**1) Study Title:** Long-term Gallbladder and Biliary Disease in Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study

**2) Working group and investigators:** The study 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.

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**3) Background and rationale:**

Cholelithiasis is a significant health problem affecting between 10-15% of Americans.[1] Of those with cholelithiasis, between 1-4% will develop symptomatic cholelithiasis and, untreated, about 20% will develop acute cholecystitis.[2, 3] Ultimately, approximately 750,000 cholecystectomies are performed yearly for consequences of cholelithiasis including biliary colic, acute calculous cholecystitis, choledocholithiasis, and gallstone pancreatitis.[4] As a result, the economic burden related to the inpatient and outpatient management of cholelithiasis accounts for direct costs exceeding six billion dollars annually, representing a 20% increase in expenditures over the past three decades.[5]

There is limited data related to the development of early post-treatment cholelithiasis and other biliary disease following multimodality management of childhood cancer. In a 1991 single-center retrospective study, Mahmoud et al. showed that prevalence of cholelithiasis for childhood cancer survivors was 0.4% at 10 years and 1% at 18 years (follow-up time not reported), which is higher than cited rates in the general population. The median interval from primary diagnosis of malignancy to diagnosis of cholelithiasis was 3 years. The specific risk factors contributing to

this finding were not robustly evaluated and the analysis was did not incorporate follow-up time or censoring. The authors concluded that treatment-related factors including ileal resection, parenteral nutrition, abdominal surgery, and abdominal radiation may be associated with increased risk for development of cholelithiasis.[6, 7] Acute acalculous cholecystitis has also been described as an early post-treatment complication in neutropenic patients undergoing myelosuppressive chemotherapy.[8] Due to the relative infrequency of these early complications, the rate of early post-treatment cholecystectomy in this population has not been described.

Childhood cancer survivors are also at risk for gallbladder and biliary tract disease as a late-effect of cancer treatments. Goldsby et al. demonstrated that childhood cancer survivors have a two-fold increased relative risk of developing cholelithiasis compared to siblings.[9] However, risk factors for gallbladder disease among childhood survivors have yet to be carefully elaborated. For example, adult survivors of childhood cancer are also at increased risk for obesity, an established risk factor for cholelithiasis, which may contribute to disease in this population.[10] Furthermore, the timing and rate of cholecystectomy in childhood cancer survivors compared to the general population remains unknown.

The proposed study will characterize the incidence of self-reported, early and late cholelithiasis and related biliary disease among survivors of childhood cancer. We also seek to elaborate the treatment-based risk factors for the development of cholelithiasis and establish a rate for early and late cholecystectomy in the CCSS cohort.

## 4) Specific aims:

### a) Specific aim 1

To determine the cumulative incidence of self-reported cholelithiasis and cholecystectomy among survivors.

*Hypothesis:* There is a higher cumulative incidence of cholelithiasis and cholecystectomy among survivors compared to sibling controls.

### b) Specific aim 2

To identify risk factors for cholelithiasis and cholecystectomy including: body mass index, sex, race, age, prior pregnancy, oral contraceptive use, diabetes, cholesterol disorder, statin use, tobacco use, alcohol use, cirrhosis, chemotherapy, and radiotherapy.

*Hypothesis:* There is a higher relative risk for cholelithiasis and cholecystectomy in survivors who receive anti-neoplastic therapy and/or radiation to the abdomen and harbor other previously described risk factors, compared to sibling controls after adjusting for relevant risk factors.

## 5) Analysis framework:

**a) Outcomes of interest**

The primary outcome in this study will be late (i.e. ≥5 years after diagnosis) development of cholelithiasis. Secondary outcomes will include: late cholecystectomy, early (i.e. within 5 years of cancer diagnosis) development of cholelithiasis, and early cholecystectomy. Early and late outcomes will be analyzed separately to account for selection/survivor bias. These above outcomes will be ascertained in the following manner:

- Cholelithiasis: affirmative response to #H1 or related response to #H2 on the baseline survey. Self-reported response of "gallstones", "cholelithiasis" or other related response to #H3 on the expanded survey, #I3 on LTFU2007, #I4 on LTFU2014, #I9 on LTFU2014
- Cholecystectomy: self-reported response of "cholecystectomy", "gallbladder surgery", "gallbladder removed/removal", "gallstone surgery", or other related response on #I31 on the baseline survey ("Any other surgery"), #I37 on the expansion baseline survey ("Any other surgery"), #J37 on LTFU2007, #J40 on LTFU2014, other related response on #I31 on the baseline survey ("Any other surgery"), #I37 on the expansion baseline survey ("Any other surgery"), #J37 on LTFU2007, #J40 on LTFU2014

Multiple imputation will be used (if required) for age at event among participants who reported the primary and/or secondary outcomes, but not the age at which the respective outcome occurred.

**b) Subject population**

All survivors and siblings in the original and expansion cohorts will be included.

**c) Exploratory variables**

- <u>Demographic and social variables</u>
  - Age at diagnosis (continuous and categorical; Baseline #A1; ExpBaseline #A1)
  - Sex (categorical; Baseline #A2; ExpBaseline #A2)
  - Race (categorical; Baseline #A4; ExpBaseline #A5)

- <u>Additional Variables</u>
  - Treatment era (categorical: 1970-1979, 1980-1989, 1990-1999)
  - Time from initial cancer diagnosis (years; continuous and categorical: 0-5, 6-10, 11-15, 16-20, 21-25, 26-30, 31-35)
  - 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, LTFU 2014 #A1-2)
    - Calculated *as BMI = (weight [kg]) / (height [m])*$^2$

- Tobacco use (categorical: never smoker, former smoker, current smoker; Baseline #N1-2, ExpBaseline #O1-8, LTFU 2003 #L1-8, LTFU 2007 #N7-14, LTFU 2014 #N7-14) and binary (ever/never)
- Alcohol use (continuous： # drinks on a typical day – Baseline #N7. ExpBaseline O11, LTFU2007#N3, LTFU2014 #N3) and binary (ever/never)
- Pregnancy (binary; Baseline #M9-11, ExpBaseline #N6, LTFU 2000 #19C, LTFU 2003 #N1, LTFU 2007 #F15, Q1; LTFU 2014 #V5) and pregnancy within 1 year of developing cholelithiasis
    - Parity (categorical; Baseline #M10, ExpBaseline #N7, LTFU 2003 #N1-3, LTFU 2007 #Q1-5, LTFU 2014 #V5)
- 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)
- Diabetes (categorical:diet controlled, pills/tablets, insulin. Baseline #E5-7, ExpBaseline #E5-7, LTFU2007 #F5-7, LTFU2014#G5-7）
- Hyperlipidemia (categorical: ExpBaseline#F12, LTFU2007#G12，LTFU2014 #F12）
- Hepatitis (categorical: HAV, HBV, HCV, other, Baseline #H4, ExpBaseline #H1, LTFU2007 #I1 LTFU2014 #I1)
- Jaundice (categorical: Baseline #H5)
- Cirrhosis: affirmative response to #H3 on the baseline survey ("Cirrhosis of the liver?"), #H2 on the expansion baseline survey ("Cirrhosis of the liver?"), #I2 on LTFU2007, #I2 on LTFU2014.
- Hepatic Steatosis: affirmative response to #H5 on the expansion baseline survey (Fatty liver?), #I5 on LTFU2007, and #I3 on LTFU2014.
- Hepatic SMN: self-reported response of liver tumor, liver cancer or other related response on #H6 on the baseline survey, affirmative response to #K1 with self-reported response of "liver tumor", "liver cancer" or other related response on #K2 on the baseline survey and/or affirmative response to #K5 with self-reported response of "liver tumor", "liver cancer" or other related response on #K6 on the baseline survey. Self-reported response of "liver tumor", "liver cancer" or other related response on #H3 on the expanded survey. Affirmative response to #L1 with self-reported response of "liver tumor", "liver cancer" or other related response on #L2 on the baseline survey and/or affirmative response to #L6 with self-reported response of liver tumor, liver cancer or other related response on #K7 on the expanded survey. Affirmative response to #17 or #17a with self-reported response of "liver tumor", "liver cancer" or other related response on #L2 on LTFU2000. Affirmative response to #R1 with self-reported response of "liver tumor", "liver cancer" or other related response on LTFU2003. Affirmative response to #B1 with self-reported response of "liver tumor", "liver cancer" or other related response on LTFU2005. Self-reported response of "liver tumor", "liver cancer" or other related response on #I3 and/or affirmative response to #P1 with self-reported response of "liver tumor", "liver cancer" or other related response on LTFU2007. Self-

reported response of "liver tumor", "liver cancer" or other related response on #I4 and/or affirmative response to #S1 with self-reported response of "liver tumor", "liver cancer" or other related response on #S2-S3 on LTFU2014.

- Liver Transplant: self-reported response of "liver transplant" or other related response on #I31 on the baseline survey, affirmative response to #I28 of expanded cohort, LTFU2007#J28, LTFU2014 #J30
- "Any other liver trouble" (Baseline #H6, ExpBaseline #H3, LTFU2007 #I3, LTFU2014 #I4)
- Number of severe/life-threatening (grade 3-4) CTCAE chronic conditions (categorical; 0 vs. 1 vs. 2 vs. 3+)
- "Any other surgery" (Baseline #I31, ExpBaseline #I37, LTFU2007 #J37, LTFU2014 #J40) to include bowel resection

- Treatment variables (within 5 years of cancer diagnosis)
  - Any chemotherapy (binary)
    - Alkylating agent (binary)
      - Cyclophosphamide equivalent dose (CED) score (categorical: 0, 1-3999, 4000-7999, ≥8000mg/m$^2$)[10]
      - Busulfan
    - Anthracycline (binary)
      - Anthracycline score (categorical: 0, <250, ≥250 mg/m$^2$)[12]
    - Platinum agent (binary)
      - Platinum agent score (categorical: 0, 1, 2, 3)[13]
    - Antimetabolites (binary)
      - 6-Mercaptopurine
      - 6-Thioguanine
      - Methotrexate
    - Microtubule targeting drugs
      - Vinca alkaloids (vincristine, vinblastine, vinorelbine)
      - Taxanes (paclitaxel, docetaxel)
    - Topoisomerase inhibitors
      - Topotecan
      - Irinotecan
      - Etoposide
  - Any radiotherapy
    - Body region dosimetry:
      - Any (categorical: 0, <10, 10-19, 20-29, 30-39, 40-49, >49 Gy)
      - maxTD for the abdomen (categorical: 0, <10, 10-19, 20-29, 30-39, 40-49, >49 Gy)
      - TBI
  - Hematopoietic stem cell transplant

- Autologous
- Allogeneic

- Medication variables
  - Cholesterol meds (Baseline #B8,16, ExpBaseline #B8,6, LTFU2003#Q7, LTFU2007 #C8,6, LTFU2014 #C2,6)
  - Chemotherapy (See above)

**d) Statistical methods**

We will describe proportions of demographic and clinical characteristics among childhood cancer survivors (and siblings) who develop and do not develop the primary outcome of cholelithiasis (**Table 1A**). We will also separately perform the above descriptive statistics for the secondary outcome, cholecystectomy **(Table 1B)**. Additionally, as part of a separate analysis, we will collect parallel demographic and clinical data from survivors who develop the outcome of cholelithiasis or cholecystectomy within 5 years of cancer diagnosis (**Table 2A-B**).

In the overall cohort, cumulative incidence of late-occurring cholelithiasis will be calculated for survivors and siblings **(Figure 1A)**. We will also calculate the cumulative incidence of late-occurring cholecystectomy for both survivors and siblings **(Figure 1B)**. Cumulative incidence of late cholelithiasis and cholecystectomy among childhood cancer survivors by radiotherapy dose categories will be calculated **(Figure 2)**. Among the entire cohort of survivors (excluding siblings), we will use multivariable piecewise exponential models to estimate the association between development of late cholelithiasis and prior multimodal cancer treatments (including surgery, chemotherapy, and radiotherapy) as well as relevant demographic and clinical factors **(Table 3A).** Similar analysis will be performed to evaluate the secondary endpoint of late cholecystectomy **(Table 3B).** Finally, we will calculate rate ratios for late cholelithiasis and cholecystectomy according to number of risk factors, to see if there is an additive effect (cumulative burden) of individual risk factors **(Tables 4A and B)**. For analysis of late cholelithiasis and late cholecystectomy, mortality will be treated as a competing risk.

With regard to outcomes that occur within 5 years of diagnosis, we will additionally report prevalence of early cholelithiasis and early cholecystectomy. We will estimate prevalence ratios for the above risk factors and the outcomes of early cholelithiasis and cholecystectomy using generalized linear models (log link function), adjusting for appropriate demographic and clinical variables and accounting for within-family correlation for survivor/sibling analyses (**Tables 5A and B**).

**e) Examples of tables and figures**

**Table 1A.** Comparison of demographic and treatment characteristics of childhood cancer survivors and siblings who did and did not develop late cholelithiasis.

| | ***Survivors*** | | | | ***Siblings*** | | | |
|---|---|---|---|---|---|---|---|---|
| *Variable* | *Overall* | *GS* | *No GS* | *P* | *Overall* | *GS* | *No GS* | P |
| Female | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Age at diagnosis, y | | | | | | | | |
| 0-3 | | | | | | | | |
| 4-9 | | | | | | | | |
| 10-14 | | | | | | | | |
| 15-20 | | | | | | | | |
| Year of diagnosis | | | | | | | | |
| 1970-1979 | | | | | | | | |
| 1980-1989 | | | | | | | | |
| 1990-1999 | | | | | | | | |
| Race/ethnicity | | | | | | | | |
| Non-Hispanic white | | | | | | | | |
| Non-Hispanic black | | | | | | | | |
| Hispanic | | | | | | | | |
| Other | | | | | | | | |
| Cancer diagnosis | | | | | | | | |
| CNS | | | | | | | | |
| Leukemia | | | | | | | | |
| Lymphoma | | | | | | | | |
| Wilms tumor | | | | | | | | |
| Neuroblastoma | | | | | | | | |
| Bone/soft tissue sarcoma | | | | | | | | |
| Other | | | | | | | | |
| Any chemotherapy[a]<br>No<br>Yes | | | | | | | | |
| Alkylating agent CED, mg/m$^{2}$[a] | | | | | | | | |
| 0 | | | | | | | | |
| 1-3999 | | | | | | | | |
| 4000-7999 | | | | | | | | |
| >7999 | | | | | | | | |
| Platinum agent score[10] | | | | | | | | |
| 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| Anthracycline dose, mg/m$^{2}$[a] | | | | | | | | |
| None | | | | | | | | |
| <250 | | | | | | | | |
| ≥250 | | | | | | | | |
| Other chemotherapy agents | | | | | | | | |
| Any radiotherapy, Gy (total dose) [a] | | | | | | | | |
| 0 (no radiotherapy) | | | | | | | | |
| <10 | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 10-19 | | | | | | | | |
| 20-29 | | | | | | | | |
| 30-39 | | | | | | | | |
| 40-49 | | | | | | | | |
| >49 | | | | | | | | |
| MaxTD to abdomen, Gy[a] | | | | | | | | |
| 0 (no radiotherapy) | | | | | | | | |
| <10 | | | | | | | | |
| 10-19 | | | | | | | | |
| 20-29 | | | | | | | | |
| 30-39 | | | | | | | | |
| 40-49 | | | | | | | | |
| >49 | | | | | | | | |
| Hematopoietic stem cell transplant | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Prior pregnancy | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Parity | | | | | | | | |
| 0 | | | | | | | | |
| 1-3 | | | | | | | | |
| >3 | | | | | | | | |
| Tobacco use | | | | | | | | |
| Current | | | | | | | | |
| Former | | | | | | | | |
| Never | | | | | | | | |
| Alcohol use | | | | | | | | |
| Current | | | | | | | | |
| Former | | | | | | | | |
| Never | | | | | | | | |
| BMI, kg/m$^{2}$[b] | | | | | | | | |
| <18.5 | | | | | | | | |
| 18.5-24.9 | | | | | | | | |
| 25-29.0 | | | | | | | | |
| 30-34.9 | | | | | | | | |
| 35-40 | | | | | | | | |
| >40 | | | | | | | | |
| Diabetes | | | | | | | | |
| Never | | | | | | | | |
| Diet-controlled | | | | | | | | |
| Pills/tablets | | | | | | | | |
| Insulin | | | | | | | | |
| Hyperlipidemia | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Never | | | | | | | | |
| Yes, never medication | | | | | | | | |
| Yes, was on medication | | | | | | | | |
| Yes, currently on meds | | | | | | | | |
| History of hepatitis | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Hepatitis A | | | | | | | | |
| Hepatitis B | | | | | | | | |
| Hepatitis C | | | | | | | | |
| Other | | | | | | | | |
| Other liver dysfunction | | | | | | | | |
| No | | | | | | | | |
| Yes | | | | | | | | |
| Follow-up, years (median, IQR) | | | | | | | | |
| No. of severe/disabling/life-threatening chronic conditions (CTCAE grade 3-4) | | | | | | | | |
| 0 | | | | | | | | |
| 1 | | | | | | | | |
| ≥2 | | | | | | | | |

*GS, gallstones; CED*, cyclophosphamide equivalent dose; *RUQ*, right upper quadrant; *BMI*, body mass index; *IQR*, interquartile range

[a]Within 5 years of cancer diagnosis

[b]At last follow-up

**Table 1B.** Comparison of demographic and treatment characteristics of childhood cancer survivors and siblings who did and did not undergo late cholecystectomy

*Note: this table will include the same variables as Table 1A, replacing "GS" and "no GS" with "cholecystectomy" and "no cholecystectomy."*

**Table 2.** Comparison of demographic and treatment characteristics of childhood cancer survivors and siblings who did and did not develop early (within 5 years of diagnosis) post-diagnosis cholelithiasis or undergo early post-diagnosis cholecystectomy*

*Note: this table will include the same variables as Tables 1A-B using data from the separate analysis*

* Prevalence and prevalence ratios to be determined from the associated data.

**Table 3A.** Multivariable analysis of factors associated with late cholelithiasis among childhood cancer survivors

**Table 3B.** Multivariable analysis of factors associated with late cholecystectomy among childhood cancer survivors

**Table 4A.** Treatment-specific rate ratios for late cholelithiasis and late cholecystectomy among childhood cancer survivors

**Table 4B.** Treatment-specific rate ratios for cholelithiasis and cholecystectomy occurring within 5 years of diagnosis among childhood cancer survivors

**Table 5A.** Multivariable analysis of factors associated with early cholelithiasis among childhood cancer survivors

**Table 5B.** Multivariable analysis of factors associated with early cholecystectomy among childhood cancer survivors

*Note: Tables 3A-B, 4A-B, and 5A-B based on the results of stepwise selection procedure.*

**Figure 1A.** Cumulative incidence of late cholelithiasis among childhood cancer survivors vs. siblings

**Figure 1B.** Cumulative incidence of late cholecystectomy among childhood cancer survivors vs. siblings

**Figure 2.** Cumulative incidence of late cholelithiasis and late cholecystectomy among childhood cancer survivors by (risk factors)

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

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