Childhood Cancer Survivor Study Analysis Concept Proposal
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Project Title
Growth hormone deficiency and its long-term outcomes, safety of growth hormone replacement therapy in childhood cancer survivors: A study from the Childhood Cancer Survivor Study

Working Group
Chronic Disease (Primary)
Subsequent Neoplasm (Secondary)
Biostatistics/Epidemiology (Secondary)
Psychology (Secondary)

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1. Background

Growth hormone deficiency (GHD) is one of the most common endocrine late effects among childhood cancer survivors, especially those with suprasellar tumors and those treated with radiation exposure to the hypothalamic-pituitary (HP) region.[1,2] While GHD is most commonly associated with growth impairment in childhood, GHD in adulthood is also associated with significant metabolic alterations including body composition, bone mineral density, exercise capacity, cardiovascular function, lipid metabolism, and quality of life.[3-6] Most, but not all, of these adverse health effects of GHD have been shown to be reversible following GH therapy (GHT), which is accomplished by subcutaneous injection of recombinant human growth hormone (GH).[3-6] However, the long-term outcomes of these comorbidities and safety with GHT among the cancer survivor population in adulthood is very limited.

In our recent paper from the St. Jude Lifetime Cohort Study (SJLIFE), we observed underutilization of GHT among survivors with severe GHD [defined by insulin-like growth factor-1 (IGF1) z-score ≤ -2)]. Despite the availability of GHT, only 9.0% of adult survivors with GHD were using it.[7] There was a substantial number of adult survivors with severe GHD who underwent GHT for linear growth in childhood and stopped taking it after becoming adults. In this concept proposal, we plan to assess two potential reasons for underutilization of GHT among survivors: (i) concerns for long-term safety of GHT use, and (ii) lack of evidence regarding the outcomes of untreated GHD in this population.

There has been historical concerns about the safety of GHT, i.e., risk of second neoplasms (SN), recurrence of primary cancer, and increased mortality after GHT use, due to the mitogenic properties of GH. It may be true that survivors/caregivers/health care providers are nervous about this potential risk because survivors are already at an increased risk for SN and mortality due to their primary cancer and its treatment. From the Childhood Cancer Survivor Study (CCSS), there have been three studies assessing the safety of GHT, focusing on the survivor population. One was published in 2002 by Sklar *et al*., examining 361 survivors with GHT and 12,963 non-GHT survivors (including those with and without a diagnosis of GHD) at the time of the baseline assessment.[8] There was no increased risk of primary cancer recurrence and mortality associated with GHT. However, the relative risk (RR) of overall SN was higher in survivors with GHT compared with those without GHT [RR 3.2, 95% confidence interval (CI) 1.9-5.5]. The follow-up paper of the same cohort with an additional 32 months of follow-up still observed the increased risk of overall SN in survivors with GHT (RR 2.2, 95%CI 1.3-3.5).[9] Patterson et al. reported another follow-up study in 2014 focusing on SN of the central nervous system (CNS), assessing 338 survivors with GHT and 11,760 non-GHT survivors. In this study, the authors did not observe an increased risk for meningioma, glioma, or any other CNS-SN among the survivors with GHT.[10] Still, the long-term effects of GHT on overall SNs in adult survivors of childhood cancer remain unclear, and each of these studies was limited by a lack of long-term data regarding GHT after the baseline assessment, so the implications of GHT that was continued throughout follow-up was not addressed. Aside from these CCSS studies, several studies have addressed the safety of GHT. However, many of these studies were not focused

specifically on the cancer survivor population. In 2022, a consensus statement from the Growth Hormone Research Society, the European Society of Endocrinology, and nine international societies, regarding the safety of GHT in survivors of cancer and intracranial and pituitary tumors was published.[11] This publication stated that although previous reports are generally reassuring regarding the long-term safety of GHT in terms of recurrence, SN, and mortality, longer-term studies with bigger sample sizes are still needed to fully assess the risk of GHT use among the survivor population. Also, it stated that there is a lack of data in the risk assessment of GHT use especially among subjects with genetic mutation in cancer predisposition genes.[11]

Although the data showing the adverse effects of untreated GHD and benefits of GHT for GHD are reassuring,[3-6] the evidence is mainly from the non-cancer survivor population, and the data focusing on the childhood cancer survivor population has been limited. To address this knowledge gap, we examined associations between serum IGF1 levels and prevalences of multidimensional health outcomes among survivors in the SJLIFE cohort.[7] Since the IGF1 level is a marker of GH action, the analysis enabled us to assess the adverse effects of untreated GHD indirectly. We observed dose-response associations between lower IGF1 levels (indicative of untreated severe GHD) and higher prevalences of a wide range of adverse health outcomes, such as obesity, weak hand grip strength, diabetes mellitus, impaired health-related quality of life (HRQOL) and neurocognitive outcomes. A noteworthy finding was decreased neurocognitive functions, which are highly prevalent among survivors compared to the general population. Although the relationship between GHD and neurocognitive impairment in the non-cancer survivor population has been unclear,[12] in our study focusing on survivors, there were dose-response relationships between lower IGF1 levels and higher prevalence of impairment in all 20 neurocognitive outcomes assessed in various specific domains (e.g., global intelligence, memory, processing speed). Because neurocognitive impairment affects the QOL of survivors and can affect their education level or even employment status,[13] GHT may be an intervention that improves survivors' QOL through potentially improving neurocognitive functioning. Yet, because our study assessed the effect of GHD indirectly using IGF1 levels, further study with direct assessment of GHD/GHT status and associations with neurocognitive and other adverse outcomes is warranted.

In this proposal, we will assess two knowledge gaps of GHD/GHT as two distinct specific aims: (i) long-term safety of GHT use among survivors with GHD, and (ii) the outcome of untreated GHD, focusing on the childhood cancer survivor population. We will utilize CCSS, a large study of childhood cancer survivors with a median follow-up of 22 years, and with available genetic information. Although those two aims share methodologies and variables, the implications of the findings will be different. Thus, we plan to publish the findings from two specific aims in different papers, working with co-investigators listed here for each aim. Additional evidence of the effects of GHD and its treatment in adult survivors will help to inform clinical management of this common condition, particularly regarding decision-making about GHT use in survivors of childhood cancer with GHD.

2. Specific aims and hypotheses

Aim 1: GHT safety [Risk of subsequent neoplasm (SN) and mortality]
To examine the association between GHT use and overall subsequent neoplasm/cancer-related mortality risk among long-term survivors of childhood cancer
Hypothesis: There is no increased risk of SN/cancer-related mortality with GHT use.

Aim 2: Clinical outcomes among survivors with GHD
To examine the associations between untreated GHD and adverse physical, neuropsychological, and HRQOL outcomes
Hypothesis: Untreated GHD is associated with higher prevalences of adverse physical/neuropsychological/HRQOL outcomes.

3. Study Design and Measures

Study data source
The most recent data freeze of the CCSS
The most recent data freeze of the SJLIFE [for participants who enrolled in both CCSS and SJLIFE ("CCSS-SJLIFE dual participant population" hereafter)]

Study population: inclusion criteria
All CCSS participants (childhood cancer survivors) with the medical record abstraction agreement

Study population: exclusion criteria
Aim 1 and 2: Participants who never answered questions required to determine GHD/GHT status [Reasons of exclusion are: (i) we anticipate this to be <5% of the population based on our experience using the same information in the SJLIFE questionnaire, and (ii) previous CCSS papers also excluded survivors who did not report their GH status]
Aim 2 only: We will decide whether to exclude survivors with a genetic syndrome associated with neurocognitive impairment but unrelated to their primary cancer diagnosis (eg, Klinefelter or Turner syndrome) from the analyses setting neurological CHCs, neurocognitive function, and HRQOL as outcomes by running supplementary analyses with or without these survivors.

Outcome

SA1: GHT safety (occurrence of outcomes will be treated as events in time-to-event analyses)

- SN

  Subsequent neoplasm risk: subsequent neoplasm overall and major SNs by type
  - All the SNs without non-melanoma skin cancers
  - All the SNs including non-melanoma skin cancers
  - All the subsequent malignant neoplasms
  - All the CNS neoplasms[10]

- SN by type (with checking the number of events, e.g., meningioma, glioma, breast cancer for female participants, thyroid cancer, non-melanoma skin cancer, melanoma, colorectal cancer)

- Mortality

  Date and cause of death through December 2021, will be ascertained through CCSS' existing linkages with the National Death Index (NDI) and will be classified using the International Classification of Disease 9th and 10th revisions (ICD-9 and ICD-10).[14]
  - Primary outcome: Primary cancer-related mortality (death caused by recurrence or progression of primary cancer)[14]
  - Secondary outcomes: All-cause mortality and health-related mortality (subsequent neoplasm, cardiac, pulmonary, and other health-related causes)[14]

SA2: Clinical outcomes of GHD

- Health conditions

  [Chronic health conditions (CHCs) defined in CTCAE grading; treated as events in time-to-event analyses]

  CHC grading information will be utilized to assess the following CHCs with known effects of GHD in the general population.[3-6] The CTCAE grading is defined as grade 0 (none), 1 (mild), 2 (moderate), 3 (severe or disabling), 4 (life-threatening) or 5 (fatal).[15] We will assess the association of GHD/GHT and the presence of these conditions with the clinically-relevant cut-offs shown below.
  - Cardiovascular
    - Heart attack (grade 3+)
    - Congestive heart failure [grade 3+ (on medications)]
    - Hypertension [grade 2+ (on medications)]
    - Stroke (grade 4+)
    - Dyslipidemia [grade 2+ (on medications)]
  - Neurological (supplemental for NCQ outcomes, but we will check as time-to-event outcomes)
    - Memory problems (grade 2+)
    - Weakness in leg (grade 2+)
    - Weakness in arm (grade 2+)
  - Endocrine
    - Diabetes mellitus [grade 2+ (on medications)]
    - Osteoporosis (grade 2)

  [Obesity (treated as binary outcome using the most recent available information in cross-sectional analyses)]

  BMI will be calculated using self-reported height and weight information. This will be examined in two ways; as the presence of overweight (overweight and obesity combined, cut-off of BMI $\geq$25 kg/m^2 vs. <25 kg/m^2) and as the presence of obesity (cut off of BMI $\geq$30 kg/m^2 vs. <30 kg/m^2).

  [Frailty (treated as binary outcome using the most recent available information in cross-sectional analyses)]

Frailty will be assessed by using the modified Fried frailty criteria which has been previously defined and applied to the CCSS cohort by Hayek et al.[16] The information is available at FU-2, 5, and FU7. These measures include 1) low lean muscle volume mass (defined by BMI , 18.5 kg/m^2 or unintentional weight loss of ≥ 10 pounds in the past year); 2) exhaustion [the medical outcomes Short Form 36 (SF36), vitality subscale]; 3) low energy (convert frequency and duration of low, moderate and vigorous physical activity levels into kilocalories); 4) slowness (limitations in walking uphill/upstairs or limitation in walking one block); 5) weakness (answer of "yes and the condition is still present" to "have you ever been told that you have/had or have had weakness or inability to move arms?"). The status will be assessed in two ways: the presence of prefrail/frail (≥2 criteria) vs. non-frail and the presence of frail (≥3 criteria) vs. non-frail.

- Neurocognitive function (treated as a binary outcome using the most recent available information in cross-sectional analyses)
  Information from the Childhood Cancer Survivor Study-Neurocognitive Questionnaire (CCSS-NCQ, available from FU-2, 5/6, 7) will be used to assess neurocognitive outcomes. The CCSS-NCQ was developed and validated for use in cancer survivors.[17,18] In CCSS-NCQ, raw scores for each factor are converted to T-scores based on sibling norms, with higher scores indicative of more neurocognitive problems. We will assess each domain separately as binary variables, i.e., impaired or not. Impairment will be defined as scores ≥ 90th percentile of sibling norms.
  - Task efficiency (ie, processing speed and attention)
  - Emotional regulation (ie, control of emotions and frustration tolerance)
  - Organization (of materials, environments and activities)
  - Memory (ie, short-term and long-term)

  *We will consider running supplemental analysis utilizing CNS Vital Signs based on its availability (As of now, it is available for approximately 5,400 survivors who completed follow-up. We will use the revised version since we are not looking at longitudinal change)

- HRQOL (treated as a binary outcome using the most recent available information in cross-sectional analyses)
  Information from the Medical Outcomes Study Short Form 36 (SF36), available from FU-2, 5, 6, 7, will be utilized for HRQOL assessment. SF-36 includes questions regarding general health and mental well-being over the previous four weeks. Eight domains of HRQOL (physical functioning, role limitations resulting from physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations resulting from emotional problems, and mental health) and Physical (PCS) and Mental (MCS) Component Summaries are included in SF36. Population-normalized T scores ≤40 in each subscale will be defined as impairment.
- Psychological distress (treated as a binary outcome using the most recent available information in cross-sectional analyses)
  Information from the Brief Symptom Inventory-18 (BSI-18), available from FU-2, 5, 7, will be utilized for psychological assessment[19,20]. Three subscales will be considered: anxiety, depression, and somatization. T-scores ≥63 in each subscale will represent emotional distress.

Variable of interest

GHD/GHT status

- SA1 and SA2 (CHCs only): as time-dependent variables in time-to-event analyses
  - GHD-treated
  - GHD-untreated
  - Non-GHD
- SA2 (For analyses exclusive of CHCs): as categorical variables in the cross-sectional analyses. We will start with getting a sample size of each category and will consider how to handle those if there are categories with limited sample size.
  - Childhood GHD (GHT+) + adulthood GHD (GHT+)
  - Childhood GHD (GHT+) + adulthood GHD (no GHT)
  - Childhood GHD (no GHT) + adulthood GHD (GHT+)
  - Childhood GHD (no GHT) + adulthood GHD (no GHT)
  - GHD-adulthood GHD only (GHT+)
  - GHD-adulthood GHD only (no GHT)
  - Non-GHD

Covariates

<u>Sociodemographic/Clinical</u>

- Sex (male/female)
- Self-reported race/ethnicity
- Age at cancer diagnosis (by 5 years)
- Follow-up length (by 5 years)
- Major brain surgery (within 5 years of cancer diagnosis)
- Maxseg2dose (0, 1 to 17.9 Gy, 18 to 29.9Gy, ≥30Gy)
- Brain radiation (by 10Gy)
- Chest radiation (by 10Gy)
- Abdominal radiation (by 10Gy)
- Pelvic radiation (by 10Gy)
- Hematopoietic cell transplantation (yes/no)
- Alkylating agents (Cyclophosphamide equivalent dose in mg/m^2; by 5000)[14]
- Platinum agents (None, 1 to 400, 401 to 750, >750 in mg/m^2)[21]
- Anthracycline (None, 0-100, 101-300, 301-600, >600 in mg/m^2)[21]
- Morbidity (grade ≥3 CHCs among SMN, endocrine, respiratory, cardiovascular, GI, renal, other hematological, Other infectious/immunologic conditions; categorized as the counts of 0, 1, 2, 3+) *Only in SA1-mortality analysis

<u>Lifestyle factors</u>

SA1 and SA2 (CHCs only): as time-dependent variables in time-to-event analyses (shifted back 5 years as in Dixon *et al.*[14], to minimize the possibility of bias dur to reverse causality because these factor affect health over prolonged time periods)
SA2 (For analyses exclusive of CHCs): as binary or categorical variables using information at baseline survey in the cross-sectional analyses

- Smoking status (Never/ever/missing)
  Information only from participants 18+ at the time of survey completion will be used)
- Heavy/risky drinking (Yes/No/missing)
  Information only from participants 18+ at the time of survey completion will be used
- Physical activity [0 metabolic equivalent task (MET)-hours/week, 3 to 6 MET-hours/week, 9 to 12 and 15-21 MET-h/wk. We will follow the methodology in Scott et al. [22 23])

Socioeconomic variables
SA1 and SA2 (CHCs only): as time-dependent variables in time-to-event analyses (shifted back 5 years)
SA2 (For analyses exclusive of CHCs): as binary or categorical variables using information at baseline survey in the cross-sectional analyses

- Education attainment
- Health insurance
- Social Vulnerability Index
- Healthcare access

Mutation-carrier status of cancer predisposition genes (SA1 only)
Mutation-carrier status of germline cancer predisposition genes [survivors with a P/LP (pathogenic/likely pathogenic) mutation in 60 genes with well-established associations with monogenic cancer risk inherited in an autosomal dominant fashion at moderate to high penetrance, examined in a previous paper from SJLIFE (e.g., *BRCA1, BRCA2, TP53;* shown in Appendix), will be categorized as carrier, non-carrier otherwise][24]

4. **Analytical Methods**

Step 1: Check the agreement rate between self-reported information (CCSS) and clinically validated information (Resource 1 and 2 as described below): For both SA1 and SA2
To address the potential inaccuracies of self-reported information in CCSS, we will first check the rate of agreement between self-reported GHD/GHT status from CCSS and clinically validated information. As the clinically validated information, we will utilize two resources described below. The agreement information will be utilized in step 2 to address any bias in self-reported data.

GHD/GHT assignment strategy in CCSS (self-report)

- GHD assignment (Yes-childhood, Yes-adulthood, No)
  - "Deficiency of growth hormone?" (GHDEF, answer = yes) and/or
  - "Have you ever received injections of growth hormone?" (INJGHR, answer = yes)

- GHT assignment (Yes-childhood, Yes-adulthood, No)
  - "Have you ever received injections of growth hormone?" (INJGHR, answer = yes) and/or
  - "Other medications to replace body hormones such as prednisone, DDVAP (desmopressin), hydrocortisone, growth hormones or other", "Other prescribed drugs?" (answer = any of: "growth hormone, Norditropin, Nutropin, Genotropin, Humatrope, Saizen, Omnitrope, Zomacton, somatropin, lonapegsomatropin (Skytrofa), somapacitan, Sogroya, somatrogon, Ngenla")

Table 1. The list of questionnaires in CCSS to be utilized for GHD/GHT assignment

	Deficiency of growth hormone?*	Have you ever received injections of growth hormone (such as Nutropin, Genotropin, Humatrope…)?*	Other medications to replace body hormones such as predonisone, DDVAP (desmopressin), hydrocortisone, growth hormones or other	Other prescribed drugs? (If yes, age at first use)
Original Baseline	E8 (Yes, No, Not sure, If yes-age at first occurence)	E9 (Yes, No, Not sure, If yes-age at first occurence)	N/A	B8-16 (yes, no, not sure, and specify the name of the drug(s))
Original Baseline Under 18	E8 (Yes, No, Not sure, If yes-age at first occurence)	E9 (Yes, No, Not sure, If yes-age at first occurence)	N/A	B8-16 (yes, no, not sure, and specify the name of the drug(s))
Expansion baseline	E8 (Yes-present, Yes-no longer present, No, Not sure, If yes-age at first occurence)	E9 (Yes-present, Yes-no longer present, No, Not sure, If yes-age at first occurence)	N/A	B8-10 (yes, no, not sure, If yes, age at first use/If yes currently taking?)
Expansion baseline Under 18	E8 (Yes-present, Yes-no longer present, No, Not sure, If yes-age at first occurence)	E9 (Yes-present, Yes-no longer present, No, Not sure, If yes-age at first occurence)	N/A	B8-10 (yes, no, not sure, If yes, age at first use/If yes currently taking?)
Follow-Up 1 (2000)	N/A	N/A	6-f (yes, no, not sure)	N/A
Follow-Up 2 (2003)	N/A	N/A	N/A	Q-9 (yes, no, not sure, If yes age at first use)

Follow-Up 4 (2007)	F8 (Yes-present, Yes-no longer present, No, Not sure, If yes-age at first occurence)	F9 (Yes-present, Yes-no longer present, No, Not sure, If yes-age)	N/A	C8-10 (yes, no, not sure, If yes, age at first use/If yes currently taking?)
Follow-Up 5 (2014)	G8 (Yes-present, Yes-no longer present, No, Not sure, If yes- age at first occurence)	G9 (Yes-present, Yes-no longer present, No, Not sure, If yes-age)	N/A	C2-10 (yes, no, not sure, If yes, age at first use/If yes currently taking?)
Follow-Up 6 (2017)	N/A	N/A	N/A	N/A
Follow-Up 7 (2019)	G8	G9	N/A	N/A

- *By utilizing the combination of longitudinal information of "If yes-age at first occurrence", and "Yes-present/Yes-no longer present", we will distinguish childhood GHT and adulthood GHT status, using 18 years old at the cut-off.
- Original Baseline/Original Baseline Under 18 (B8-16) and Follow-up 1 (6-f) do not ask for age at the first occurrence.

GHD/GHT assignment strategy in Resource 1 (clinically-validated dataset)

Resource 1: The clinically-ascertained SJLIFE data from the CCSS-SJLIFE dual participant population (particularly whose CCSS survey data and SJLIFE data were collected within 2 year of each other)

- GHD assignment: ever having any of following core concepts in the SJLIFE, assuming survivors do not recover from GHD[7] (Yes-childhood, Yes-adulthood, No)
  - Adult-onset growth hormone deficiency
  - Adult-onset growth hormone deficiency, previously on hormonal replacement therapy
  - Adult-onset growth hormone deficiency, receiving adult growth hormone replacement therapy
  - Childhood-onset growth hormone deficiency requiring growth hormone replacement therapy
  - Childhood-onset growth hormone deficiency, growth hormone replacement not pursued

- GHT assignment: we will conduct medical record review for survivors who indicated the use of GHT by meeting at least one of the followings (Yes-childhood, Yes-adulthood, No)
  - Answer=yes for othpdrug (Survey Home: B8-13) and indicated in opdrug1-29 any of: growth hormone, Norditropin, Nutropin, Genotropin, Humatrope, Saizen, Omnitrope, Zomacton, somatropin, lonapegsomatropin (Skytrofa), somapacitan, Sogroya, somatrogon, Ngenla
  - Answer=yes for injghr (Survey Home: F9) "Have you received injections of growth hormone (such as Nutropin, Genotropin, Humatrope, Norditropin, Saizen)?
  - Answer=yes for injghr_c (Survey Home: F9) "If yes, do you currently take injections of growth hormone? (injghr_c)"

GHD/GHT assignment strategy in Resource 2 (clinically-validated dataset)

Resource 2: The previously validated group of participants with GHD/GHT as described by previous CCSS papers from the CCSS original cohort[8 9 10]

We will use the population in Patterson *et al.*[10] (algorithm in the paper is shown below), especially for the GHT information at baseline of n=100+338, whose GHT information was previously confirmed (framed in a red square).

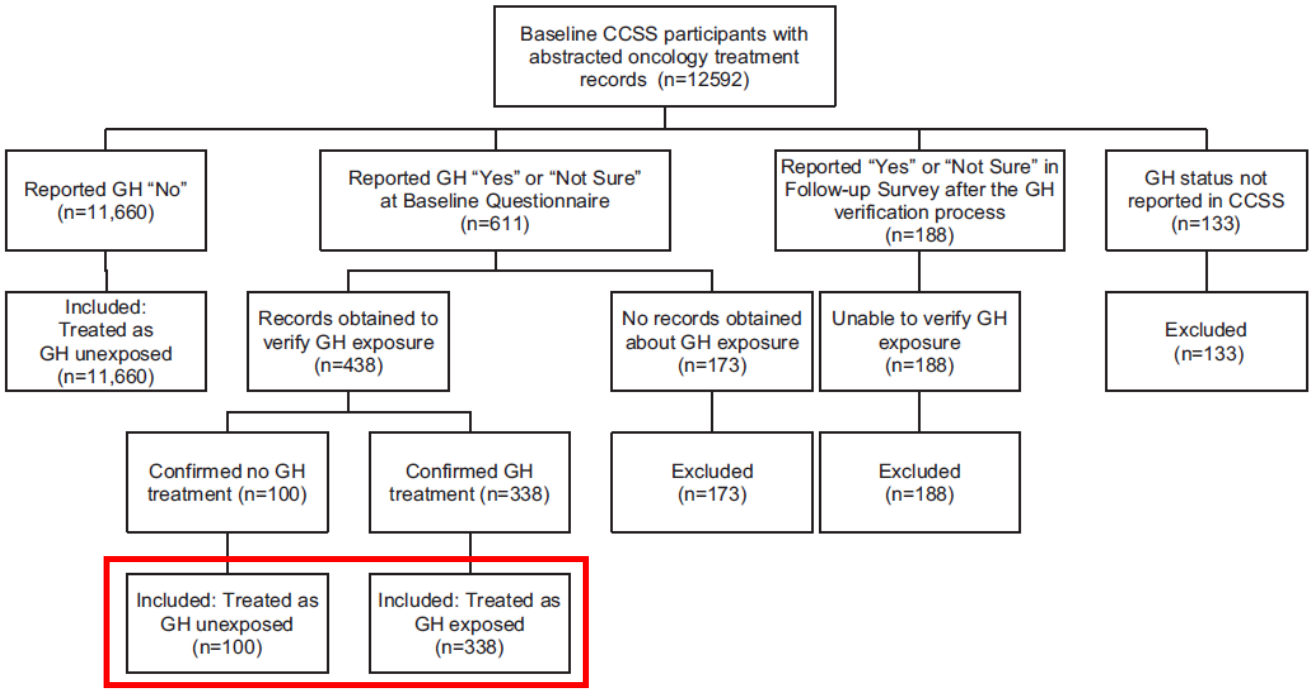

Figure 1. Inclusion and exclusion of CCSS subjects.

Step 2: Main analysis (SA1, GHT safety)

This will be a time-to-event analysis using the earliest event date of SN/mortality and setting GHD/GHT status as a time-dependent variable. Piece-wise exponential models will be run, adjusting for sociodemographic/clinical and socioeconomic/lifestyle variables. Lifestyle variables will be used as time-dependent variables following the previous mortality paper from the CCSS (Dixon *et al.*[14]) The piece-wise exponential model will incorporate the Weighted Generalized Linear Model (WGLM), that was proposed in Mirzaei *et al.* (a report from SJLIFE and CCSS study).[25] In the WGLM, the subgroup whose agreement data were obtained through Step 1 will be utilized as the validation data which inform the rest of the non-validation data in weighting the agree vs. disagree possibilities given covariates, to address the potential bias of self-report data.[25]

As the main interest of this aim is to examine whether the use of GHT increases the risk of SN/mortality among the GHD population, we will only include survivors with GHD in the

primary analysis (i.e., GHD-treated and GHD-untreated populations). Here, if a survivor was categorized as non-GHD at the baseline and later developed GHD, the survivor can enter the analysis from the time point where the survivor was first assigned to be GHD positive. The start time is self-reported age of GHD diagnosis. Most of the versions of surveys allow us to assign the age at GHD diagnosis by asking age at first occurrence of GHD/GHT (Table 1). If the survivor only responded as having GHD at FU1, the onset age information will be unavailable (Table 1). In that scenario, we will use the age at survey as an onset timing as proxy. If there is an event occurrence prior to the first GHD development, we will remove the survivor from the analysis.

To supplement the main analysis, we will run analysis for the overall population, including non-GHD survivors (comparison of GHD-treated, GHD-untreated, and non-GHD).

As another supplementary analysis, we will perform analyses including genetic variables (mutation-carrier status of pathogenic/likely pathogenic variants among cancer predisposition genes[24]) for those participants with available whole genome sequencing/whole exome sequencing data. We will also run analysis setting all-cause mortality and health-related mortality (second neoplasm, cardiac, pulmonary, and other health-related causes) as outcomes for mortality analysis.

Finally, it is possible that the decision of GHT use was affected by GHT safety concern, which can be subject to reverse causality. To address this concern, we will consider yet another supplementary analysis of jointly modeling the longitudinal GHT status using a logistic regression model and time-to-event outcomes using Cox proportional hazard regression models[26], adjusting for the same demographics, cancer treatment, socioeconomic, and lifestyle variables.

Step 2: Main analysis (SA2, Outcome of GHD)

There will be two types of analyses for this aim. First is a time-to-event analysis, which sets the earliest event date of CHCs as outcomes, and uses GHD/GHT status as a time-dependent variable. Piece-wise exponential models will be run with the WGLM methodology, adjusting for sociodemographic/clinical and lifestyle variables as in SA1.

For outcomes for which the dates of the first event occurrence are unclear (obesity, frailty, impairment in neurocognitive function/HRQOL, psychological distress), we will run cross-sectional analysis, using the latest available survey information for each outcome (multivariable logistic regression). The GHD/GHT status will be categorized by the timing of GHD onset and GHT receipt, as it is possible that the GHD/GHT effect in childhood vs. adulthood is different on the outcomes. Socioeconomic/lifestyle variables will be treated as categorical variables from the baseline survey, because these factors can affect health over prolonged time periods, and we try to minimize the possibility of bias due to reverse causality from the change of these factors. The WGLM methodology will be utilized as in the analyses in SA1.[25]

Same as in SA1, as a supplementary analysis, the longitudinal GHT status and outcomes will be modeled jointly to evaluate the impact of the potential time-varying confounding.

Tables

Characteristics of study population.

	Participants overall (n=)		Participants for SA1 (n=)		Participants for SA 2 (n=)	
	N	%	N	%	N	%
Demographic factors						
Sex						
Female						
Male						
Race/ethnicity						
Non-Hispanic White						
Non-Hispanic Black						
Hispanic						
Other						
Unknown						
Cancer information						
Age at primary cancer diagnosis (years)						
Median (IQR)						
0-4						
5-9						
10-14						
15-21						
Age at last follow-up (years)						
5-17						
18-25						
25-34						
35-44						
45-54						
≥55						
Survival after diagnosis, years						
5-9						
10-19						
20-29						
30-39						
≥40						
Primary cancer diagnosis						
Leukemia						
Acute lymphoblastic leukemia						
Acute myeloid leukemia						
Other leukemia						
Hodgkin lymphoma						
Non-Hodgkin lymphoma						
CNS tumor						
Astrocytoma						
Ependymoma						
Medulloblastoma						
Other CNS tumor						
Kidney tumors						
Neuroblastoma						
Soft tissue sarcoma						
Bone tumors						
Ewing sarcoma						

Osteosarcoma		
Other bone tumors		
Tumors in hypothalamic-pituitary region		
Yes		
No		
Treatment factor-Radiation		
Radiation dose to the hypothalamic-pituitary region		
≤2 Gy		
2 to <18 Gy		
18 to <30 Gy		
≥30 Gy		
Missing		
Cranial radiation (Gy)*, any exposure, median (IQR)		
Any exposure		
Median dose (IQR)		
Chest radiation (Gy)		
Any exposure		
Median dose (IQR)		
Abdominal radiation (Gy)		
Any exposure		
Median dose (IQR)		
Pelvic radiation (Gy)		
Any exposure		
Median dose (IQR)		
TBI		
<10		
=> 10		
Treatment factor-Chemotherapy		
Anthracycline (mg/m²)		
Any exposure		
Median dose (IQR)		
Alkylating agents (mg/m2)		
Any exposure		
Median dose (IQR)		
Platinum agents (mg/m2)		
Any exposure		
Median dose (IQR)		
HSCT		
yes		
no		
Treatment factor-other		
Major brain surgery		
yes		
no		
HSCT		
yes		
no		
GHD/GHT status (for cross sectional analysis in SA2)	-	-
Childhood GHD (GHT+) + adulthood GHD (GHT+)	-	-
Childhood GHD (GHT+) + adulthood GHD (no GHT)	-	-

Childhood GHD (no GHT) + adulthood GHD (GHT+)	-	-
Childhood GHD (no GHT) + adulthood GHD (no GHT)	-	-
GHD-adulthood GHD only (GHT+)	-	-
GHD-adulthood GHD only (no GHT)	-	-
Non-GHD	-	-

Time to event analyses

Main analysis: GHD only (example of primary cancer-related mortality)

	Primary cancer-related mortality		
	RR	95%CI	p- value
GHD-treated			
GHD-untreated			

Supplementary analysis: with non-GHD (example of primary cancer-related mortality)

	Primary cancer-related mortality		
	RR	95%CI	p- value
GHD-treated			
GHD-untreated			
Non-GHD			

Cross-sectional analysis: GHD only (example of obesity)

	Obesity		
	OR	95%CI	p- value
Childhood GHD (GHT+) + adulthood GHD (GHT+)			
Childhood GHD (GHT+) + adulthood GHD (no GHT)			
Childhood GHD (no GHT) + adulthood GHD (GHT+)			
Childhood GHD (no GHT) + adulthood GHD (no GHT)			
GHD-adulthood GHD only (GHT+)			
GHD-adulthood GHD only (no GHT)			

Cross-sectional analysis: with non-GHD (example of obesity)

	Obesity		
	OR	95%CI	p- value
Childhood GHD (GHT+) + adulthood GHD (GHT+)			
Childhood GHD (GHT+) + adulthood GHD (no GHT)			
Childhood GHD (no GHT) + adulthood GHD (GHT+)			
Childhood GHD (no GHT) + adulthood GHD (no GHT)			
GHD-adulthood GHD only (GHT+)			
GHD-adulthood GHD only (no GHT)			
Non-GHD			

Appendix. List of cancer predisposition genes[24]

Gene
ALK
APC
BAP1
BMPR1A
BRAF
BRCA1
BRCA2
CBL
CDC73
CDH1
CDK4
CDKN1C
CDKN2A
CEBPA
DICER1
EPCAM
FH
GATA2
HRAS
KRAS
MAP2K1
MAP2K2
MAX
MEN1
MLH1
MSH2
MSH6
NF1
NF2
NRAS
PALB2
PAX5
PHOX2B
PMS2
PRKAR1A
PTCH1
PTEN
PTPN11
RAF1
RB1

RET
RUNX1
SDHA
SDHAF2
SDHB
SDHC
SDHD
SHOC2
SMAD4
SMARCA4
SMARCB1
SOS1
STK11
SUFU
TMEM127
TP53
TSC1
TSC2
VHL
WT1

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