1) **Study title:** Long-term Incidence of Venous Thromboembolism among Survivors of Childhood Cancer

2) **Working group and investigators:** The study of the long-term incidence of venous thromboembolism will be performed with the assistance of the Childhood Cancer Survivor Study (CCSS) Chronic Disease Working Group. Secondary oversight will be provided by the CCSS Epidemiology/Biostatistics Working Group. Roster:


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3) **Background and rationale:**

In the first five years after diagnosis, children with cancer may have up to 30-fold increased incidence of venous thromboembolism (VTE), compared to the general pediatric population.[1] The incidence of VTE ranges from 1.4-6.0 events per 100,000 person-years in the general pediatric population and 152 events per 100,000 person-years among children with cancer.[1–4] Furthermore, the overall incidence of VTE has increased by 70-88% among all pediatric inpatients over the past decade.[5,6] This finding may reflect improvements in diagnostic tests or increasing exposure to risk factors for VTE, such as central venous catheters,[5] chemotherapy treatments,[7] and surgery.[4] Survivors of childhood cancer are often exposed to multiple risk factors, as a result of the underlying disease and manifold treatment modalities. Furthermore, the risk of VTE is elevated in the presence of an increasing number of medical risk factors, compared to a single medical risk factor.[8] However, long-term risk of VTE among childhood cancer survivors (CCS) has never been defined.

Several aspects of multimodal cancer treatment may contribute to elevated VTE risk. From the adult literature, there is evidence that patients with breast cancer who are treated with chemotherapy possess an elevated risk of VTE, compared to those treated with placebo or hormonal therapy alone.[9] The mechanism by which chemotherapy contributes to a hypercoagulable state is posited to be related to endothelial cell dysfunction[10] or inflammatory mediators.[11] Among children with hematologic malignancies, treatments such as L-asparaginase and corticosteroids may contribute to thrombosis.[2] Inflammation and immobility from lower extremity lymphedema contribute to the development of deep venous thrombosis (DVT**).**[12] A recent series by Palmer and colleagues reported a 32% occurrence rate of lymphedema after inguinal dissection for children with melanoma.[13] An association between radiotherapy and lymphedema has also been reported in the breast and gynecologic cancer literature, with a synergistic effect on lymphedema among patients who undergo both surgery and

radiotherapy.[14,15] Similarly, functional limitations from surgery or chemotherapy-induced neuropathy may contribute to immobility and thereby predispose to VTE. Among a general population of children diagnosed with VTE, many underwent a prior surgical procedure.[3] The long-term effects on VTE of surgery and other treatments are unknown.

Demographic and disease-related factors also may affect VTE risk. Older age was found to be associated with higher risk of VTE in several large database studies of children who develop VTE.[5–7] The prevalence of VTE varies with underlying malignancy type, although the relationship may be confounded by differential use of cancer treatments. In a 2011 study of the Pediatric Hospital Information System Database, O'Brien and colleagues demonstrated an increased risk of VTE among adolescents and young adults with leukemia and sarcoma, compared with those with brain tumors.[7] The most common sites for VTE are the veins of the lower extremities (e.g. iliofemoral, popliteal), veins of the upper extremities (e.g. subclavian, axillary, brachial), and intra-abdominal central veins (e.g. inferior vena cava, portal vein, splenic vein).[6,16]

In examining the long-term risk of VTE among childhood cancer survivors, several factors may pre-dispose to VTE years after cancer diagnosis. For example, oral contraceptive use (especially in the presence of ongoing tobacco use) confers an increased risk of VTE in the general population.[17] A recent meta-analysis by Meng and colleagues reported a 1.4% rate of VTE during pregnancy and the puerperium.[18] Stein and colleagues in analysis from the National Hospital Discharge Survey note that pregnancy among girls age 15-17 was associated with double the incidence rate of VTE.[19] It is unknown if the rates of VTE with hormonal alterations are higher among CCS, compared to the already elevated risk of VTE with hormonal alterations in the general population. Finally, the development of second malignant neoplasms may be associated with increased VTE risk, although a recent trial reports a low overall occult cancer rate among the general adult population with newly diagnosed DVT.[20] These factors may be associated with a particularly elevated risk of VTE among CCS compared to the general adult population, which would be useful knowledge to guide counseling, screening, and prevention.

Finally, the clinical significance of VTE in CCS is unknown. Among adults with cancer, VTE is the second leading cause of death.[21] The in-hospital mortality rate for children treated for VTE is approximately 9% and significantly higher than that of children admitted for reasons other than VTE, although a causal relationship between VTE and mortality has not been convincingly demonstrated.[6,22] Children with VTE may be at increased risk of mortality from sequelae such as pulmonary embolism or, alternatively, VTE may be a harbinger of severe disease rather than a mechanism of mortality.

The proposed study will characterize the incidence, risk factors, and consequences of self-reported, late (≥5 years from diagnosis) VTE among survivors of childhood cancer.

4) **Specific aims:**

a) **Specific aim 1**

To describe the cumulative incidence and incidence rate of late (≥5 years post-diagnosis) venous thromboembolism (VTE; i.e. deep vein thrombosis or pulmonary embolism) among childhood cancer survivors compared to siblings.

*Hypothesis:* There is a higher cumulative incidence and incidence rate of long-term VTE among survivors compared to sibling controls.

b) **Specific aim 2**

To identify factors associated with late (≥5 years post-diagnosis) VTE (i.e. deep vein thrombosis or pulmonary embolism) among childhood cancer survivors.

*Hypothesis:* There is a higher incidence rate of late VTE among survivors who have specific demographic risk factors, cancer treatments (i.e. chemotherapy, radiotherapy, surgery including extremity surgery), and other long-term health measures (i.e. severe/disabling chronic health conditions defined as Common Terminology Criteria for Adverse Events [CTCAE] grade 3-4, joint replacement surgery, hospitalizations, second malignant neoplasm [SMN], lower physical activity status, history of pregnancy, oral contraceptive/estrogen replacement) compared to survivors without such factors.

c) **Specific aim 3**

To define the incidence of late (≥5 years post-diagnosis) mortality among survivors who developed VTE, compared to those who did not develop VTE. Note: will separately assess: 1) VTE-specific mortality [CTCAE grade 5] and 2) mortality not related to SMN, progression, or external mortality.

*Hypothesis:* There is a higher incidence rate of late mortality among survivors who developed VTE, compared to those who did not.

5) **Analysis framework:**

a) **Outcomes of interest**

The primary outcome is occurrence of late VTE (≥5 years post-diagnosis), defined as pulmonary embolism or deep vein thrombosis. This will be ascertained using the CTCAE grading system, including affirmative response to #F10 on the expansion baseline survey ("Blood clot in head, lung, arm, leg, or pelvis"), #G10 on 2007 follow-up survey ("Blood clot in head, lung, arm, leg, or pelvis"), #11M on FU2000, or F16 on the original baseline survey or as hospitalization for VTE based on #21 on 2000 follow-up survey ("Have you been admitted to a hospital?"). Survivors who documented an affirmative response to stroke (baseline #F9, baseline expansion #J14, FU2000 #10g, FU2007 #K14) during the same year as the VTE event will not be considered to have had VTE. The secondary outcome will be late mortality, defined in three ways: 1) as VTE-specific mortality [CTCAE grade 5], 2) mortality not related to SMN, progression/recurrence, or external mortality, and 3) all-cause mortality. Time of occurrence (based on age at occurrence) will be incorporated into the analysis for each outcome.

b) **Subject population**

We will include all childhood cancer survivors in the CCSS cohort (diagnosed 1970-99) who participated in the baseline survey. As comparators, we will include all siblings in the CCSS cohort. We will also compare long-term mortality (see above) among participants who developed VTE, compared to those who did not develop VTE.

c) **Exploratory variables**

- Demographic and social variables
  - Age (continuous and categorical; Baseline #A1; ExpBaseline #A1)
  - Sex (categorical; Baseline #A2; ExpBaseline #A2)
  - Race and ethnicity (categorical: non-Hispanic white, non-Hispanic black, Hispanic, other; Baseline #A4, ExpBaseline #A5)

- Chronic conditions
  - Common Terminology Criteria for Adverse Events (CTCAE)[23]
    - No condition
    - Grade 1 condition (mild)
    - Grade 2 condition (moderate)
    - Grade 3 condition (severe)
    - Grade 4 condition (life-threatening or disabling)
    - Grade 5 condition (fatal; secondary outcome: fatal VTE)
  - Tobacco use (categorical: never smoker, former smoker, current smoker; Baseline #N1-2, ExpBaseline #O1-8, LTFU 2003 #L1-8, LTFU 2007 #N7-14)
  - Physical activity (binary: active vs. inactive; Baseline #N9, ExpBaseline #O15, LTFU 2003 #D1-7, LTFU 2007 #N15-21)
    - *Active defined per Centers for Disease Control and Prevention guidelines as: ≥150 minutes/week of moderate intensity physical activity or ≥75 minutes/week of vigorous activity per week*[24]
  - Body mass index (BMI; continuous and categorical: <18.5, 18.5-24.9, 25-29.9, 30.0-34.9, 35.0-39.9, ≥40; Baseline #A10-11, ExpBaseline #A3-4, LTFU 2003 #7-8, LTFU 2007 #A1-2)
    - Calculated *as BMI = (weight [kg]) / (height [m])*$^2$
  - Hospitalizations (binary and ordinal: 0, 1, 2, >2 times; LTFU 2000 #21A-C, LTFU 2005 #A1-2)
  - Reproductive or endocrine variables
    - Pregnancy (binary; Baseline #M9-11, ExpBaseline #N6, LTFU 2000 #19C, LTFU 2003 #N1, LTFU 2007 #F15, Q1)
      - Parity (categorical; Baseline #M10, ExpBaseline #N7, LTFU 2003 #N1-3, LTFU 2007 #Q1-5)
    - Use of oral contraceptive pills or hormone therapy including fertility treatment (binary; Baseline #2-3, ExpBaseline #B8, LTFU 2000 #6C, 19C, LTFU 2007 #C8, F15)
  - Cancer variables
    - Second malignant neoplasm (binary; ExpBaseline #L1, LTFU 2003 #R1, LTFU 2005 #B1, LTFU 2007 #P1)
- Treatment variables (within 5 years of cancer diagnosis)
  - Any surgery (binary; MRAF for any surgery and LTFU 2007 #J1-37 for the below surgeries)
    - Amputation (categorical; Baseline #I1, ExpBaseline #I1, LTFU 2007 #J1)
    - Major joint replacement (categorical; Baseline #I5, ExpBaseline #I5, LTFU 2007 #J5)
    - Limb-sparing procedure (categorical; Baseline #I4, #I6, ExpBaseline #I4, I6, LTFU 2007 #J4, J6)
      - Will review Baseline/ExpBaseline #I6 and LTFU 2007 #J6 procedures to determine if applicable
    - Splenectomy (categorical; ExpBaseline #I18, LTFU 2007 #J18)
    - Nephrectomy (categorical; ExpBaseline #I37, LTFU 2007 #J37)

        - Thrombectomy (categorical; Baseline #I14)
    - Any chemotherapy (binary)
        - Alkylating agent (binary)
            - Cyclophosphamide equivalent dose (CED) score (categorical: 0, 1-3999, 4000-7999, ≥8000mg/m$^2$)[25]
        - Anthracycline (binary)
            - Anthracycline score (categorical: 0, <250, ≥250 mg/m$^2$)[26]
        - Platinum agent (binary)
            - Platinum agent score (categorical: 0, 1, 2, 3)[27]
    - Any radiotherapy
        - Total dose (categorical: 0, <10, 10-19, 20-29, 30-39, 40-49, >49 Gy)
        - Body region dosimetry ~~(continuous)~~:
            - Brain (categorical: 0, <10, 10-19, 20-29, 30-39, 40-49, >49 Gy~~continous, average dose: 0, >0-1, 2-5, 6-10 Gy~~)
            - Chest (categorical: 0, <10, 10-19, 20-29, 30-39, 40-49, >49 Gy ~~continous, average dose: 0, >0-1, 2-5, 6-10 Gy~~)
            - Abdomen/pelvis (categorical: 0, <10, 10-19, 20-29, 30-39, 40-49, >49 Gy~~continous, average dose: 0, >0-1, 2-5, 6-10 Gy~~)
            - Arms (categorical: 0, <10, 10-19, 20-29, 30-39, 40-49, >49 Gy ~~continous, average dose: 0, >0-1, 2-5, 6-10 Gy~~)
            - Legs (categorical: 0, <10, 10-19, 20-29, 30-39, 40-49, >49 Gy~~continous, average dose: 0, >0-1, 2-5, 6-10 Gy~~)
- Medication variables
    - Hormone replacement therapy (see above)
    - Estrogens / Progesterones (see above)
    - Anticoagulants (categorical; including vitamin K antagonists, heparin medications, thrombin inhibitors; Baseline #B8, ExpBaseline #B8, LTFU 2000 #6, LTFU 2007 #C8)

d) **Statistical methods**

We will compare demographic and clinical characteristics between survivors who develop and do not develop VTE. Similarly, we will compare categorical variables and continuous variables between siblings who develop and do not develop VTE. For these initial univariable analyses, categorical variables will be compared between groups (survivors with VTE vs. survivors with no VTE; siblings with VTE vs. siblings with no VTE) using the Chi-square test or Fisher's exact test, when appropriate. Continuous variables will be compared between groups using the two-sample t-test (ANOVA for >2 groups) or Mann-Whitney *U* test (Wilcoxon rank-sum test for >2 groups), for non-normally distributed variables. **(Table 1)**

In the overall cohort (survivors and siblings), cumulative incidence of VTE will be calculated for survivors and siblings. **(Figure 1)** Among survivors (excluding siblings), we will use piecewise exponential models to evaluate the association between late VTE and prior multimodal therapy (including surgery, chemotherapy, and radiotherapy) as well as relevant demographic and clinical factors. **(Table 2)** Analysis will be stratified as needed by

diagnosis, tumor location, and treatment variables. For example, cumulative incidence curves will be calculated for: 1) survivors who underwent surgery as prior treatment, compared to those who did not undergo surgery, 2) survivors with different dose categories of radiotherapy, 3) survivors who received chemotherapy as prior treatment, compared to those who did not receive chemotherapy, 4) survivors with different underlying diseases, and 5) female survivors who have been pregnant ~~or used estrogen/progesterone-containing medications~~, compared to female survivors who have not been pregnant ~~or used estrogen/progesterone-containing medications~~. **(Figures 2A-C, 3)** We will calculate rate ratios for VTE according to risk factors, conditioned on prior treatment with chemotherapy, surgery, or radiotherapy. **(Table 3)**

Because the reporting of medications is restricted to the two years prior to each questionnaire, we will carry out a separate analysis evaluate the association of estrogen/progesterone-containing medications with the primary outcome of VTE using Cox regression models. In these models, relevant medication exposures will be coded as time-dependent covariates and will be set to missing during time periods outside the 2 year windows in which a given subject has data. Effectively, this will mean subjects enter and leave the analysis corresponding to the two years prior to the age at which they responded to each survey. As such, only VTE events during the two years prior to a survey will be utilized in these analyses. Because of the reduced data available in these analyses, this model will be fit separately from those without the medication data.

Finally, among survivors (and siblings, if not precluded by low event occurrence) we will use piecewise exponential models to compare mortality prior to (vs. following) the development of VTE. Mortality will be assessed in three ways: 1) VTE-related mortality, defined as CTCAE grade 5 VTE, 2) mortality not related to cancer progression/recurrence or external cause of mortality, and 3) all-cause mortality. Causes of mortality in the CCSS cohort have been ascertained by the National Death Index.[28] The models used for this analysis will again be adjusted for relevant demographic and clinical variables. Standardized mortality ratios for survivors and siblings before and after VTE will be calculated based on the expected number of deaths for age-, sex-, race/ethnicity-, and year-specific United States mortality rates.[28] (Table 4)

All time-dependent multivariable analyses will be performed by incorporating age as a time-dependent variable because time since diagnosis will be the time scale for the model, however we plan to also use age as a second time variable. Multiple imputation will be employed when a participant experiences VTE, but age at time of VTE is missing. Mortality will be considered a competing risk to VTE. As such, cumulative incidence curves of death will be plotted alongside those of VTE. Person-years at risk for VTE will be calculated and will start at cohort entry (at 5 years since diagnosis of childhood cancer) and end at the earliest occurrence of censoring, VTE, or death.

e) **Examples of tables and figures**

**Table 1.** Comparison of demographic and treatment characteristics of childhood cancer survivors and siblings who did and did not develop venous thromboembolism (VTE)

| | ***Survivors*** | | | | ***Siblings*** | | | |
|---|---|---|---|---|---|---|---|---|
| *Variable* | *Overall* | *VTE* | *No VTE* | *P* | *Overall* | *VTE* | *No VTE* | P |
| Female | | | | | | | | |
| Age at diagnosis, y | | | | | | | | |

- 0-3
- 4-9
- 10-14
- 15-20

Race/ethnicity
- Non-Hispanic white
- Non-Hispanic black
- Hispanic
- Other

Cancer diagnosis
- CNS
- Leukemia
- Lymphoma
- Wilms tumor
- Neuroblastoma
- Bone/soft tissue sarcoma
- Other

Surgery
- No
- Yes
  - 1 surgery
  - 2 surgeries
  - >2 surgeries

Extremity surgery

Major joint replacement

Amputation

Splenectomy

Nephrectomy

Childhood cardiac surgery

Any chemotherapy

Alkylating agent CED, $mg/m^2$
- 0
- 1-3999
- 4000-7999
- >7999

Platinum agent score
- 1
- 2
- 3

Anthracycline dose, $mg/m^2$
- None
- <250
- ≥250

Radiotherapy, Gy (total dose)

0 (no radiotherapy)
<10
10-19
20-29
30-39
40-49
>49

Brain radiotherapy, Gy
0 (no radiotherapy)
<10
10-19
20-29 ~~0~~
30-39 ~~>0-1~~
40-49 ~~2-5~~
>49 ~~6-10~~

Chest radiotherapy, Gy
0 (no radiotherapy)
<10
10-19
20-29 ~~0~~
30-39 ~~>0-1~~
40-49 ~~2-5~~
>49 ~~6-10~~

Abdomen/Pelvis radiotherapy, Gy
0 (no radiotherapy)
<10
10-19
20-29 ~~0~~
30-39 ~~>0-1~~
40-49 ~~2-5~~
>49 ~~6-10~~

Arms radiotherapy, Gy
0 (no radiotherapy)
<10
10-19
20-29 ~~0~~
30-39 ~~>0-1~~
40-49 ~~2-5~~
>49 ~~6-10~~

Legs radiotherapy, Gy
0 (no radiotherapy)
<10
10-19
20-29 ~~0~~
30-39 ~~>0-1~~

| | |
|---|---|
| 40-49 2-5 | |
| >49 6-10 | |
| Hormonal medications | |
| Prior pregnancy | |
| Second malignant neoplasm | |
| Low physical activity | |
| Tobacco use | |
| Current | |
| Former | |
| Never | |
| BMI | |
| <18.5 | |
| 18.5-24.9 | |
| 25-29.0 | |
| 30-34.9 | |
| 35-40 | |
| >40 | |
| Year of diagnosis | |
| 1970-1974 | |
| 1975-1979 | |
| 1980-1984 | |
| 1985-1989 | |
| 1990-1994 | |
| 1995-1999 | |
| Follow-up, years (median, IQR) | |
| No. of severe/disabling/life-threatening chronic conditions (CTCAE grade 3-4) | |
| 0 | |
| 1 | |
| ≥2 | |

*CED*, cyclophosphamide equivalent dose; *CNS*, central nervous system; IQR, interquartile range

**Table 2.** Multivariable analysis of factors associated with venous thromboembolism (VTE) among childhood cancer survivors

| *Variable* | *Hazard ratio* | *95% Confidence interval* | P |
|---|---|---|---|
| Cancer diagnosis | | | |
| CNS | | | |
| Leukemia | | | |
| Lymphoma | | | |
| Wilms tumor | | | |
| Neuroblastoma | | | |

- Bone/soft tissue sarcoma
- Other

Surgery
- No
- Yes
  - 1 surgery
  - 2 surgeries
  - >2 surgeries

Extremity surgery
Major joint replacement
Amputation
Splenectomy
Nephrectomy
Childhood cardiac surgery
Chemotherapy
Alkylating agent CED, $mg/m^2$
- 0
- 1-3999
- 4000-7999
- >7999

Platinum agent score
- 1
- 2
- 3

Radiotherapy, Gy (total dose)
- 0 (no radiotherapy)
- <10
- 10-19
- 20-29
- 30-39
- 40-49
- >49

Brain radiotherapy, Gy
- 0 (no radiotherapy)
- <10
- 10-19
- 20-29~~—0~~
- 30-39~~—>0 1~~
- 40-49~~—2 5~~
- >49~~—6 10~~

Chest radiotherapy, Gy
- 0 (no radiotherapy)
- <10
- 10-19
- 20-29~~—0~~
- 30-39~~—>0 1~~

- 40-49 2-5
- >49 6-10

Abdomen/Pelvis radiotherapy, Gy
- 0 (no radiotherapy)
- <10
- 10-19
- 20-29 0
- 30-39 >0-1
- 40-49 2-5
- >49 6-10

Arms radiotherapy, Gy
- 0 (no radiotherapy)
- <10
- 10-19
- 20-29 0
- 30-39 >0-1
- 40-49 2-5
- >49 6-10

Legs radiotherapy, Gy
- 0 (no radiotherapy)
- <10
- 10-19
- 20-29 0
- 30-39 >0-1
- 40-49 2-5
- >49 6-10

~~Hormonal medications~~

Prior pregnancy

Second malignant neoplasm

Low physical activity

Tobacco use
- Current
- Former
- Never

BMI
- <18.5
- 18.5-25
- 25-30
- 30-35
- 35-40
- >40

Female

Race/ethnicity
- Non-Hispanic white
- Non-Hispanic black

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| | |
|---|---|
| Hispanic | |
| Other | |
| Year of diagnosis | |
| 1970-1974 | |
| 1975-1979 | |
| 1980-1984 | |
| 1985-1989 | |
| 1990-1994 | |
| 1995-1999 | |
| Age at diagnosis, y | |
| 0-3 | |
| 4-9 | |
| 10-14 | |
| 15-20 | |
| No. of severe/disabling/life-threatening chronic conditions (CTCAE grade 3-4) | |
| 0 | |
| 1 | |
| ≥2 | |

*BMI*, body mass index; *CED*, cyclophosphamide equivalent dose; *CNS*, central nervous system

**Table 3.** Treatment-specific rate ratios for venous thromboembolism (VTE) among childhood cancer survivors

| | ***Radiotherapy*** | | | ***Extremity surgery*** | | | ***Chemotherapy*** | | |
|---|---|---|---|---|---|---|---|---|---|
| *Variable* | *Rate ratio* | *95% CI* | P | *Rate ratio* | *95% CI* | P | *Rate ratio* | *95% CI* | P |
| Number of risk factors | | | | | | | | | |
| 6 | | | | | | | | | |
| Any 5 | | | | | | | | | |
| Any 4 | | | | | | | | | |
| Any 3 | | | | | | | | | |
| Any 2 | | | | | | | | | |
| Any 1 | | | | | | | | | |
| None | 1.0 | | | 1.0 | | | 1.0 | | |
| Individual and combinations of risk factors | | | | | | | | | |
| Obesity | | | | | | | | | |
| Sedentary | | | | | | | | | |
| Pregnancy/ Hormones | | | | | | | | | |
| CTCAE 3-4 | | | | | | | | | |
| SMN | | | | | | | | | |
| Tobacco | | | | | | | | | |

| | | | |
|---|---|---|---|
| SMN + obesity | | | |
| SMN + tobacco | | | |
| SMN + sedentary | | | |
| No risk factors | 1.0 | 1.0 | 1.0 |

*CI*, confidence interval; *CTCAE*, Common Terminology Criteria for Adverse Events; *SMN*, second malignant neoplasm

**Table 4.** Standardized mortality ratios (SMR) of childhood cancer survivors and siblings by VTE status

| | ***Survivors*** | | | | ***Siblings*** | | | |
|---|---|---|---|---|---|---|---|---|
| *Variable* | *N* | *Deaths* | *SMR* | *95% Confidence interval* | *N* | *Deaths* | *SMR* | *95% Confidence interval* |
| VTE | | | | | | | | |
| No VTE | | | | | | | | |

*SMR*, standardized mortality ratio; *VTE*, venous thromboembolism

**Table 5.** Association between estrogen- or progesterone-containing medication and VTE among childhood cancer survivors and siblings

| | ***Survivors*** | | ***Siblings*** | |
|---|---|---|---|---|
| *Variable* | *Hazard Ratio (95% CI)* | P | *Hazard Ratio (95% CI)* | P |
| Estrogen/progesterone-containing medication | | | | |
| No | 1.0 | | 1.0 | |
| Yes | | | | |

*CI*, confidence interval

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**Figure 1.** Cumulative incidence of venous thromboembolism among childhood cancer survivors vs. siblings, with mortality as a competing risk.

**Figure 2A.** Cumulative incidence of venous thromboembolism among childhood cancer survivors with surgery as prior treatment vs. no surgery as prior treatment, with mortality as a competing risk.

**Figure 2B.** Cumulative incidence of venous thromboembolism among childhood cancer survivors by radiotherapy dose categories, with mortality as a competing risk.

**Figure 2C.** Cumulative incidence of venous thromboembolism among childhood cancer survivors with chemotherapy as prior treatment vs. no chemotherapy as prior treatment, with mortality as a competing risk.

**Figure 3.** Cumulative incidence of venous thromboembolism among childhood cancer survivors by type of first cancer diagnosis, with mortality as a competing risk.

**Figure 4.** Cumulative incidence of mortality among childhood cancer survivors who did vs. did not develop venous thromboembolism.

6) **Special consideration:** N/A

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