution of GH Deficiency Post-RT

- Dose and time dependent
  - HPA doses >30 Gy, ~80% deficient by 5 yrs
  - HPA doses 18-24 Gy, GH deficiency may not develop for 10 or more yrs

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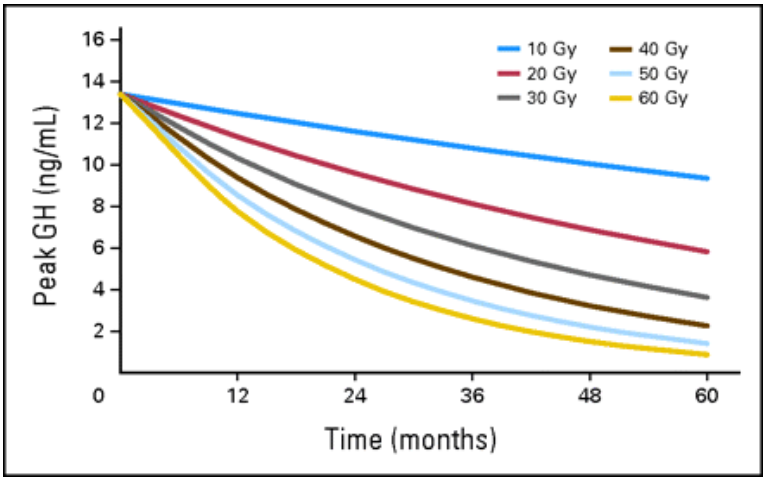
Peak GH According to Hypothalamic Dose and Time After RT



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Merchant TE. JCO 2011;29:4776

Thyroid Abnormalities

Primary Hypothyroidism

Hyperthyroidism

Thyroid cancer

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Thyroid Dysfunction In Survivors of Hodgkin Lymphoma

Among 1791 five year survivors in the CCSS , 34% were diagnosed with at least one thyroid abnormality.

Hypothyroidism was the most common abnormality with a relative risk of 17.1 ($p<0.001$).

Risk factors for hypothyroidism

- Increasing dose of radiation
- older age at diagnosis
- female sex

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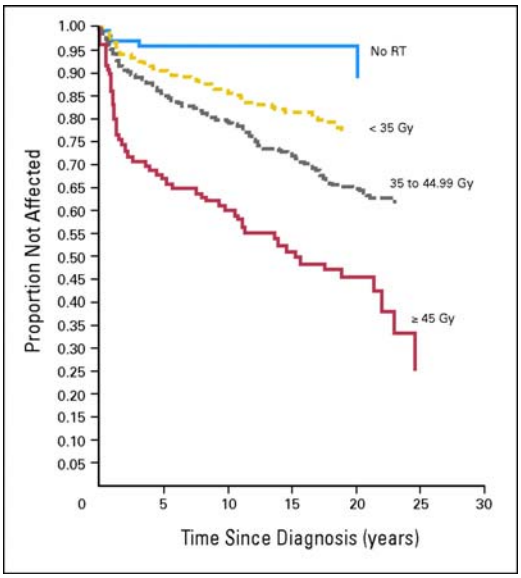
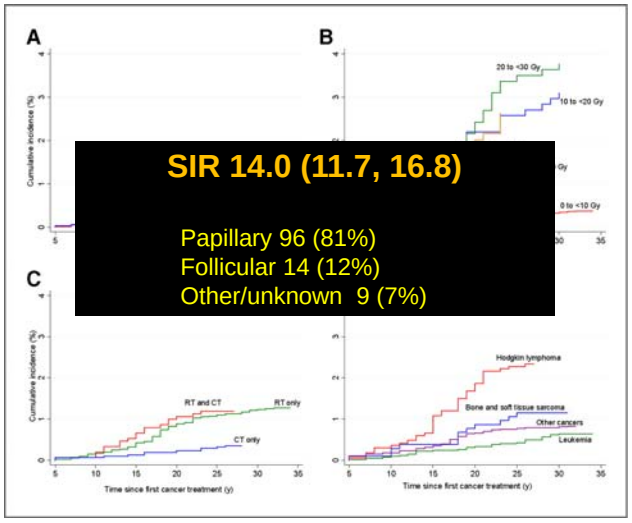
Probability of developing an underactive thyroid after diagnosis of Hodgkin's lymphoma

N=1,791



Sklar et al, JCEM 85:3227, 2000

Cumulative incidence of thyroid cancer in the CCSS cohort according to time since first cancer treatment.



Veiga L H et al. Cancer Epidemiol Biomarkers Prev 2012;21:92-101

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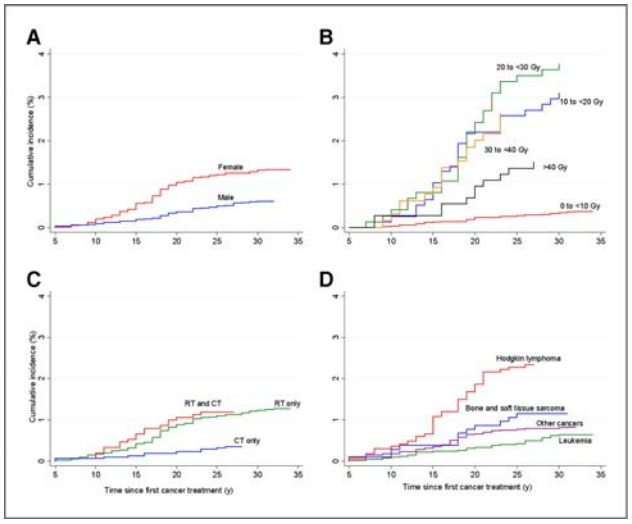
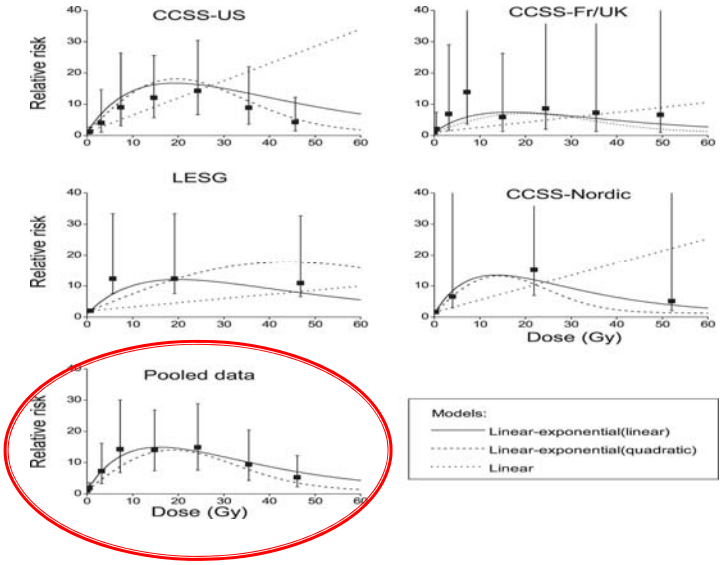


Veiga L H et al. Cancer Epidemiol Biomarkers Prev 2012;21:92-101

Thyroid Cancer Risk vs Dose of RT



Veiga et al, Radiation Res 2012;178:365

Bone Health

BMD, Fracture Risk, Vitamin D status

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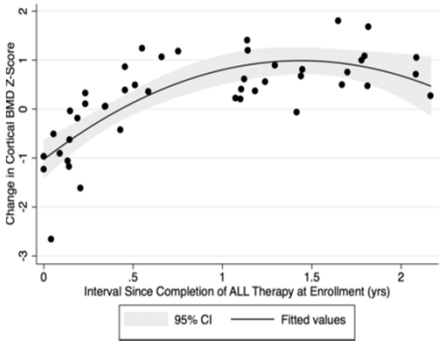
Reduced BMD and Fracture Risk



- **CCSS: no increased fracture risk between survivors and siblings (n=7417; median age 36 yrs)**

Wilson CL et al. 2012. Cancer. 118:5920-8.

Mostoufi-Moab S et al. 2012. J Clin Endocrinol Metab. 97:3584-3592.

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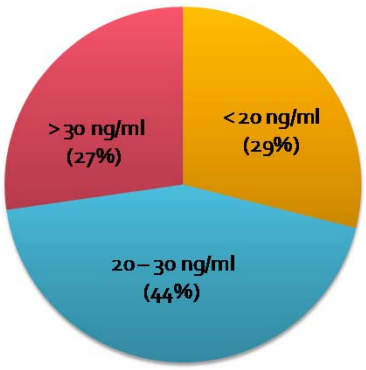
25-OH Vitamin D Status: MSKCC (n=484)



Choudhary et al, Pediatr Blood Cancer 2013, 60:1237

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Metabolic Disease

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Risk of DM in CCSS: Multiple Logistic Regression Model

Variable	OR	95% CI
Age <4 dx	2.4	1.3-4.6
Attained age	1.9	1.2-3.1
BMI, cur		
18.5-24		
25-29.9		
≥ 30		
Inactivity		
AA		
ABD RT		
TBI	7.2	3.4-15.0

RR of DM
1.8 (95% CI 1.3-2.5)

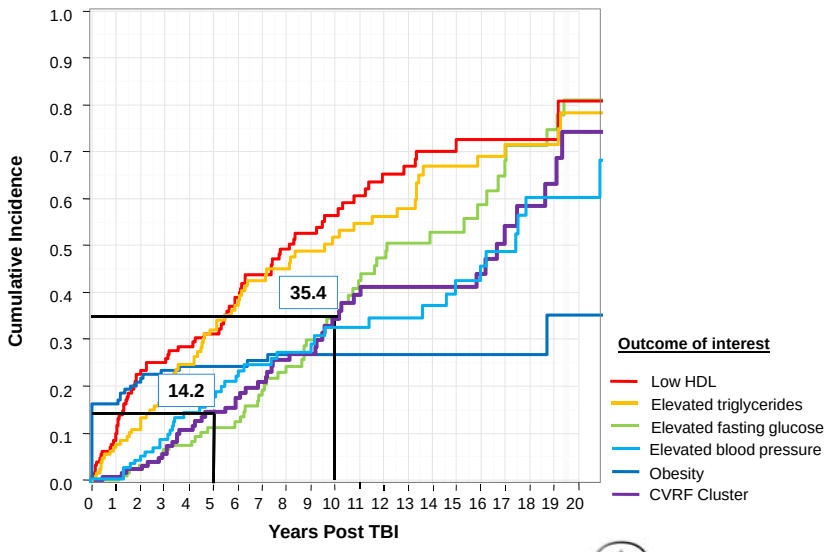
Meacham et al, Arch Int Med 2009

Risk of DM in CCSS: Multiple Logistic Regression Model

Variable	OR	95% CI
Age <4 dx	**2.4**	**1.3-4.6**
Attained age	1.9	1.2-3.1
BMI, current		
18.5-24.9	1.0	ref
25-29.9	2.0	1.3-3.0
≥ 30	**4.3**	**2.9-6.4**
Inactivity	1.5	1.2-2.1
AA	1.5	1.1-2.1
ABD RT	**2.7**	**1.9-3.8**
TBI	**7.2**	**3.4-15.0**

Meacham et al, Arch Int Med 2009

Cumulative Incidence Estimates of CVRF Cluster in 136 SCT Survivors treated with TBI



Friedman D, et al, 2015

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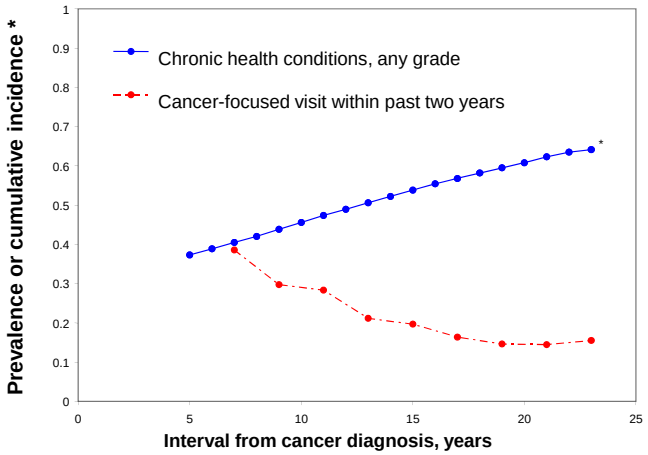
Trajectory of Medical Follow-up and Development of Chronic Health Conditions Over Time (CCSS)



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Transitioning Survivors of Childhood Cancer: Issues to Consider

- Due to long latency between specific exposures and development of some endocrine complications:
  - Many "at risk" survivors (eg, hx of low dose CRT) without identified endocrine issues, nonetheless, require long-term endocrine surveillance
  - Survivors with known endocrine issues may be at risk for additional endocrinopathies over time
- Survivors at high-risk for non-endocrine co-morbidities
- Subset (eg, BT survivors) cognitively impaired

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Barriers to Transitioning Survivors of Childhood Cancer to Adult Providers

- Survivors
  - Unaware of, or underestimate future risks
  - Lack of access to specialty care
  - Under-employed and under-insured compared to sibs
- Providers
  - Knowledge deficits
  - Discomfort managing disease in cancer patient
  - Difficulty obtaining adequate treatment records

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Conclusions

- Endocrine complications highly prevalent among survivors of childhood cancer
- Risk for late effects determined largely by the individual's therapeutic exposures
- Risk for late effects increases over time
- Lifelong surveillance required for those at risk

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Children's Oncology Group Guidelines for Follow-Up of Survivors

http://www.survivorshipguidelines.org/

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A Resource for Research

- The **Childhood Cancer Survivor Study** is an NCI-funded resource to promote and facilitate research among long-term survivors of cancer diagnosed during childhood and adolescence.
- Investigators interested in potential uses of this resource are encouraged to visit www.stjude.org/ccss

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GH and Risk of Subsequent Neoplasm

Reference	n	Agent	RR (95% CI)
Leung et al, 2001	47	rhGH	4.2% vs 2.9%
*Sklar et al, 2002	361	pitGH and rhGH	3.21 (1.88 – 5.46)
*Ergun-Longmire et al, 2006	361	pitGH and rhGH	2.15 (1.3 – 3.5)
Mackenzie et al, 2011	110	rhGH	4.5% vs 2.7%
*Patterson et al, 2014	338	pitGH and rhGH	1.0 (0.6-1.8) for subsequent CNS tumor

* Childhood Cancer Survivor Study