1. STUDY TITLE: Injury-Related Mortality Among Survivors of Childhood Cancer

2. WORKING GROUP AND INVESTIGATORS
   2.1. Working Group: Psychology, Epidemiology/Biostatistics
   2.2. Investigators:

Ibrahim Qaddoumi	ibrahim.qaddoumi@stjude.org
Meg Lubas	mlubas1@radford.edu
Biostatistician	TBA
Yutaka Yasui	yutaka.yasui@stjude.org
Christopher Recklitis	christopher_recklitis@dfci.harvard.edu
Jordan Gilleland Marchak	jgillel@emory.edu
Wendy Leisenring	wleisenr@fredhutch.org
Les Robison	les.robison@stjude.org
Greg Armstrong	greg.armstrong@stjude.org
Kevin Krull	kevin.krull@stjude.org
Tara Brinkman	tara.brinkman@stjude.org

3. BACKGROUND AND RATIONALE

In 2017, unintentional injury (i.e., accidents) was the leading cause of death among Americans ages 1-44[1] and intentional injury (i.e., suicide and homicide) was the second and fourth leading cause of death among individuals ages 10-34 and 35-54,[2] respectively. Rockett *et al.*,[3] reported that between 2000 and 2009, except for motor vehicle accidents, there was an increase in every subtype of unintentional and intentional injury-related mortality. From 1999 to 2017, it is estimated that suicide mortality has increased by over 30%.[2] Despite an increase in both unintentional and intentional injury-related deaths in the US, little is known about the prevalence or associated risk factors of injury-related mortality among adult survivors of childhood cancer.

Unintentional Injury-Related Mortality

The prevalence of unintentional injury-related mortality has been rarely studied among cancer survivors. A Scottish national study reported a nearly four-fold increase in accidental poisonings, and a 1.6-fold increase in all other accidental causes of death among individuals recently diagnosed with cancer (<5 years), compared to an age, sex, and calendar year matched population.[4] This increased risk of accidental deaths remained significantly elevated even when only examining cancer patients without a preceding history of self-harm related behavior, suggesting that aspects of a recent cancer diagnosis or cancer-related treatment may pose a risk to injury-related mortality.[4] Although previous research in CCSS has indicated similar rates of injury-related mortality (i.e., external causes of death) among survivors of childhood cancer compared to the general population,[5,6] these analyses did not take into account competing risks,

as survivors have an elevated risk for all-cause mortality compared to the general population.[5,6] Risk factors associated with injury-related mortality have not been previously studied in CCSS. However, a previous examination of mortality in the CCSS cohort identified two diagnosis groups, AML and CNS tumors (excluding astrocytomas and medulloblastomas), with elevated SMRS for external causes of death.[6] These findings suggest that subgroups of survivors may be at increased risk for injury-related mortality and a further examination of risk factors is needed.

Intentional Injury-Related Mortality

Several studies have reported increased rates of suicide among cancer survivors[7-10] compared to the general population. A retrospective population-based study using SEER data (patients diagnosed between 1973-2015) reported that the standardized mortality ratio of suicide was four times higher among cancer survivors compared to the general population.[9] However most study samples were dominated by survivors of adult onset cancers.[9] Among childhood/young adult survivors, Gunnes et al.[7] reported a more than two-fold risk of death by suicide in a population-based cohort of Norwegian cancer survivors diagnosed before age 25. In a Swedish cohort of nearly 8 million individuals, Lu et al.[8] reported a 1.6-fold increase of suicidal behavior (attempts and completed suicides) in cancer survivors diagnosed in adolescence or young adulthood. Using national death registry data from Denmark, Finland, and Sweden, Korhonen et al.[10] found that childhood cancer survivors had an increased risk of suicide mortality (RR, 1.37) and an overall increased risk of dying from risky health behavior (RR, 1.25), defined as suicides, substance use, accidents, and violence, compared to a non-cancer matched comparison cohort. Despite these findings, previous examinations of mortality among the CCSS and SJLIFE cohort have not reported a higher prevalence of suicidal deaths among adult survivors of childhood cancer.[6,11,12] Thus, more research is needed and, specifically, studies are needed to examine risk factors associated with suicide mortality.

Shared Risk Factors Associated with Unintentional and Intentional Injury-Related Mortality

When examining rates and predictors of injury-related mortality, unintentional and intentional deaths are often grouped together. In part, this is due to the difficulty in distinguishing between the intent of some deaths after they have occurred.[13] Additionally, psychological theories pose the potential for shared mechanisms between the two causes of death (e.g., indirect or sub-intentional self-destructive behaviors).[14,15] Several shared risk factors have been identified when comparing intentional and unintentional injury-related deaths in large cohorts.[14,16,17] A CCSS report by Brinkman et al.[11] indicated that the risk of all-cause mortality was greater in survivors with a history of suicidal ideation compared to those without. Moreover, survivors with a history of suicidal ideation had a 2.4-fold increase in mortality related to external causes of death.[11] It is unknown whether this finding represents a high occurrence of misclassified deaths or the potential for overlapping etiologies. Thus, in this study we propose to examine both shared and independent risk factors associated with external causes of death in the CCSS cohort by

examining all external causes of death, then conducting subgroup analyses for intentional deaths (suicide) and unintentional deaths (MVA, unintentional falls, unintentional poisoning).

Purpose of the Study

Whether adult survivors of childhood cancer are at increased risk for injury-related mortality is largely unknown and even less is known about the risk factors associated with these deaths among this vulnerable population. Subgroups of long-term survivors who experience cognitive, psychological and physical late effects may be at increased risk for injury-related mortality. Examining the prevalence and risk factors associated with external deaths in the CCSS cohort can help inform strategies to prevent such deaths.

3. SPECIFIC AIMS

Aim 1: To compare the rates of external causes of mortality in the CCSS cohort to the general population. We will examine rates for all deaths classified as due to external causes, and then for three subgroups (data permitting): intentional (suicide), homicide, and unintentional (MVA, unintentional falls, unintentional poisoning, other).

Hypothesis 1a: Survivors will have significant excess risk of external cause mortality, relative to the general US population (matched by age, sex, race, and calendar year).

Hypothesis 1b: Survivors will have significant decreased risk of suicide mortality, relative to the general US population (matched by age, sex, race, and calendar year).

Hypothesis 1c: Survivors will have an equal risk of death due to homicide, relative to the general US population (matched by age, sex, race, and calendar year).

Hypothesis 1d: Survivors will have significant excess risk of unintentional injury-related mortality (i.e. MVA, unintentional falls, unintentional poisoning), relative to the general US population (matched by age, sex, race, and calendar year).

Aim 2.1: To examine demographic, treatment, and health-related factors that may be associated with external causes of mortality in the CCSS cohort. We will examine external causes of death overall, then examine risk factors associated with suicide mortality, and risk factors associated with unintentional injury-related mortality.

Hypothesis 2.1a: Subgroups of survivors (e.g., males, CNS tumors, with pain, with depression) will be at increased risk for all external causes of death.

Hypothesis 2.1b: Subgroups of survivors (e.g., males, with pain, with depression) will be at increased risk for intentional injury-related mortality (suicide).

Hypothesis 2.1c: Subgroups of survivors will be at increased risk for unintentional injury-related mortality (MVA, unintentional falls, unintentional poisoning, other).

Aim 2.2 (exploratory): To examine the association between neurocognitive impairment and external causes of death (excluding homicide) among a subset of survivors who completed the NCQ measure in CCSS. Age, race/ethnicity, sex, and time since diagnosis will be adjusted.

Hypothesis 2.2: Neurocognitive impairment in the domain of emotional regulation will be associated with a higher prevalence of injury-related mortality among survivors. We will examine all external causes of death as the outcome, grouping intentional and unintentional injury-related mortality together.

Aim 3: To examine the rate of cause-specific mortality among survivors who endorsed suicide ideation or psychological distress (e.g., depression, somatization, or anxiety).

Hypothesis 3: Survivors who endorsed suicide ideation and/or psychological distress on their baseline surveys will have a higher subsequent mortality rate due to external causes, compared to survivors who did not endorse these measures on their baseline survey.

4. ANALYSIS FRAMEWORK

4.1. Overview: We plan to examine the rate of external causes of death in the CCSS cohort, by comparing the prevalence of external deaths in survivors compared to the general population. Additionally, we aim to identify demographic, treatment and health-related factors unique to cancer survivors that may be associated with an increased rate of injury-related mortality.

4.2. Population: All survivors eligible for CCSS (including non-participants) (Aim 1).

For aims 2 & 3, the analysis will include CCSS participants who completed the baseline questionnaire in either the original or expansion CCSS cohort prior to their death, we will exclude survivors with proxy data. Survivors whose baseline questionnaires were completed after they died will be excluded for aims 2 & 3 analyses. For exploratory aim 2.2, we will examine external causes of mortality among a subgroup of survivors that completed the CCSS-NCQ at either FU2 or FU5.

5.3 Outcome of interests: Deaths due to external causes.
External causes of death will be examined as an overall group. If data permits, we also plan to examine intentional (suicide) and unintentional (MVA, accidental poisonings, falls) separately for aims 1, 2.1, and 3.
*Homicide is included in aim 1 but will be excluded for aims 2-3 unless we find that there is a higher prevalence of homicide among survivors compared to the general population (though previous mortality papers in CCSS have not indicated this).

5.4 Primary Predictors

Demographic Factors

- Sex (A2)
  - Male
  - Female
- Race/Ethnicity (A4, A4a)
  - White NH
  - Black NH
  - Hispanic
  - Others
- Health Insurance (public, private/military, none) (Questions Q2, and Q3)
- Employment (full-time, part-time, retired, disabled, unemployed) (Questions O5-O7)
- Marriage (married/living as married, single/widowed/divorced) (Questions L1-L3)
- Educational attainment (< high school, completed high school, training after high school/some college, college graduate/post graduate) (Questions O1-3)
- House Income (less than $19,999; $20,00 – 39,000; $40,000-$60,000; over $60,000) (Q8)

Cancer-Related Factors

- Age at diagnosis, Years (continuous)
- Age during follow up, Years
- Treatment Era
  - 1970s
  - 1980s
  - 1990s
- Cancer diagnosis
  - CNS Tumors
    - Astrocytoma
    - Medulloblastoma
    - Ependymoma
  - Leukemia
    - ALL
    - AML
  - Hodgkin lymphoma
  - Non-Hodgkin lymphoma
  - Wilms

- o Neuroblastoma
- o Soft tissue sarcoma
- o Bone tumors
- Chemotherapy variables (Yes/No)
    - o Anthracyclines
    - o Alkylating agents
    - o Antimetabolites
        - o Methotrexate
        - o Cytarabine
    - o Corticosteroids
    - o Vina Alkaloids & Heavy Metals
    - o Platinum based agents
- Radiation variables
    - o Cranial
        - ▪ 0-29 Gy
            - - Focal
            - - Craniospinal
        - ▪ 30-49 Gy
            - - Focal
            - - Craniospinal
        - ▪ 50 and more Gy
            - - Focal
            - - Craniospinal
    - o Other bodily
        - ▪ Yes
        - ▪ No

Health-Related Factors

- Suicide ideation question (item 17 of BSI-18)
- Depression (items 8, 2, 5, 14, 11 of BSI-18) *because suicide ideation will be explored separately, we will not include item 17 in the calculation of the depression subscale, we will treat item 17 as missing
- Cancer Related Pain (J36)
- Smoking (N1, N1a, N1c, N1d)
- Alcohol (N3, N4, N6, N7)
- Physical inactivity (N9)
- Medications (B8)
    - o Psychiatric medications (15)
    - o Hormonal therapy (3,4,6)

- o Pain medication (opioid analgesics) (9)
- o Anti-seizure drugs (11)
- o Other
- o None
- Health status (number of CTCAE conditions, grades 3-4)
- Subsequent Malignant Neoplasm (y/n)
- Self-reported health (N15)
- Fear of Recurrence (R3)
- Sensory loss (C1-7, C8-15)
  - o Hearing
  - o Vision
  - o (Both)

Primary Predictor for Sub-aim

- Neurocognitive impairment was assessed using the Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ; FU2: J1-J25, FU5: Q1-Q33). The CCSS-NCQ was developed and validated for use in cancer survivors and assesses four specific domains: task efficiency, emotional regulation, organization, and memory. Scores for each of the four domains will be operationalized as binary variables (impaired vs not) for exploratory aim 2.2. Participants will be considered impaired if their score is ≥ the 90th percentile based on values obtained in the sibling cohort.

5. ANALYSIS APPROACH

Aim 1 Sex-specific SMR

Standardized mortality ratios (SMRs) for external causes of death will be computed to compare CCSS mortality with that expected in the age-race/ethnicity-calendar-year-matched US population for each sex of survivors.

Aim 2.1
The associations between injury-related mortality and demographic, diagnosis, treatment, and health-related risk factors will be examined using multivariable piecewise exponential models to estimate rate ratios and corresponding 95 CIs. Depending on the available data, we will likely examine these associations in separate models.

  Diagnosis model adjusted for age, sex, race/ethnicity
  Treatment model adjusted for age, sex, race/ethnicity
  Health/psychological risk factors adjusted for age, sex, race/ethnicity: these variables are assessed at multiple time points; thus, we will create time-dependent variables.

*As we plan to examine treatment effects on external causes of mortality, if any associations are observed, then we may look at temporal changes in the cohort (era effects).

Exploratory Aim 2.2

The associations between injury-related mortality and neurocognitive impairment in the domain of emotional regulation will be examined using multivariable piecewise exponential models to estimate rate ratios and corresponding 95 CIs. These models will be adjusted for age, race/ethnicity, sex, and age at diagnosis. This analysis will start at the survey of neurocognitive assessment (survivors who did not complete this survey will be excluded).

Aim 3 (same analytic approach as Aim 2.2)

The associations between injury-related mortality and psychological distress/suicide ideation will be examined using multivariable piecewise exponential models to estimate rate ratios and corresponding 95 CIs. These models will be adjusted for age, race/ethnicity, sex, and age at diagnosis. This analysis will start at the baseline assessment (survivors who did not complete this survey will be excluded).

Additional Information on External Causes of Death

Breakdown of External Causes of Death by Era
-all eligible survivors, excludes survivors from Toronto and Dana Farber

External Causes of Death	1970-1985 (N=693)*	1986-2001 (N=2268)	2002-2017 (N=3238)	2010-most recent NDI search (N=1729)	Overall (N=6199)
	N (%)	N (%)	N (%)	N (%)	N (%)
All External Causes	14 (2.0%)	194 (8.6%)	363 (11.2%)	199 (11.5%)	571 (9.2%)
Suicide	1 (0.1%)	37 (1.6%)	66 (2.0%)	36 (2.1%)	104 (1.7%)
Homicide	0 (0.0%)	18 (0.8%)	21 (0.6%)	9 (0.5%)	39 (0.6%)
MVA	8 (1.2%)	83 (3.7%)	87 (2.7%)	41 (2.4%)	178 (2.9%)
Unintentional falls	1 (0.1%)	4 (0.2%)	21 (0.6%)	14 (0.8%)	26 (0.4%)
Unintentional poisoning	0 (0.0%)	20 (0.9%)	85 (2.6%)	59 (3.4%)	105 (1.7%)
Other (external cause)	4 (0.6%)	32 (1.4%)	83 (2.6%)	40 (2.3%)	119 (1.9%)

% reflects proportion with regards to all-cause death during that time period

*N is all cause of death

Breakdown of External Causes of Death by Era
-Survivors who participated baseline questionnaire

External Causes of Death	1970-1985 (N=395)*	1986-2001 (N=1420)	2002-2017 (N=2265)	2010-most recent NDI search (N=1239)	Overall (N=4080)
	N (%)	N (%)	N (%)	N (%)	N (%)
All External Causes	11 (2.8%)	101 (7.1%)	237 (10.5%)	126 (10.2%)	349 (8.6%)
Suicide	1 (0.3%)	19 (1.3%)	42 (1.9%)	22 (1.8%)	62 (1.5%)
Homicide	0 (0.0%)	8 (0.6%)	16 (0.7%)	7 (0.6%)	24 (0.6%)
MVA	6 (1.5%)	47 (3.3%)	56 (2.5%)	22 (1.8%)	109 (2.7%)
Unintentional falls	1 (0.3%)	2 (0.1%)	13 (0.6%)	8 (0.7%)	16 (0.4%)
Unintentional poisoning	0 (0.0%)	10 (0.7%)	56 (2.5%)	40 (3.2%)	66 (1.6%)
Other (external cause)	3 (0.8%)	15 (1.1%)	54 (2.4%)	27 (2.2%)	72 (1.8%)

% reflects proportion with regards to all-cause death during that time period

*N is all cause of death

References

1. Centers for Disease Control and Prevention NCfIPaC. Key Injury and Violence Data. https://www.cdc.gov/injury/wisqars/overview/key_data.html. Published 2018. Accessed 5/13/2019, 2019.
2. Health NIoM. Suicide is a Leading Cause of Death in the United States. https://www.nimh.nih.gov/health/statistics/suicide.shtml. Published 2019. Accessed 5/13/2019, 2019.
3. Rockett IR, Regier MD, Kapusta ND, et al. Leading causes of unintentional and intentional injury mortality: United States, 2000-2009. *American journal of public health.* 2012;102(11):e84-92.
4. Camidge DR, Stockton DL, Frame S, Wood R, Bain M, Bateman DN. Hospital admissions and deaths relating to deliberate self-harm and accidents within 5 years of a cancer diagnosis: a national study in Scotland, UK. *British journal of cancer.* 2007;96(5):752-757.
5. Mertens AC, Yasui Y, Neglia JP, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2001;19(13):3163-3172.
6. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *Journal of the National Cancer Institute.* 2008;100(19):1368-1379.
7. Gunnes MW, Lie RT, Bjorge T, et al. Suicide and violent deaths in survivors of cancer in childhood, adolescence and young adulthood-A national cohort study. *International journal of cancer.* 2017;140(3):575-580.
8. Lu D, Fall K, Sparen P, et al. Suicide and suicide attempt after a cancer diagnosis among young individuals. *Annals of oncology : official journal of the European Society for Medical Oncology.* 2013;24(12):3112-3117.
9. Zaorsky NG, Zhang Y, Tuanquin L, Bluethmann SM, Park HS, Chinchilli VM. Suicide among cancer patients. *Nature communications.* 2019;10(1):207.
10. Korhonen LM, Taskinen M, Rantanen M, et al. Suicides and deaths linked to risky health behavior in childhood cancer patients: A Nordic population-based register study. *Cancer* 2019; 125(20): 3631-3638.
11. Brinkman TM, Zhang N, Recklitis CJ, et al. Suicide ideation and associated mortality in adult survivors of childhood cancer. *Cancer.* 2014;120(2):271-277.
12. Lubas MM, Mirzaei Salehabadi S, Lavecchia J, et al. Suicidality among adult survivors of childhood cancer: A report from the St. Jude Lifetime Cohort Study. *Cancer.* 2020.
13. Tollefsen IM, Hem E, Ekeberg O. The reliability of suicide statistics: a systematic review. *BMC psychiatry.* 2012;12:9.
14. Neeleman J, Wessely S, Wadsworth M. Predictors of suicide, accidental death, and premature natural death in a general-population birth cohort. *Lancet (London, England).* 1998;351(9096):93-97.
15. Neeleman J. A continuum of premature death. Meta-analysis of competing mortality in the psychosocially vulnerable. *International journal of epidemiology.* 2001;30(1):154-162.
16. Gray D, Coon H, McGlade E, et al. Comparative analysis of suicide, accidental, and undetermined cause of death classification. *Suicide & life-threatening behavior.* 2014;44(3):304-316.
17. Bergen H, Hawton K, Kapur N, et al. Shared characteristics of suicides and other unnatural deaths following non-fatal self-harm? A multicentre study of risk factors. *Psychological medicine.* 2012;42(4):727-741.

Tables

Table 1. Demographic, Treatment, and Health-Related Characteristics and Life Status in Survivors of Childhood Cancer

Variable	Death due to external causes		Death due to medical conditions and cancer		Alive Patients	
	N	%	N	%	N	%
Sex - Male - Female						
Race - White, Non-Hispanic - Black, Non-Hispanic - Other						
Age at diagnosis - 0-10 - 10-15 - > 15						
Age at death - 0-10 - 10-20 - 20-30 - >30						
Time from diagnosis to death - 0-5 - 6-10 - >10						

Cancer diagnosis
 - CNS
   • Ependymoma
   • Astrocytoma
   • Meulloblastoma
   • Others
 - Leukemia
   • ALL
   • AML
 - Lymphoma
 - Hodgkin lymphoma
 - Wilms tumor
 - Neuroblastoma
 - Soft tissue sarcoma
 - Bone tumors						

Chemotherapy - Alkylating agents - Anthrayclines - Antimetabolites & Corticosteroids						

- Vina Alkaloids & Heavy Metals - Others						

Radiation field and dose
 - Cranial
   • 0-29 Gy
      o Focal
      o CSI
   • 30-49 Gy
      o Focal
      o CSI
   • 50 and more Gy
      o Focal
      o CSI
 - Other bodily
 - None						

Response to suicide ideation question - Yes - No						
Response to depression questionnaires - Yes - No						
Pain - Yes - No						
Smoking (ever) - Yes - No						
Risky Drinking or Heavy Drinking - yes - no						
Physical Inactivity - ≥ 3 sessions per week (active) - < 3 sessions per week (inactive)						
Medications - Psychiatric - Hormonal - Pain - Anti seizure - Others - None						
Health Status (number of CTCAE conditions; M(SD))						
Self-reported Health						

- Poor, fair - Good, very good, excellent						

Sensory Loss
   - Hearing
   - Vision
   - Both						

Secondary Malignant Neoplasm
   - Yes
   - No						

Fear of Recurrence
   - Yes
   - No						

Table 2. External Cause Mortality Standard Mortality Ratios in Survivors Compared with the US Population (Aim 1.2)

	All External Causes		Intentional (suicide)		Unintentional		Homicide	
	No. of Deaths	SMR (95% CI)	No. of Deaths	SMR (95% CI)	No. of Deaths	SMR (95% CI)	No. of Deaths	SMR (95% CI)
All Survivors								
Sex								
Male								
Female								

Table 3. Unadjusted Odds Ratios for Risk Factors* Associated with External Causes of Death Among Survivors (Aim 2.1)

	External Causes (all)		Intentional Injury		Unintentional Injury	
	OR	95% CI	OR	95% CI	OR	95% CI
Predictors						
Sex						
Race						
Marital Status						
Household Income						
Educational Attainment						
Age at diagnosis						
Age at death						
Diagnosis Group						
Cranial Radiation						
Any Radiation						
Suicide Ideation						
Depression						
Anxiety						
Pain						
Smoking History						
Alcohol Abuse						
Physical inactivity						
Psychiatric medications						

Pain medications					
Health Status					
Secondary Malignant Neoplasm					
Self-Reported Health					
Fear of Recurrence					
Sensory Loss					

* The ability to examine these risk factors, how to define these variables and whether we can examine them for all external causes or can examine intentional vs. unintentional injury will be informed by the data distributions in Table 1.

Table 4. Association Between Neurocognitive Impairment* and External-Causes of Death (Aim 2.2)

	External Causes (all)	
	OR	95% CI
Predictor		
Executive Function Impairment[a]		
Attention Impairment[b]		

* Neurocognitive impairment is defined as a domain score that is $\geq$ the 90th percentile based on values obtained in the sibling cohort
[a] Separate model for executive function, adjusted for age, race, sex, and time since diagnosis
[b] Separate model for attention domain, adjusted for age, race, sex, and time since diagnosis

Table 5. Prevalence of Mortality due to External Causes by suicide Ideation and Psychological Distress (Aim 3)

	Suicide Ideation (yes)	Suicide Ideation (no)		Psych. Distress (yes)	Psych. Distress (no)	
	N (%)	N (%)	Chi-Sq	N (%)	N (%)	Chi-Sq
External Deaths (all)						
Intentional						
Unintentional						