Title: Subsequent genitourinary cancers among survivors of childhood cancer: a report from the Childhood Cancer Survivor Study (CCSS)

Working Groups: Subsequent Neoplasm (primary) and Biostatistics/Epidemiology (secondary)

Investigators

Anne Boldt, MD	boldt085@umn.edu
Cindy Im, PhD	imcindy@umn.edu
Takuto Takahashi, MD, PhD	Takuto.Takahashi@childrens.harvard.edu
Rebecca Howell, PhD	rhowell@mdanderson.org
Michael Arnold, MD	Michael.Arnold@childrenscolorado.org
Kenneth Liao, MS	liao0265@umn.edu
Vikki Nolan, PhD	Vikki.Nolan2@stjude.org
Greg Armstrong, MD, MSCE	Greg.Armstrong@stjude.org
Joseph Neglia, MD, MPH	jneglia@umn.edu
Lucie Turcotte, MD, MPH, MS	turc0023@umn.edu

Background and Rationale

Approximately 15,000 pediatric patients receive a cancer diagnosis each year in the United States[1] and current 5-year survival rates are estimated to be 85%, with > 511,000 survivors of childhood cancer currently living in the US as of 2021.[2,3] A recent analysis demonstrated an increase in average life expectancy for childhood cancer survivors from approximately 48 years in the 1970s to 57 years for those diagnosed in the 1990s.[4] With the significant increase in the number of survivors of childhood cancer, enhanced understanding of the risks for subsequent malignancies becomes imperative for their care. Compared to the general population, childhood cancer survivors experience 3 times the number of severe or life-threatening health conditions by the age of 50 years[5] and they have a 5.4-fold increased risk for subsequent malignant neoplasms (SMNs) compared to the general population,[6] and that risk persists as survivors age into the fifth, sixth and seventh decade of life.[7,8] SMNs are defined as new, non-recurrent invasive cancers. Subsequent breast and colorectal cancers are among the few SMNs that have established screening guidelines based on childhood cancer treatment exposures.[9, 10] However, screening guidelines for genitourinary (GU) cancers are not currently represented in the COG Long Term Follow Up Guidelines aside from patient monitoring for gross hematuria in those that have received pelvic or lower spine radiation and alkylating agents. GU malignancies include cancers affecting the kidneys, bladder, prostate, ureters or urethra. Currently, there are few studies highlighting cumulative incidence, risk in cancer survivors compared to the general population, or documentation of specific risk factors for the development of this particular subgroup of SMNs. One previous analysis from the Childhood Cancer Survivor Study (CCSS) demonstrated a significantly increased risk for renal cell carcinoma among survivors compared to the general population, with highest risk associated with renal-directed radiotherapy and platinum chemotherapy exposure.[11] However, this study had a small number of events and did not explore other GU malignancies. One additional analysis from the British CCSS did discuss secondary bladder malignancies and showed 0.4% incidence by the age of 55, though this cohort is likely underpowered in high risk ages as the median age for cyclophosphamide

associated secondary bladder malignancies is 55 years of age.[12, 13] This study also did not include information regarding chemotherapy exposure.[12] Given the lack of data surrounding the development of genitourinary cancers as a subsequent malignancy in pediatric cancer survivors, the goal of this study is to determine the cumulative incidence, risk compared to the general population, and assess possible risk factors for the development of subsequent genitourinary malignancies. This data may shape long term follow up guidelines and screening recommendations for subsequent genitourinary malignancies.

Specific Aims and Hypotheses

Aims

1. Quantify the cumulative incidence of genitourinary cancers (kidney, bladder, prostate, urethra, ureter) among survivors of childhood cancer. Further quantify cumulative incidence by primary malignancy type.
2. Compare the incidence of genitourinary cancers in childhood cancer survivors with that of the sex-/age-/year-matched general population.
3. Assess incidence of secondary GU malignancies by demographics (age, sex, race)
4. Assess the association between various therapeutic exposures and the development of subsequent genitourinary malignancies
    a. Alkylating agents
        i. Cyclophosphamide will be analyzed within the alkylating agent group as well as separately
    b. Epipodophyllotoxins
    c. Platinating agents
    d. Anthracyclines
    e. Methotrexate
    f. Radiation: by location (abdominal, pelvic radiation, TBI, or spinal) and cumulative dose (Gy)
5. Assess the impact of socioeconomic status and lifestyle factors on the development of secondary genitourinary malignancies in pediatric cancer survivors
6. Assess conditional mortality of survivors due to subsequent GU malignancies compared to the matched general population

Hypotheses

1. Compared to the general population, pediatric cancer survivors are at a higher risk of development of a genitourinary malignancy
2. Higher doses of alkylating agents, platinating agents, and abdominal/pelvic radiation are associated with higher risk of developing secondary genitourinary malignancy
3. Conditional mortality from secondary GU malignancies is higher in cancer survivors than the general population

Analysis Framework

A. Population of interest: This analysis will include survivors enrolled in the CCSS cohort with all included cancer diagnoses from 1970-1999.

a. Descriptive characteristics of cohort including age at diagnosis, sex, race, ethnicity, childhood malignancy, attained age, time from initial diagnosis, decade of diagnosis (1970s, 80s, 90s)
b. Environmental/lifestyle exposures: smoking status (ever smoked more than 100 cigarettes, yes/no)[14], alcohol use (risky drinking, yes/no or heavy drinking, yes/no), physical activity (maximum metabolic equivalent of task hours/week [MET-h/wk]), BMI (time-varying prior to outcomes of interest), lifestyle score (0-4).
c. Sociodemographic characteristics:
    i. Neighborhood level: area deprivation index (ADI), social vulnerability index (SVI)
    ii. Individual level: Educational attainment, household income, health insurance status

B. Therapeutic exposures: Treatments for these patients may include chemotherapy, HCT, and/or radiation therapy.
    a. Specific chemotherapy groups of interest include anthracyclines[11], epipodophyllotoxins, alkylating agents[11], and platinating agents.
    b. Radiation information includes TBI (yes/no), thoracic spine radiation (yes/no), lumbar spine radiation (yes/no), abdominal radiation (yes/no), pelvic radiation (yes/no), and maximum dose to exposed body region
C. Outcomes of interest: Subsequent GU malignancy (kidneys, bladder, prostate, ureters or urethra) cumulative incidence, risk in cancer survivors compared to the general population (standardized incidence ratios [SIRs]), and specific risk factors for the development of genitourinary secondary malignancies. Conditional mortality of survivors with GU malignancies.

Statistical Approach

1. Summarize the distribution of GU cancer types by age, sex, race, treatment exposure, alcohol use, smoking status.
2. Descriptive statistics: Present the clinical characteristics and treatment exposures of survivors with subsequent GU malignancies and compare to remainder of CCSS cohort without subsequent GU malignancies
3. Cumulative incidence: Estimate cumulative incidence and 95% confidence intervals for subsequent GU malignancies. Time from five years post-diagnosis will be used as the time scale and death will be treated as a competing risk event.
4. Absolute excess risk (AER) and standardized incidence ratios (SIR) and 95% confidence intervals for subsequent GU malignancies will be calculated, using age, sex, race, and calendar year U.S. cancer rates from SEER to evaluate the expected number of events. SIRs will be reported by primary childhood cancer diagnosis, lifestyle factors and treatment exposure. AERs will be reported per 1000 person-years. This will be completed with disease matching as long as sample size will allow for it.
5. Multivariable models: Cox proportional hazards models will be used to assess associations between patient and treatment characteristics and the risk of subsequent GU malignancies. Multivariable analysis will be limited to survivor characteristics and treatment variables with univariate association at p-value less than or equal to 0.2. Age

will be used as the time scale with entry to analysis at the age at cohort entry and censoring at age of the last follow-up or death.

Proposed Tables and Figures

Table. Characteristics of survivors with and without subsequent GU malignancy.

	Total cohort (N=)	Survivors with secondary GU malignancy	Survivors without secondary GU malignancy
Mean age at primary diagnosis, years			
Age at primary diagnosis, years 0-4 y 5-9 y 10-14 y ≥ 15 y			
Sex Male Female			
Race and ethnicity Non-Hispanic White Non-Hispanic Black Hispanic Asian Other			
Decade of diagnosis 1970-79 1980-89 1990-99			
Childhood cancer diagnosis ALL AML Other leukemia Hodgkin lymphoma Non-Hodgkin lymphoma CNS malignancy Wilms tumor Osteosarcoma Ewing sarcoma			

Other bone cancer Neuroblastoma Soft tissue sarcoma			
Chemotherapy Anthracycline (mg/m2) None 1-100 101-300 >300 Epipodophyllotoxin (mg/m2) None 1-1000 1001-4000 >4000 Alkylating agent (CED) (mg/m2) None 1-3999 4000-7999 8000+ Platinum agents (mg/m2) None 1-400 401-750 >750 Methotrexate None Any			
Radiation None Abdominal radiation 0-10 Gy 10.1-20 Gy 20.1-35 Gy > 35 Gy Pelvic radiation			

0-10 Gy 10.1-20 Gy 20.1-35 Gy > 35 Gy Spinal radiation (thoracic or lumbar) 0-10 Gy 10.1-20 Gy 20.1-35 Gy > 35 Gy Total body irradiation 0-10 Gy 10.1-20 Gy 20.1-35 Gy > 35 Gy Maximum radiation dose to any body region (Gy) (range) 0-10 Gy 10.1-20 Gy 20.1-35 Gy > 35 Gy			
Hematopoietic cell transplantation None Autologous Allogeneic			
Smoking status Never smoker Current smoker Ever smoked			
Heavy Drinking* Yes No			
Risky Drinking* Yes No			
Vital status Alive Deceased			
Survival after childhood cancer			

diagnosis, years 5-9 y 10-14 y 15-19 y 20-24 y 25-29 y 30-34 y ≥35 y			
Number of person-years since cohort entry			
Mean years of follow up from diagnosis, years			

*Risky drinking defined as > 6 per day for men and > 5 per day for women at least once per month in the last year. Heavy drinking defined as > 4 drinks per day or 14 per week for men, > 3 per day, or 7 per week for women.

Table. Cumulative incidence at 20 years, SIR, and AER per 1000 person years for subsequent GU malignancies (by childhood cancer diagnosis and/or treatment exposures).

Characteristic	Number observed	Number expected	SIR (95% CI)	AER (95% CI)	Cumulative Incidence % (95% CI)
All cases					

Table. Multivariable analyses of subsequent GU malignancy.

Characteristic	Hazard ratio (95% CI)	p-value
Gender Male Female		
Age at primary diagnosis, years 0-4 y 5-9 y 10-14 y ≥ 15 y		
Any Radiation 0-10 Gy 10.1-20 Gy		

20.1-35 Gy > 35 Gy		
Total body radiation 0-10 Gy 10.1-20 Gy 20.1-35 Gy > 35 Gy		
Abdominal radiation (Gy) 0-10 Gy 10.1-20 Gy 20.1-35 Gy > 35 Gy		
Pelvic radiation (Gy) 0-10 Gy 10.1-20 Gy 20.1-35 Gy > 35 Gy		
Spinal radiation (thoracic + lumbar) (Gy) 0-10 Gy 10.1-20 Gy 20.1-35 Gy > 35 Gy		
Alkylating agent CED (mg/m2) None 1-3999 4000-7999 8000+		
Anthracycline CD (mg/m2) None 1-100 101-300 >300		
Epipodophyllotoxin CD (mg/m2) None 1-1000 1001-4000 >4000		

Platinum agents CD (mg/m2) None 1-400 401-750 >750		
Smoking status Current Former Never		

Figure. Cumulative incidence and standardized incidence ratios for subsequent GU malignancy.

Figure. Risk factors for development of subsequent GU malignant neoplasm. Multivariate models assessed demographic and treatment-related risk factors for development of subsequent GU malignancies. Shown are forest plots for the association of primary childhood cancer diagnosis, total radiotherapy dose exposures, radiotherapy location exposure, and chemotherapy agent exposures with risk for subsequent GU malignancy.

Figure. Mortality associated with subsequent GU malignant neoplasm.

References

1. Siegel, D. A., King, J. B., Lupo, P. J., Durbin, E. B., Tai, E., Mills, K., ... & Wilson, R. J. (2023). Counts, incidence rates, and trends of pediatric cancer in the United States, 2003-2019. *JNCI: Journal of the National Cancer Institute*, *115*(11), 1337-1354.
2. Goldstick, J. E., Cunningham, R. M., & Carter, P. M. (2022). Current causes of death in children and adolescents in the United States. *New England journal of medicine*, *386*(20), 1955-1956.
3. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2018/, based on November 2020 SEER data submission, posted to the SEER web site, April 2021.
4. Yeh, J. M., Ward, Z. J., Chaudhry, A., Liu, Q., Yasui, Y., Armstrong, G. T., ... & Diller, L. (2020). Life expectancy of adult survivors of childhood cancer over 3 decades. *JAMA oncology*, *6*(3), 350-357.
5. Narayan, H. K., Narezkina, A., & Ehrhardt, M. J. (2023). Second Malignancies and Cardiovascular Disease in Childhood Cancer Survivors: Double Trouble. *Cardio Oncology*, *5*(6), 804-806.

6. Turcotte, L. M., Liu, Q. I., Yasui, Y., Arnold, M. A., Hammond, S., Howell, R. M., ... & Neglia, J. P. (2017). Temporal trends in treatment and subsequent neoplasm risk among 5-year survivors of childhood cancer, 1970-2015. *Jama*, *317*(8), 814-824.
7. 1. Bhandari R, Chen Y, Chow EJ, Howell RM, Kenney LB, Krull KR, Leisenring W, Nathan PC, Neglia JP, Ness KK, Oeffinger KC, Snyder C, Turcotte LM, Wong FL, Yasui Y, Armstrong GT, Armenian SH. Health Outcomes Beyond Age 50 Years in Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. J Clin Oncol. 2025 Sep 20;43(27):2998-3010.
8. 2. Turcotte LM, Whitton JA, Friedman DL, et al: Risk of Subsequent Neoplasms During the Fifth and Sixth Decades of Life in the Childhood Cancer Survivor Study Cohort. J Clin Oncol 33:3568-75, 2015
9. Mulder RL, Hudson MM, Bhatia S, et al: Updated Breast Cancer Surveillance Recommendations for Female Survivors of Childhood, Adolescent, and Young Adult Cancer From the International Guideline Harmonization Group. J Clin Oncol 38:4194-4207, 2020
10. Children's Oncology Group. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers, Version 6.0. Monrovia, CA: Children's Oncology Group; October2023; Available on-line: www.survivorshipguidelines.org.
11. Wilson CL, Ness KK, Neglia JP, Hammond S, Shnorhavorian M, Leisenring WL, Stovall M, Robison LL, Armstrong GT. Renal carcinoma after childhood cancer: a report from the childhood cancer survivor study. J Natl Cancer Inst. 2013 Apr 3;105(7):504-8. doi: 10.1093/jnci/djt014. Epub 2013 Mar 20. PMID: 23515901; PMCID: PMC3691945.
12. Frobisher C, Gurung PM, Leiper A, Reulen RC, Winter DL, Taylor AJ, Lancashire ER, Woodhouse CR, Hawkins MM. Risk of bladder tumours after childhood cancer: the British Childhood Cancer Survivor Study. BJU Int. 2010 Oct;106(7):1060-9. doi: 10.1111/j.1464-410X.2010.09224.x. Epub 2010 Feb 22. PMID: 20184574.
13. Chou WH, McGregor B, Schmidt A, Carvalho FLF, Hirsch MS, Chang SL, Kibel A, Mossanen M. Cyclophosphamide-associated bladder cancers and considerations for survivorship care: A systematic review. Urol Oncol. 2021 Oct;39(10):678-685. doi: 10.1016/j.urolonc.2021.05.017. Epub 2021 Jun 13. PMID: 34134927.
14. Dixon SB, Liu Q, Chow EJ, Oeffinger KC, Nathan PC, Howell RM, Leisenring WM, Ehrhardt MJ, Ness KK, Krull KR, Mertens AC, Hudson MM, Robison LL, Yasui Y, Armstrong GT. Specific causes of excess late mortality and association with modifiable risk factors among survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort. Lancet. 2023 Apr 29;401(10386):1447-1457. doi: 10.1016/S0140-6736(22)02471-0. Epub 2023 Apr 5. PMID: 37030315; PMCID: PMC10149583.