Childhood Cancer Survivor study
Study Proposal: Chronic Endocrine Disorders in Cancer Survivors
February 2014

1. **STUDY TITLE:** Chronic endocrine disorders in adult survivors of childhood cancer: A Report from the Childhood Cancer Survivor Study

2. **WORKING GROUP AND INVESTIGATORS:** This proposed publication will be within the Chronic Disease Working Group. Proposed investigators will include:

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3. BACKGROUND AND RATIONALE

Cancer and its treatment predispose survivors to late morbidity and an increased risk for early mortality.(1-3) Prior studies have reported an increased risk for significant chronic conditions in survivors after successful curative cancer therapies.(4, 5) As recognized by Oeffinger et al, three-fourths of long-term childhood survivors exhibit a chronic health disorder within 30 years of diagnosis and treatment. Of these, up to 42.4% have a severe, disabling, and life-threatening condition or experience death from a chronic illness.(5) Furthermore, survivors of all primary cancer diagnosis have an increased risk of developing debilitating chronic conditions when compared to siblings, adjusted for age, sex, race, and ethnicity. Specifically, survivors exposed to radiation, chemotherapy, or treatment combinations demonstrate significantly higher prevalence of life-threatening disorders compared to siblings.(5)

Endocrine morbidities compromise a substantial proportion of treatment-related sequelae in cancer survivors with a rising cumulative incidence of dysfunction in various endocrine glands over time.(4) For example, abnormalities of the thyroid gland, including primary hypothyroidism, hyperthyroidism, and thyroid neoplasms all have been reported to occur at a higher rate among survivors compared with the general population.(6, 7) Growth hormone deficiency is among the most common endocrine abnormalities noted in survivors of childhood cancer particularly after radiation injury to the hypothalamic-pituitary axis.(8) Notably, 13% of irradiated brain tumor survivors enrolled in CCSS demonstrated adult heights of two or more standard deviations below population norms.(9) Unfortunately, the damaging effects of radiation on the hypothalamic pituitary neuroendocrine axis persist over time, resulting in a greater cumulative incidence of hypothalamic-pituitary dysfunction in long-term survivors extending into adulthood.(8) Cancer survivors treated with allogeneic hematopoietic stem cell transplantation and exposure to total body irradiation have an increased prevalence of diabetes mellitus, hypertension, and the metabolic syndrome.(10) Survivors of acute lymphoblastic leukemia and brain tumors treated with cranial radiation, particularly females at a young age, have an increased risk of obesity in adulthood as well as alterations in pubertal timing and risk for early menarche.(11-13) Furthermore, analysis of the CCSS 2000 questionnaire data demonstrated an increased risk of premature menopause due to direct effects of chemotherapy and

radiation on the ovaries.(14, 15) Adult survivors of childhood cancer with endocrine abnormalities are at risk for osteopenia, osteoporosis and inadequate bone health as the accumulation of bone mass during development requires the coordinated actions of growth factors and sex steroids in the setting of adequate biomechanical loading and nutrition. Therefore, the growing skeleton is particularly vulnerable to the effects of cancer therapy with subsequent reduced bone mass an important determinant of poor bone health and fracture risk during adulthood.(16)

Data from the baseline questionnaire indicate that while 18% of survivors manifest at least one low grade endocrine abnormality, the percentage of survivors reporting a severe, disabling, or life-threatening endocrine disorder is as high as 7.6%, and survivors are 6 times more likely to have a grade 3 or 4 endocrine disease (95% CI 4.4 to 7.9) compared to siblings.(4)

As the survivor cohort continues to age, additional new-onset endocrinopathies continue to emerge, evident in the rising cumulative incidence of endocrine conditions over time. Thus, adult survivors of childhood cancer are faced with the increasing risk of chronic endocrine disorders with specific subpopulations of adult survivors at highest risk for severe, debilitating, or life-threatening endocrinopathies. This longitudinal analysis of the cohort will characterize the prevalence and cumulative incidence of chronic endocrinopathies in the aging CCSS population, with special emphasis on those at highest risk based on their prior treatment exposures to facilitate earlier recognition and risk stratification of future long-term health consequences in this growing at-risk population.

4. SPECIFIC AIMS:

Specific Aim 1:
To determine the prevalence and cumulative incidence of chronic endocrinopathies, including: thyroid disease, thyroid nodules, thyroid neoplasms, premature menopause, Leydig cell dysfunction, diabetes mellitus, obesity, hypothalamic pituitary dysfunction, and osteoporosis in adult survivors of childhood cancer.
Hypothesis: The cumulative incidence and prevalence of chronic endocrinopathies in adult survivors increase with age.

Specific Aim 2:
To determine the risk of chronic endocrinopathies in adult survivors compared with their siblings.
Hypothesis: Adult survivors have higher risk of chronic and multiple endocrinopathies compared to their siblings at the same age.

Specific Aim 3:
To determine the prevalence and cumulative incidence of chronic endocrinopathies in sub-populations of adult survivors at the highest risk for multiple endocrinopathies according to the highest risk therapeutic exposure per Children's Oncology Group (COG) Long-Term Follow Up Guidelines.
Hypothesis: Adult survivors exposed to cranial radiation, total body irradiation for allogeneic hematopoietic stem cell transplantation, or abdominal radiation therapy with or without alkylating chemotherapy, are at higher risk for endocrinopathies compared to other survivors.

5. STUDY POPULATION

This study will use the latest CCSS data set of cancer survivors and siblings who responded to the baseline or any follow-up questionnaires that provide relevant outcomes. When available, we will utilize existing and updated datasets with same definitions used for common end points. Survivors with other conditions associated with increased endocrine abnormalities such as Turner Syndrome or Trisomy 21 will not be included in the analysis.

6. DEFINITION OF EXPOSURE AND OUTCOME VARIABLES OF INTEREST

When available, we will utilize existing and updated datasets with same definitions used for common end points and outcome variables.

- Outcome Variables
  - Hypothalamic Pituitary
    - ACTH deficiency, TSH deficiency, LH & FSH deficiency, central diabetes insipidus *(Baseline < 18 & Baseline B8.2-7, B8.16); [LTFU 2000: 6b-g, 6q; LTFU 2003: Q1-5, Q9 LTFU 2007: C8.2 (estrogen) C8.3 + Men's Health Questionnaire B4-B10 (testosterone), C8.8 (thyroid), C8.10 (other), F12]. (cross-sectional)*
    - Growth hormone deficiency *(Baseline <18 & Baseline E8); (LTFU 2007 F8, F9 (GHD)),with age of onset.*
    - Multiple pituitary deficits *(Baseline < 18 & Baseline B8.2-6, B8.16)*, (LTFU 2000 6b-g, 6q), (LTFU 2003 Q1-4, Q9), *(LTFU 2007 C8, F12)*
  - Thyroid
    - Hypothyroidism (*Baseline <18 & Baseline E2), (LTFU 2007 F2), with age of onset*
    - Thyroid medication (yes/no) (*Baseline <18 & Baseline B8.5), (LTFU 2000 6e), (LTFU 2007 C8.8) (cross-sectional)*
    - Hyperthyroidism (*Baseline <18 & Baseline E1), (LTFU 2007 F1), with age of onset*
    - Thyroid nodule(s) (*Baseline < 18 & Baseline E3), (LTFU 2007 F3), with age of onset*
    - Thyroid malignancy, with age of onset
  - Gonadal function
    - Spontaneous menarche (LTFU 2000 19, 19a-b), (*LTFU 2007 F13-F14), with age of onset*
    - Premature menopause (LTFU 2000 19c-d), (LTFU 2007 F15, F16), with age of onset
      (defined as menopause prior to age 40 years, no spontaneous menses for six months, exclusive of pregnancy and use of hormonal medications. Age at premature menopause will be defined as age at most recent menstrual period).
    - Testosterone replacement *(Baseline < 18 & Baseline B8.4);* (LTFU 2000 6d), (LTFU 2003 Q3), *(LTFU 2007 C8.3); (Men's Health Questionnaire B4-B10), (cross-sectional)*
  - Body Composition/Diabetes mellitus
    - Diabetes mellitus *(Baseline < 18 & Baseline B8.7, E5-E7); [LTFU 2000: 6g, LFTU 2003: Q4, LTFU 2007: C8.4 (DM meds), F5-F7, I5 (DM)], with age of onset*
    - BMI (Baseline < 18 & Baseline); (LTFU 2003, 2007), (cross-sectional)
  - Bone Health
    - Fractures *(LTFU 2007 F11), with age of onset*
    - Osteoporosis (LTFU 2003 B3, P1-3), *(LTFU 2007 B5.b, C2, F10), with age of onset*

- Exposure Variables
  - Oncology
    - Age at diagnosis
    - Primary cancer diagnosis
    - Alkylator exposure
      - Cyclophosphamide Equivalent Dose (17)
      - MOPP exposure in females will be assessed identifying subgroup of survivors diagnosed with Hodgkin's Lymphoma treated with nitrogen mustard and procarbazine with CED cut-point equivalent to three full cycles of MOPP.

- Radiation exposure (Gy)
    - Hypothalamic/pituitary
    - Cranial
    - Neck/chest
    - Total Body Irradiation (TBI)
    - Testicular
    - Abdominal
    - Pelvic

- Exposure and outcome variables stratified per Children's Oncology Group Long-Term Follow Up Guidelines

Highest Risk Therapeutic Exposures	Endocrine Late Effects
Radiation dose ≥ 20 Gy to thyroid	Hypothyroidism
Methotrexate ≥ 40 g/m^2 Glucocorticoid (yes/no)	Low bone mineral density
Alkylators - MOPP > 3 cycles - Busulfan > 600 mg/m^2 - Cyclophosphamide cumulative dose > 7.5 mg/m^2 or as conditioning for HCT Any alkylator combined with: - Pelvic radiation - TBI Pelvic irradiation Prepubertal female ≥ 15 Gy Pubertal female ≥ 10 Gy Pelvic irradiation combined with: - Cyclophosphamide - Conditioning for HCT	Gonadal dysfunction (females); ovarian failure
Testicular RT ≥ 20 Gy Combined with alkylating agents Combined with: - Cyclophosphamide - Conditioning for HCT	Leydig cell dysfunction
Hypothalamic radiation dose ≥ 20 Gy	Overweight, obesity
TBI Abdominal RT	Diabetes mellitus
Cranial Radiation dose ≥ 18 Gy	Growth Hormone deficiency
Hypothalamic Pituitary dose ≥ 30 Gy	TSH, ACTH, LH/FSH deficiency

Radiation dose ≥ 25 Gy to thyroid	Thyroid nodule(s)
Radiation dose ≤ 30 Gy to thyroid	Thyroid cancer

- Explanatory Variables
  - General
    - Ethnicity (*Baseline <18 & Baseline A4, A4.a)*
    - Age at assessment (Date of Assessment – DOB)
    - Marital status *(Baseline <18 L1, L2), (Baseline L1-L2), (LTFU 2000 2), (LTFU 2003 2), (LTFU 2007 M2)*
    - Smoking status *(Baseline <18 N1, N2), (Baseline N1, N2), (LTFU 2003 L1-L6), (LTFU 2007 N7-N14)*
    - Alcohol status *(Baseline <18 N3, N4), (Baseline N3-N8), (LTFU 2007 N1-N6)*
    - Physical activity *(Baseline <18 N5-N10), (Baseline N9-N14), (LTFU 2003 D1-D7), (LTFU 2007 N15-N26)*
    - Education level *(Baseline <18 O1), (Baseline O1), (LTFU 2000 1), (LTFU 2003 1), (LTFU 2007 A3)*
    - Employment *(Baseline <18 O6, O7), (Baseline O5-O11), (LTFU 2000 3), (LTFU 2003 4-6), (LTFU 2007 A4, A5)*
    - Income *(Baseline <18 Q8), (Baseline Q8, Q9), (LTFU 2003 S1-S3), (LTFU 2007 A6-A8)*
    - Insurance *(Baseline <18 & Baseline Q2, Q3, Q3a, Q3b), (LTFU 2000 16), (LTFU 2003 M1), (LTFU 2007 B9)*

7. ANALYSIS FRAME-WORK

Endocrine outcomes are divided into two types; those evaluated as yes/no cross-sectional outcomes at each survey, and those for which a first age of onset is identified via reporting across surveys. Each type of outcomes will be analyzed using slightly different methods.

Aim 1: For those outcomes without age of onset available, prevalence of adverse endocrine outcomes in survivors as defined above will be described across ages of follow-up, utilizing age at questionnaire, and all yes/no observations for each subject from each questionnaire. Logistic regression models will be used to estimate prevalence as a function of age at study.

Cumulative incidence estimates of the endocrine disorders with known age of onset subsequent to cancer diagnosis and treatment will be calculated using the time from 5 years after childhood cancer diagnosis to the first occurrence of a chronic endocrine diagnosis, treating death as a competing risk event and censoring at the date of last contact.(19) Standard errors of cumulative incidence estimates will be used to calculate 95% confidence intervals (CI).(20) Curves as a function of age will also be evaluated. Starting age for curves will be determined depending on available denominator and numbers of events within age intervals.

Aim 2: For cross-sectional outcomes, logistic regression models will be used to assess comparisons of prevalence between survivors and siblings of the same chronological age, in models that include age-at-study, sex, race and ethnicity. Interactions between age-at-study and survivor/sibling status will be evaluated to determine whether survivors and siblings have different patterns of endocrine outcome prevalence across ages. Generalized estimating equations for correlated data will be used to account for potential within-subject correlation.(3, 18)

For time-to-event outcomes, similarly adjusted Cox proportional hazards models will be utilized, using age as the time scale and assessment for proportional hazards will be evaluated to determine whether the hazard ratio for survivor/sibling status varies across age, and if so, categories of age will be utilized for the presentation of different HR results across age.

Aim 3: Models similar to those developed for Aim 2 (logistic and cox proportional hazards regressions, as appropriate) will be used to determine the relative risks of adverse endocrine outcomes in survivors who meet the COG LTFUG's highest-risk therapeutic exposures as compared to other survivors.

For patients with secondary malignancy, we will determine the likelihood of endocrine disorders related to treatment of secondary malignancy that may be confounding the results attributed to treatment for primary malignancy.

All statistical tests will be two-sided with statistical significance at $P \leq 0.05$ and estimates will be calculated with corresponding 95% confidence intervals (CI).

8. PUBLICATION STRATEGY

We plan to submit the overview covering the three aims to a high impact journal.

9. REFERENCES

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Table 1. Characteristics of Adult Survivors of Childhood Cancer and Siblings

Characteristic	Survivors	Siblings	P Value
Sex – n (%)			
Female			
Male			
Race – n (%)			
Non-Hispanic white			
Other			
Age at diagnosis – yr			
Mean ± SD			
Range			
Age at most recent survey – yr			
Mean ± SD			
Range			
Ever smoker			
Yes			
No			
BMI at most recent survey*			
Underweight			
Normal			
Overweight			
Obese			
Not determined			
Cancer diagnosis		NA	
Central nervous system tumor			
Acute Lymphoblastic Leukemia			
Acute Myelogenous Leukemia			
Lymphoma			
Sarcoma			
Bone tumor			
Neuroblastoma			
Wilms' Tumor			
Other			
Cancer treatment – n (%)			
No chemotherapy or radiation		NA	
Chemotherapy			
Any chemotherapy			
Alkylating agent			
Steroids			
HCT conditioning**		NA	
Other			
Radiation therapy (RT)			
Any			
Brain			
Chest			
Abdominal or pelvic		NA	
Total body irradiation (TBI)			
Combined chemotherapy and RT			
Alkylator + TBI			

Alkylator + pelvic RT	
HCT conditioning + pelvic RT	
Interval between cancer diagnosis & most recent survey – yr	NA
Mean ± SD	
Range	

*BMI (kg/m^2) Ranges:
Underweight: <18.50
Normal: 18.50 – 24.99
Overweight: ≥25.00
Obese: ≥30.00

**HCT = Hematopoietic Stem Cell Transplantation

Table 2. Endocrine Disorders by Primary Cancer Diagnosis

Primary Cancer Diagnosis	Hypothyroidism N (%)	Thyroid Nodule N (%)	Thyroid Cancer N (%)	Gonadal Dysfunction (Females); Ovarian Failure N (%)	Leydig Cell Dysfunction (Males) N (%)	Overweight/ Obesity N (%)	Diabetes Mellitus N (%)	Growth Hormone Deficiency N (%)	TSH, ACTH, LH/FSH Deficiency N (%)	Low BMD N (%
Central Nervous System Tumor (N =)										
Acute Lymphoblastic Leukemia (N =)										
Acute Myelogenous Leukemia (N =)										
Lymphoma (N =)										
Neuroblastoma (N =)										
Sarcoma (N =)										
Bone Tumor (N =)										
Wilms' Tumor (N =)										
Other (N =)										

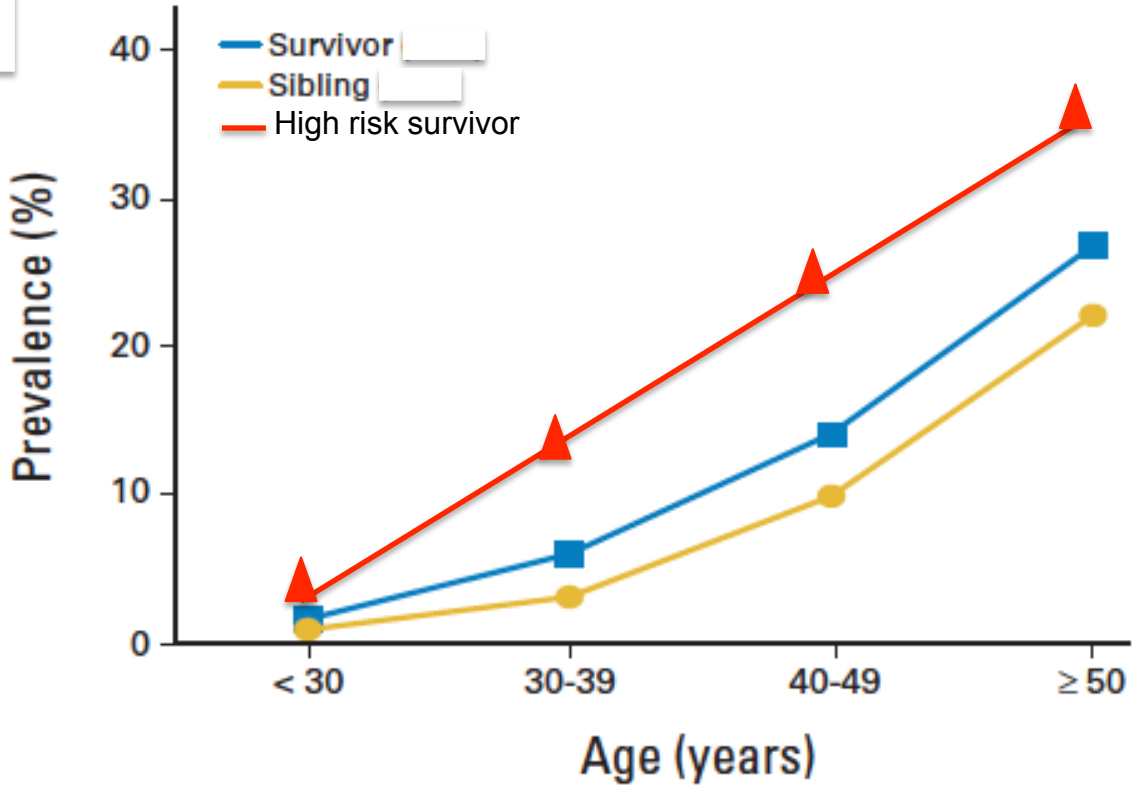
Table 3. Endocrine Disorders in Adult Survivors of Childhood Cancer and Sibling

Endocrine Disorder	HR (95% CI)	P value
Hypothyroidism		
Sibling		
Survivor		
High-Risk Survivors		
Thyroid Nodule		
Sibling		
Survivor		
High-Risk Survivors		
Thyroid Neoplasm		
Sibling		
Survivor		
High-Risk Survivors		
Gonadal Dysfunction (females); Ovarian Failure		
Sibling		
Survivor		
High-Risk Survivors		
Growth Hormone Deficiency		
Sibling		
Survivor		
High-Risk Survivors		
Overweight/Obesity		
Sibling		
Survivor		
High-Risk Survivors		
Diabetes Mellitus		
Sibling		
Survivor		
High-Risk Survivors		
Low Bone Mineral Density		
Sibling		
Survivor		
High-Risk Survivors		
Endocrine Disorder	**OR (95% CI)**	**P value**
Leydig Cell Dysfunction (males)		
Sibling		
Survivor		
High-Risk Survivors		
TSH, ACTH, LH/FSH Deficiency		
Sibling		
Survivor		

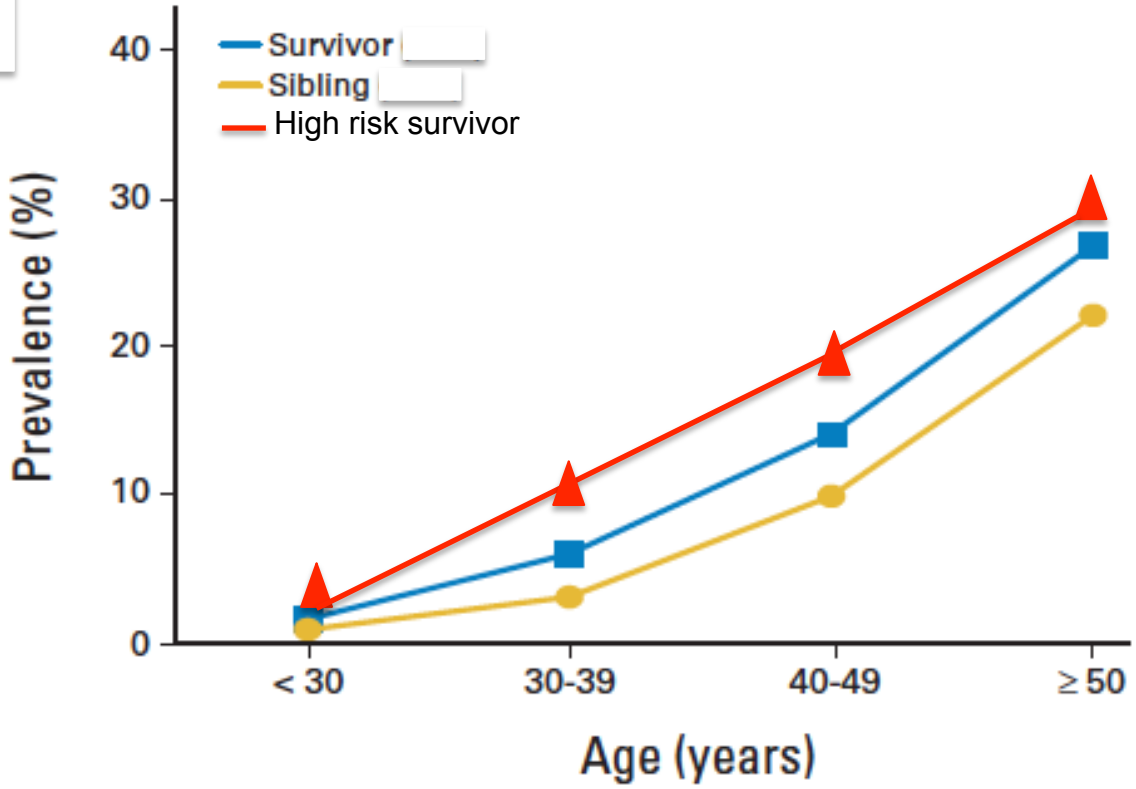
HCT=Hematopoietic Stem Cell Transplantation
TBI=Total Body Irradiation
TSH=Thyroid Stimulating Hormone
ACTH=Adrenal Corticotropic Hormone
LH=Luteinizing Hormone
FSH= Follicle Stimulating Hormone

HR=Hazard Ratio from Cox proportional hazards model
OR=Odds Ratio from logistic regression model

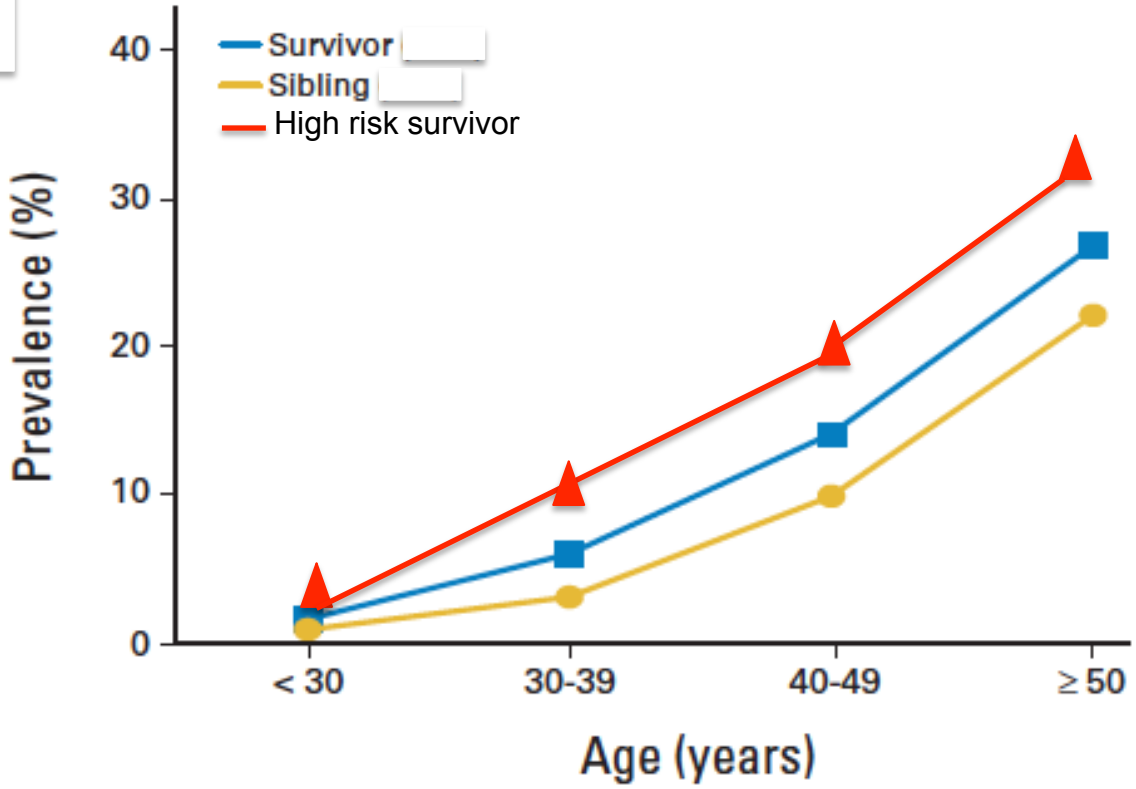
Thyroid Neoplasm



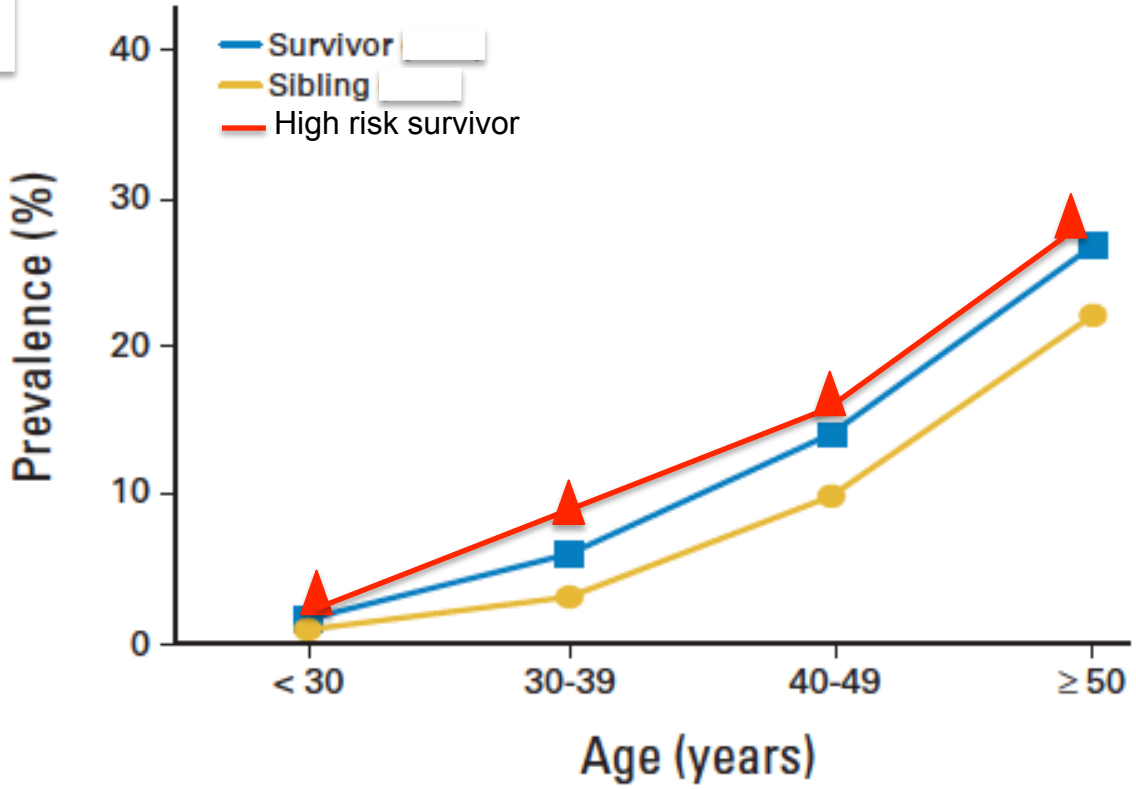
Thyroid Nodules



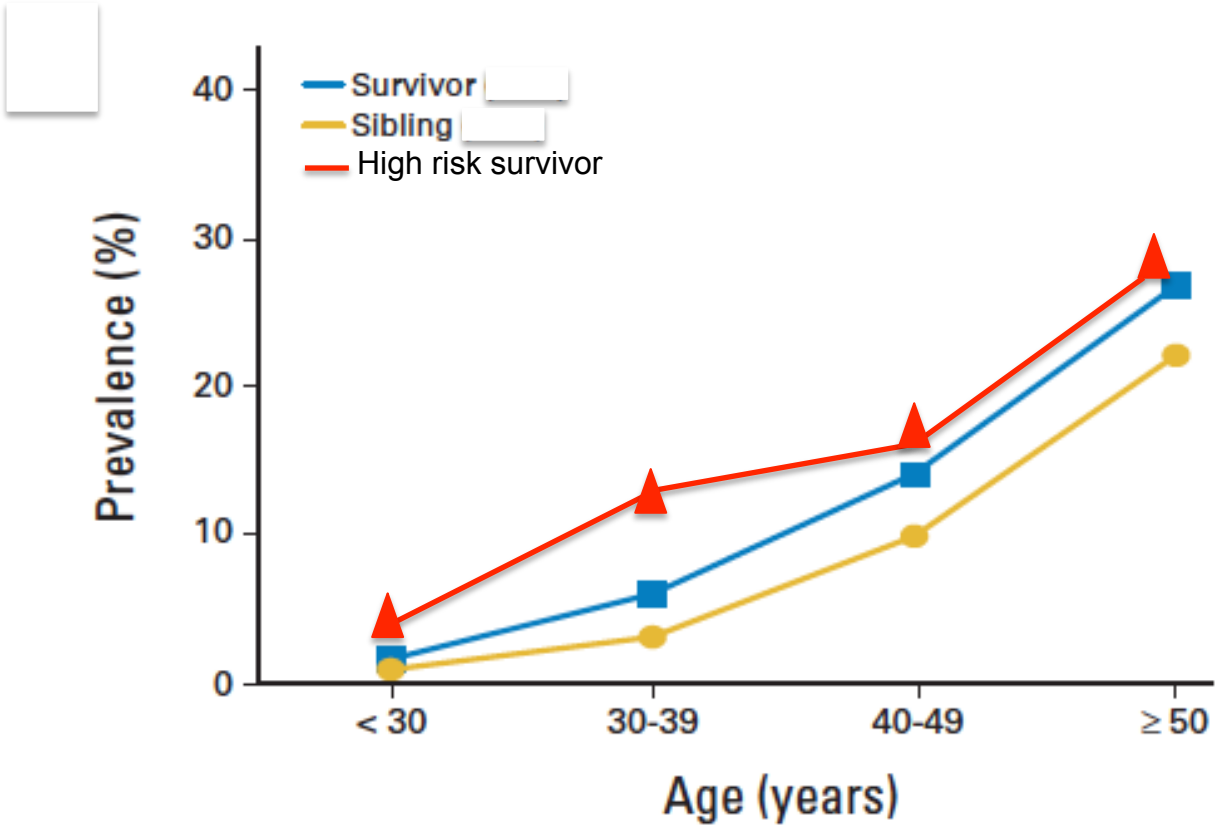
Diabetes Mellitus



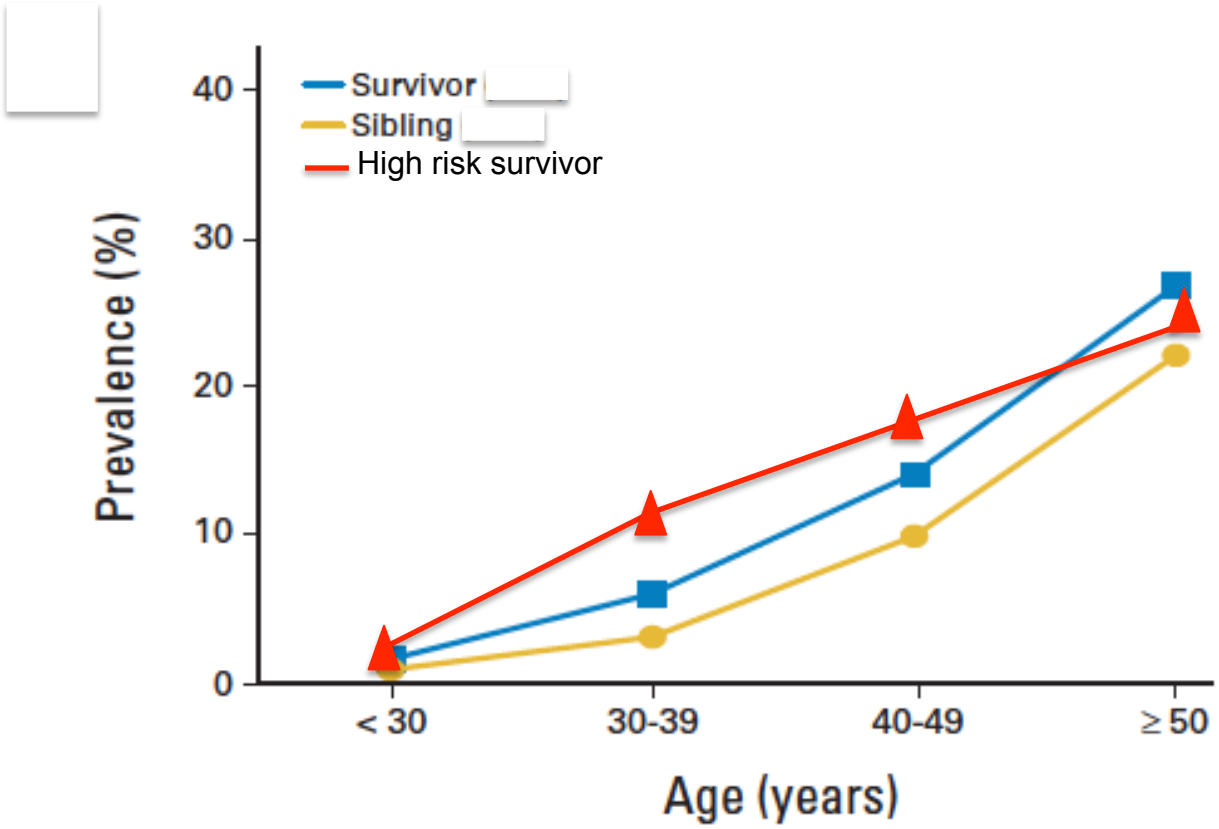
Growth Hormone Deficiency



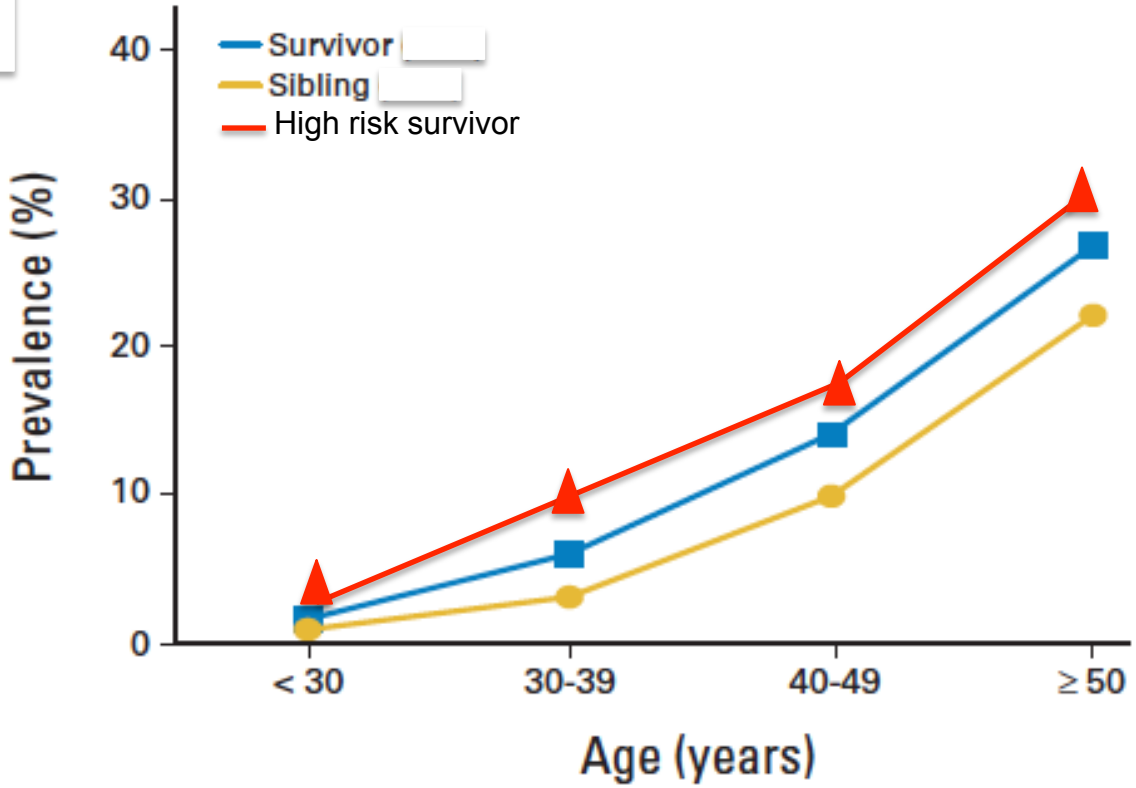
Female Gonadal Dysfunction

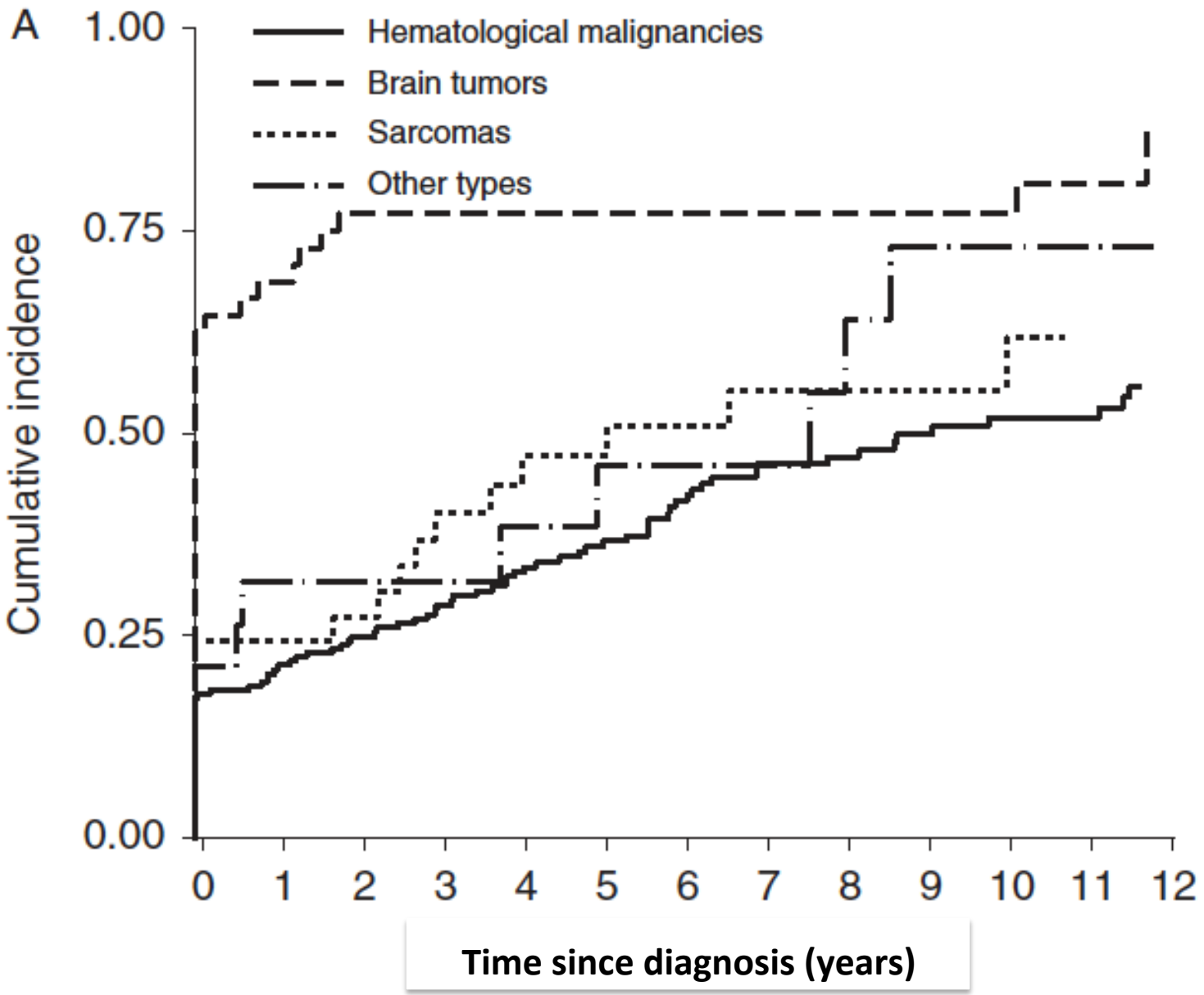


Male Leydig Cell Dysfunction



TSH/LH/FSH Deficiency

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Cumulative incidence
Hematological malignancies
Brain tumors
Sarcomas
Other types
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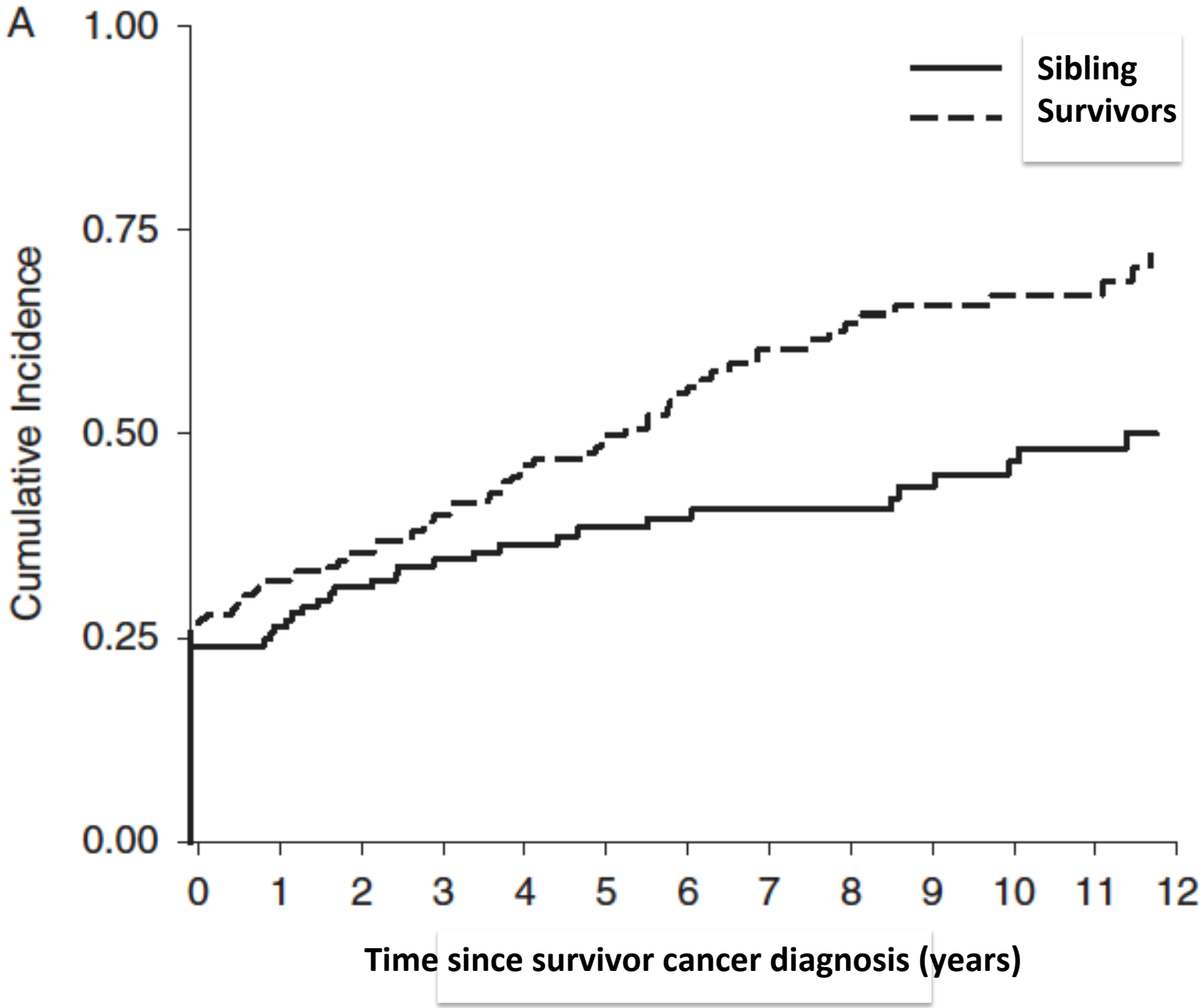
Time since diagnosis (years)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Cumulative Incidence
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Survivors
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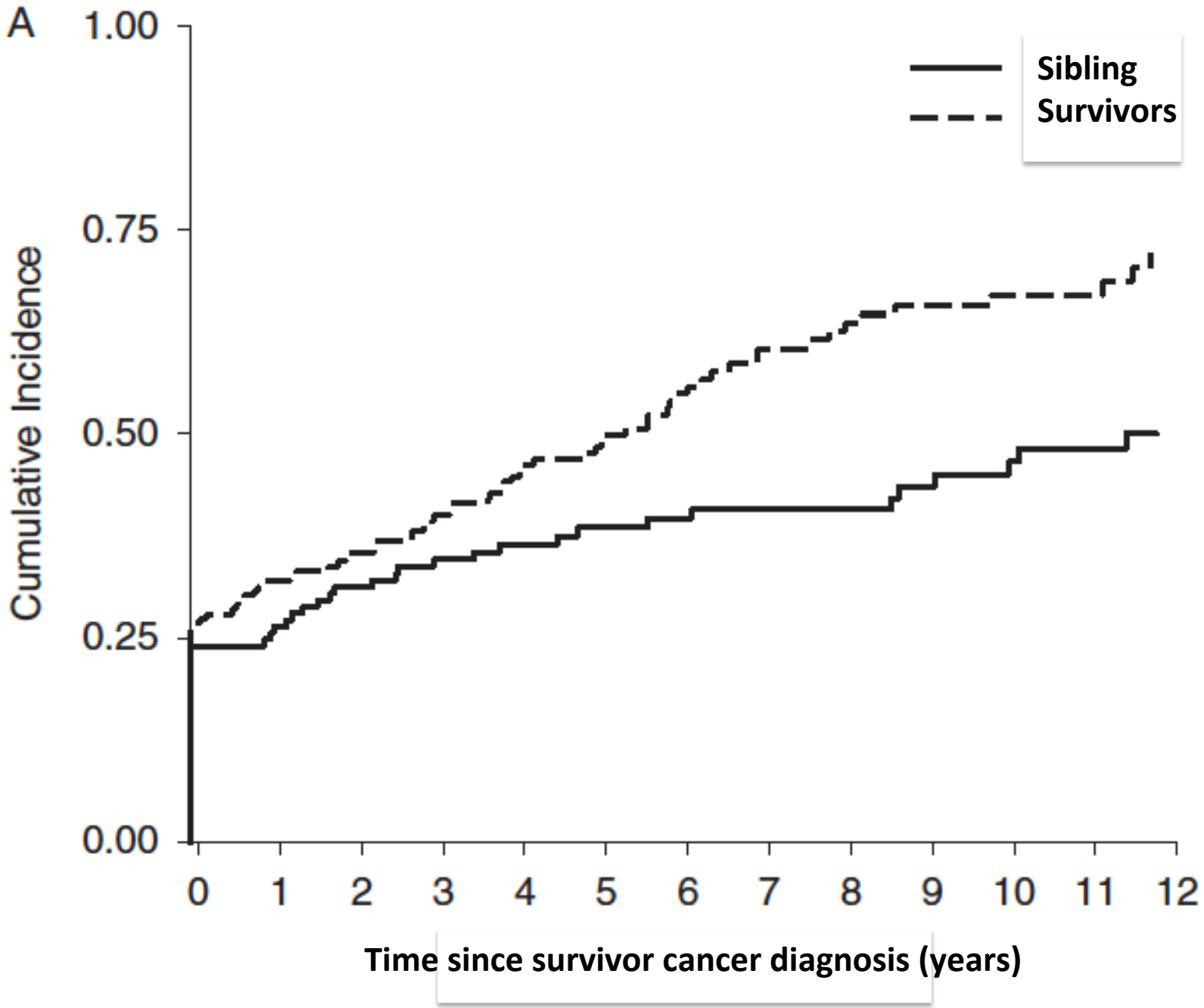
11
12
Time since survivor cancer diagnosis (years)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Cumulative Incidence
Sibling
Survivors
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Time since survivor cancer diagnosis (years)