Analysis Concept Proposal

1. STUDY TITLE

Disability Adjusted Life years in Childhood Cancer Survivors

2. WORKING GROUPS

Primary: Epidemiology/Biostatistics

Secondary: Chronic Disease and Subsequent Neoplasm

INVESTIGATORS

F. Lennie Wong, PhD	lenniewong@coh.org
Saro H. Armenian, DO, MPH	sarmenian@coh.org
Sitong Chen, MPH	sitchen@coh.org
Rusha Bhandari, MD, MS	rbhandari@coh.org
Nickhill Bhakta, MD, MPH	Nickhill.Bhakta@stjude.org
Wendy Leisenring, ScD	wleisenr@fredhutch.org
Cindy Im, PhD	imcindy@umn.edu
Joseph P. Neglia, MD, MPH	jneglia@umn.edu
Eric Chow, MD, MPH	ericchow@uw.edu
Kevin Oeffinger, MD	kevin.oeffinger@duke.edu
Lucie Turcotte, MD, MPH	turc0023@umn.edu
Rebecca Howell, PhD	rhowell@mdanderson.org
Kumar Srivastava, PhD	Kumar.Srivastava@stjude.org
Gregory Armstrong, M.D.	Greg.Armstrong@stjude.org

3. BACKGROUND AND RATIONALE

Although childhood cancer survivors now enjoy living longer lives thanks to improved therapy,[1] they continue to experience elevated risks of premature mortality and morbidity attributed to their cancer and its treatment.[2-5] These risks have been reported using standard measures such as prevalence, cumulative incidence, hazard, standardized mortality and incidence ratios based on the first occurrence of an event. More recently, cumulative burden has been used to quantify multiple disease occurrences over time.[6,7] These risk estimates are unidimensional in that they do not account for degradation in quality of life associated with living with chronic health conditions (CHCs) or illnesses that preceded death. Disability adjusted life-years (DALYs) is an established risk measure that accounts for disease burden. It is the sum of years of healthy life lost due to disability (YLD) and years of life lost (YLL) to premature death.[8] YLD weighs the years lived with a health condition by its disability weight (range: 0 for full health, 1 for death). Higher DALY, YLL, YLD indicate worse outcomes. One DALY is equivalent to the loss of one year of life lived in full health.

DALY was developed by the Global Burden of Disease (GBD) Project and the World Bank to assess and compare population health among countries and to provide relevant information for setting health policy.[8,9] Previously, mortality and life expectancy have been used as indicators of health. However, these measures do not account for morbidity, disability and dysfunction resulting from non-fatal health conditions that contribute to a reduction in quality of life. DALY combines the cause-specific shortening of life and the morbidity and ensuing reduction in quality of life lived with non-fatal debilitating health conditions. YLL is calculated as the difference between the expected life expectancy and age at death. Sex-, race-, age-, calendar-specific life expectancies are available at the Centers for Disease Control and

Prevention (https://www.cdc.gov/nchs/nvss/life-expectancy.htm). YLD is the time interval between the onset of a debilitating health condition and death. The time interval is weighted by the disability weight of that condition (0 for full health, 1 for death). Disability weights for 369 unique health conditions (or 440 including combined health states) were estimated by the GBD Project[10,11] which are available at the Global Health Data Exchange (GHDE) hosted by the Institute for Health Metrics and Evaluation (IHME) (https://www.healthdata.org/).

DALY has been used to assess the health and disease burden at the global,[12,13] national,[14-17] and regional[18] levels. It also has been applied at the individual level. The burden of intracerebral hemorrhage (ICH) and secondary injury was assessed using DALY in 1,322 patients with ICH at a tertiary care center in Germany.[19] The European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) study calculated DALY and examined the dietary- and lifestyle-related risk factors in 33,000 healthy men and women.[20-22] Struijk et al.[20] showed that a stricter adherence to a modified Mediterranean diet in this cohort was associated with a lower disease burden as measured by DALY. Beulens et al.[22] also showed that moderate drinkers in this cohort had a lower chronic disease burden (mean DALYs -0.27, 95% CI: -0.43 to -0.11) compared to light drinkers, which was attributed to lower cardiovascular disease burden but not to cancer burden. DALY was also used to quantify the benefit of thrombolytic therapy for ischemic stroke using patient-level data.[23] We recently estimated the DALY for 1577 5-year survivors who received allogeneic hematopoietic cell transplantation at City of Hope during 1976-2011.[24]

Disability weights used in YLD do not reflect the quality of life experienced by patients with the health condition, but measure the relative severity of the disease, elicited, for example, as "the best health you can imagine" (disability weight=0) to "the worst health you can imagine" (disability weight=1).[25] A systematic review found that the informants in the majority of studies that measured disability weights rarely included individuals with the health conditions under study but included the general population or more frequently medical experts and health professionals,[26] rendering disability weights as how "experts perceive the relative desirability and economic value of different health state and the quality of life experienced by people in those health states."[27] The disability weights available at the GHDE were pioneered by the GBD 1996 study based on health state valuation by 10 health professionals.[28] Iterations of the subsequent GBD studies combined results from GBD 2010 based on nationally representative samples of >30,000 participants in Bangladesh, Indonesia, Peru, Tanzania, and the USA,[29] and those of GBD 2013 with >30,000 nationally representative participants from Hungary, Italy, the Netherlands, and Sweden.[30] The surveys "…relied mainly on a paired comparison task that asked respondents to consider descriptions of two hypothetical people, each with a particular health state, and specify which person they regarded as being healthier than the other."[30] Hence, GBD disability weights were not derived from individuals with the disease state and do not reflect how well the individuals adapted to the disabling conditions. Wasserman[31] stated that "it is the consequence of limitations not the limitations themselves that determine the value of a non-fatal outcome." Thus, disability weights would not be the most appropriate weighting factor if the interest is the quality of life (QOL), particularly from the patient perspective. Additionally, disability weights provided by the GBD are fixed values for specific health conditions and do not vary by factors such as age and sex. Moreover, GBD currently does not incorporate survivorship into their framework. Instead, survivors are assumed to return to perfect health after 10 years with their risk of morbidity and mortality returning to the "general population" levels. Given these limitations, a more patient-centered measure of disutility seems equally appropriate for quantifying the years lived with disease burden. This project will provide important information relevant for survivorship research, i.e. QOL weights more suited for childhood cancer survivors.

We propose to estimate the patient-reported disutility weights using responses elicited in the CCSS Follow-up Questionnaires. The 36-item Short Form Health Survey (SF36) was incorporated into the CCSS Follow-up Questionnaires-2 (2003), -5 (2014), -6 (2017), and -7 (2019) for survivors and siblings. The number of respondents ranged from 9,000 to over 11,000 for survivors and 2,100 to 2,900 for sibling controls. SF36 scores can be mapped to SF6D preference-based index scores which quantify individuals' utility values by health states (0 for death; 1 for perfect health). [32] Utility values are weights used for computing the quality-adjusted life-years in cost-effectiveness analyses. A disutility value can be computed by subtracting the utility value of a health condition from the utility value without that health condition. For example, if the utility value for cardiovascular disease (CVD) is 0.3 and that without CVD is 0.5 (higher utility value means better), then the disutility value of CVD is 0.5-0.3=0.2. SAS programs are available to map SF36 scores to SF6D preference/utility scores (https://labs.dgsom.ucla.edu/hays/pages/programs_utilities). SF6D utility scores can then be regressed on respondents' characteristics such as sex, age, primary diagnosis, treatment exposures, and health conditions present at the time of the survey. The regression equations can be used to calculate the utility score for a specific health condition for a set of respondent's characteristics. The corresponding disutility score can then be computed from the calculated utility score as described above. The advantages of this method are that the health conditions are not limited to those available in the GHDE, and that they would be more relevant and specific to childhood cancer survivors. Additionally, the disutility scores would not be fixed values but can vary according to individuals' characteristics via the regression models. Using repeated SF36 responses from individuals also will enable estimation of longitudinal ageing-related trends in utility scores. It should be noted that the years lived with a health condition weighted by disutility results in $YLD_{isutility}$ which differs from the conventionally defined YLD, which hereon will be denoted as $YLD_{isability}$. Hence, YLL + $YLD_{isutility}$ does not equal DALY as conventionally defined. Regardless, $YLD_{isutility}$ provides an alternative measure of disease burden as experienced/reported by individuals.

As survivors in the CCSS live longer lives and experience increasing disease burden attributed to late effects of their primary cancer, treatment, and ageing, $YLD_{isutility,}$ $YLD_{isability,}$ YLL, and DALY offer an alternative holistic approach to assess health consequences combining mortality with morbidity burdens. Because survivors were found to have a 6-fold higher risk for one or more severe life-threatening CHCs compared to sibling controls,[5] we will estimate DALY in siblings for comparison.

Finally, as treatment approaches have evolved over time with a remarkable improvement in survival, examination of DALY, its components, as well as $YLD_{isutility}$ across treatment era will allow quantification of the effects of these advances on disability and quality of life in survivors. Herein, we propose to estimate these measures for the lifetimes of CCSS survivors and sibling controls and examine the relationships between DALY and socio-demographic and treatment factors, as well as treatment era in the survivors.

4. SPECIFIC AIMS

Aim 1: Estimate years of life lost from premature death (YLL), years lived with disability due to chronic conditions ($YLD_{isability}$), and Disability Adjusted Life-years (DALY = YLL + $YLD_{isability}$) for the lifetimes of the CCSS survivors and sibling controls. DALY, YLL, $YLD_{isability}$ of survivors will be compared to those of sibling controls.

Hypothesis: DALY, YLL, $YLD_{isability}$ of survivors will be greater than those of sibling controls.

Aim 2: Identify the socio-demographic (e.g. female, lower income), diagnosis and treatment-related (e.g. earlier treatment era, brain tumor, radiation therapy), and behavioral (e.g. smoker, physical inactivity) modifiers of DALY, YLL, $YLD_{isability}$ in survivors.

Hypothesis: Adjusted for relevant covariates, DALY, YLL, $YLD_{isability}$ are lower in the more recent treatment era.

Aim 3a: Estimate the Quality of Life (QOL) weights (also known as preference or utility scores) and determine the socio-demographic and, for survivors, treatment-related factors associated with QOL weights in survivors and sibling controls.

Aim 3b: Estimate the lifetime $YLD_{isutility}$ in survivors and siblings and compare $YLD_{isutility}$ to $YLD_{isability}$ in the respective group.

Hypothesis 3b.1: $YLD_{isutility}$ and $YLD_{isability}$ are different

Hypothesis 3b.2: Adjusted for relevant covariables, $YLD_{isutility}$ is lower in the more recent treatment era.

5. ANALYSIS FRAMEWORK

a. Outcome(s) of interest:

Vital status (alive, dead, lost to follow-up)
Date of last known vital status
Date of onset of malignancies and CHCs with Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grade ≥ 2

For deceased CCSS survivors and siblings:
- Cause of death (COD)
- Date of onset of the disease associated with the cause of death, if known

b. Subject population:

CCSS baseline and expansion cohort, siblings

c. Covariables for estimating mortality and disease incidence probabilities

Time-invariant:
Birthdate
Sex
Indicator for survivor/sibling control
Family ID# (to identify survivor/sibling pair)
Race/Ethnicity
Primary cancer diagnosis
Date of primary cancer diagnosis
Date of primary cancer treatment
Index date for sibling controls
Chemotherapy data (agent, cumulative dose)
- Alkylating agent
- Anthracyclines

- Bleomycin
- Dactinomycin
- Epipodophyllotoxins
- Platinum agents
- Steroids
- Vinca drugs
- Others (chemotherapy data will be examined to identify agents with large enough frequencies for consideration)

Radiation (field, dose)
Hematopoietic cell transplantation
Surgery

Time-varying (at the time of questionnaire response):
Date of questionnaire response
Marital status
BMI
Total household income
Health insurance coverage
Employment status
Ever drank alcohol (up to the time of questionnaire)
Ever smoked (up to the time of questionnaire)
Participated in any physical activity in the past month

For DALY and its components which are lifetime fixed measures, time-varying independent variables, if reasonable, will be transformed to time-invariant variables. e.g. ever drank, ever smoked, ever participated in physical activity for >70% of week, etc. On the other hand, for longitudinal estimation of QOL weights, time-varying independent variables listed below can be handled as such.

Variables needed for estimating QOL weights using SF-36 questions in the follow-up questionnaires of 2003, 2014, 2017, 2019:
Age (at questionnaire)
Highest education level attained (at questionnaire)
Employed (Yes/No) (at questionnaire)
Total household income past year (at questionnaire)
Health insurance status (at questionnaire)
Smoking (at questionnaire)
- Current smoking status
- Total years smoked (up to time of questionnaire)

Alcohol consumption (at questionnaire)
- Current drinking status
- Total years drank (up to time of questionnaire)

Body mass index (at questionnaire)
Physical activity (at questionnaire)
- Number of days in the last 7 days exercised/did sports for at least 20 minutes resulting in sweat/breath hard

Daily Activities (22 items)
Health and Well-being (14 items)

d. Estimation of DALY, YLL, $YLD_{isability}$, $YLD_{isutility}$

The following analyses will be conducted first.

Grouping of CODs:

The frequencies of CODs in the CCSS will be examined and combined to create clinically relevant COD groups. The 369 health conditions at the GHDE will also be combined into groups consistent with the COD groups created for the CCSS. From here on, COD will imply grouped COD.

Incidence functions to be estimated using the CCSS data:

All-cause mortality function. The data of the deceased participants will be used to estimate the all-cause mortality probability function. Mortality probabilities will be modeled using the exponential functions of attained age, sex, race/ethnicity, other socio-demographic and behavioral variables, and for survivors, age at primary cancer therapy, treatment era, and treatment groups.

Cause-specific mortality function. COD-specific mortality functions will be estimated using the exponential function as described above.

Disease incidence function. Age at onset of the health conditions, grouped as done for CODs with additional groups added as necessary, will be estimated using the exponential function as described above. From here on, health condition will imply grouped health conditions.

AMFIT of the EPICURE package of software will be used for estimation.[33]

The estimation procedures for DALY, YLL, $YLD_{isability}$, $YLD_{isutility}$ below apply to survivors and sibling controls but differs for the deceased and those last known to be alive.

Deceased individuals:

YLL is calculated as the difference between life expectancy (LE), conditional on the year of death, and age at death. Sex-, race (white/non-white), age-, calendar-year-specific US Life Table will be used to determine LE for each deceased individual at their age at death.

$YLD_{isability}$ is the interval between age at death and age at onset of the health condition that led to death, weighted by the disability weight of the health condition. Disability weights of 369 diseases and injuries are available at the GHDE (https://ghdx.healthdata.org/record/ihme-data/gbd-2019-disability-weights).[11] COD in the CCSS will be mapped to the health conditions in the GHDE and the corresponding disability weights obtained. The age at first occurrence of the health condition associated with the COD and other nonfatal comorbidities of grades 2 to 4 on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) structure will be determined using the baseline and follow-up CCSS questionnaires.

$YLD_{isutility}$ is the interval between age at death and onset age of the health condition that led to death, weighted by the disutility weight of the health condition. Disutility weights for various health conditions will be estimated using the SF36 portion of the CCSS Follow-up Questionnaires-2 (2003), -5 (2014), -6 (2017), and -7 (2019) data. SF36 scores will be computed for each respondent and mapped to SF6D preference-based index (or utility) scores (https://labs.dgsom.ucla.edu/hays/pages/ programs_utilities).

SF6D preference score quantifies the utility value placed by individuals on different health states (0 for death; 1 for perfect health). Utility values are quality-of-life (QOL) weights used for calculating the quality-adjusted life-years in cost-effectiveness analysis. A disutility value is computed by subtracting the utility value of a health condition from the

utility value without that health condition, e.g. if the utility value for cardiovascular disease (CVD) is 0.3 and that without CVD is 0.5, then the disutility value of CVD is 0.5-0.3=0.2.

SF6D preference (or utility) scores derived from SF36 scores will be regressed longitudinally using Generalized Estimation Equation on respondents' characteristics (e.g. age, sex, education, primary diagnosis, treatment group, smoking) and health conditions (e.g. CVD, respiratory disease, SMN). The regression equations will be used to estimate the age-specific utility score of a respondent with a particular health condition and the set of sociodemographic and treatment characteristics. The disutility score will be computed from the predicted utility score.

For individuals with known cause of death, the onset date of the health condition associated with the COD will be determined using the CCSS baseline and follow-up questionnaire data, if available. CODs will be aligned with the corresponding complications in the GHDE to obtain the disability weight. If the onset date of a COD is unknown (e.g. COD of cardiovascular disease [CVD] was not self-reported), we will estimate the onset age retrospectively by microsimulation using the disease incidence function estimated from the CCSS data. The incidence rate conditional on death at age *D* will be used to determine the onset age of the health condition before age *D.* This process will be repeated *m* times to calculate the average onset age. If an individual has *n* CHCs of grade ≥2 in addition to the one associated with the COD, $YLD_{isability}$ and $YLD_{isutility}$ will be calculated by using the overall disability or disutility weight, $1-(1-w_1) \times (1-w_2) \times \ldots \times (1-w_n) \times (1-w_{n+1})$, over the time interval lived with *n+1* CHCs (w_i = disability or disutility weight for the i^{th} CHC, *i=1,…,n+1*).

For deceased individuals with unknown cause of death, microsimulation will be conducted *z* times per person using cause-specific mortality functions to assign *z* CODs. For each COD simulated, an onset age will be assigned by microsimulation using the disease incidence function. YLDs will be computed as death age minus onset age, weighting the interval by the disability or disutility weight of the disease associated with the COD. The average of *z* YLDs will be used as the YLD estimate for the individual with unknown COD. If the individual has *n* CHCs of grade ≥2 preceding death, the disability weight will account for the *n* CHCs as described above.

Individuals last known to be alive:

YLL: The (future) age at death will be projected by simulation. All-cause mortality probabilities will be used in *r* rounds of simulation to assign *r* death ages for each person last known to be alive. For each death age, LE will be determined from the US Census table based on the year of death. YLL for an individual will be estimated by taking the difference between the projected death age and LE, averaged across *r* simulation trials. LE for death ages projected to occur beyond the latest available Census table will be extracted using the latest available LE table.

$YLD_{isability}$: Having projected the age at death, COD-specific mortality functions will be applied in simulation to determine the most likely cause of death at that age. This process will be repeated for every *r* death age simulated. The age at onset of each COD will be estimated by simulation using the disease incidence functions. We will use the mean disability weight of the CCSS participants who died of specific COD (instead of the mean of disability weights of all CODs included in the GHDE) as weight for calculating $YLD_{isability}$. The average of *r* $YLD_{isability}$ will be used as the $YLD_{isability}$ estimate for an individual last known to be alive. The process of determining YLL and $YLD_{isability}$ will be repeated in microsimulation to compute the average YLL and $YLD_{isability}$ for each individual.

$YLD_{isutility}$: Disutility weights for the health conditions will be estimated as described earlier using the SF36 portion of the CCSS Follow-up Questionnaires-2 (2003), -5 (2014), -6 (2017), and -7 (2019) data. Respondents' SF36 scores will be mapped to SF6D preference-based index scores, for calculating the disutility weights. **$YLD_{isutility}$** will be estimated using disutility weights in the method described for estimating **$YLD_{isability}$.**

e. Variability of DALY, YLL, $YLD_{isability}$, $YLD_{isutility}$

For tractability, we will assume that LEs in the US Census tables to be fixed values. Variability in DALY is introduced by the use of all-cause and COD-specific mortality functions estimated from the CCSS survivor and sibling data for projecting the age and COD in non-deceased participants and deceased participants with unknown COD. Additional variability arises from using the disease incidence function for estimating the disease onset age in non-deceased and deceased individuals with unknown disease onset age. GHDE also provides 95% uncertainty intervals for the disability weights. We will generate *m* random sets of coefficients for all-cause and COD-specific mortality functions and disease incidence functions assuming multivariate normal distribution with the coefficients as mean vector with covariance matrices estimated by AMFIT for use in simulation to obtain the 95% simulation-based uncertainty intervals for DALY and its components. Uncertainty intervals of the disability weights will also be incorporated.

f. Relationship between DALY and its determinants

The dependence of YLL, $YLD_{isability}$, $YLD_{isutility}$, DALY on their determinants will be examined by using the generalized linear models. The factors to be considered will include fixed variables such as primary diagnosis, age at diagnosis, sex, race/ethnicity, treatment group, highest education level attained and median income level, ever employed, ever had health insurance, ever smoked, ever drank, minimum/maximum/average BMI, and average number of days spent ≥20 minutes exercise. Univariable and multivariable analyses will be conducted. For comparison with siblings, we will use the Generalized Estimating Equation models to account for within-family correlations in survivors and their siblings, adjust for covariables and test the significance of the difference between survivors and siblings.

g. Examples of specific tables and figures:

Table 1. Estimates of DALY, YLL, $YLD_{isability}$, $YLD_{isutility}$ in survivors and sibling controls

	Survivors (n=)				Siblings (n=)			
	DALY	YLL	$YLD_{isability}$	$YLD_{isutility}$	DALY	YLL	$YLD_{isability}$	$YLD_{isutility}$
Overall mean ± sd								
Sex								
Male								
Female								
Race/ethnicity								
Non-Hispanic White								

Other								
Age at diagnosis (or index date)								
0-5y								
6-10y								
11-15y								
16-20y								
Year of diagnosis (or index year)								
1970 - 1974								
1975 - 1979								
1980 - 1984								
1985 - 1989								
1990 - 1994								
1995 - 1999								
Race								
White								
Non-white								
Diagnosis					NA	NA	NA	NA
Hodgkin disease					NA	NA	NA	NA
ALL					NA	NA	NA	NA
NHL					NA	NA	NA	NA
Osteosarcoma					NA	NA	NA	NA
Soft tissue sarcoma					NA	NA	NA	NA
Other					NA	NA	NA	NA
Treatment					NA	NA	NA	NA
None/Surgery only					NA	NA	NA	NA
Chemotherapy only					NA	NA	NA	NA
Radiotherapy only					NA	NA	NA	NA
Chemo+radiation					NA	NA	NA	NA

HCT					NA	NA	NA	NA

NA – not applicable

Table 2. Determinants of DALY, YLL, $YLD_{isability,}$ $YLD_{isutility}$ in childhood cancer survivors

	DALY			YLL			$YLD_{isability}$			$YLD_{isutility}$		
Variable	β	SD	p-value	β	SD	p-value	β	SD	p-value	β	SD	p-value
Age at diagnosis												
Female												
BMI (avg/min/max over follow-up)												
Diagnosis												
Hodgkin disease												
ALL												
NHL												
Osteosarcoma												
Soft tissue sarcoma												
Other												
Treatment year (continuous)												
Treatment era												
1970 - 1974												
1975 - 1979												
1980 - 1984												
1985 - 1989												
1990 - 1994												
1995 - 1999												
Treatment												
None/Surgery only												
Chemotherapy only												
Radiotherapy only												
Chemo+radiation												

HCT												
Highest education attained												
Did not complete HS												
Completed HS/GED												
Some college/training after HS												
College grad/post-graduate												
Smoking												
Never												
Ever												
Drinking												
Never												
Ever												
Average # days exercised/did sports for at least 20 minutes (across questionnaires)												
Survivors vs sibling controls*												

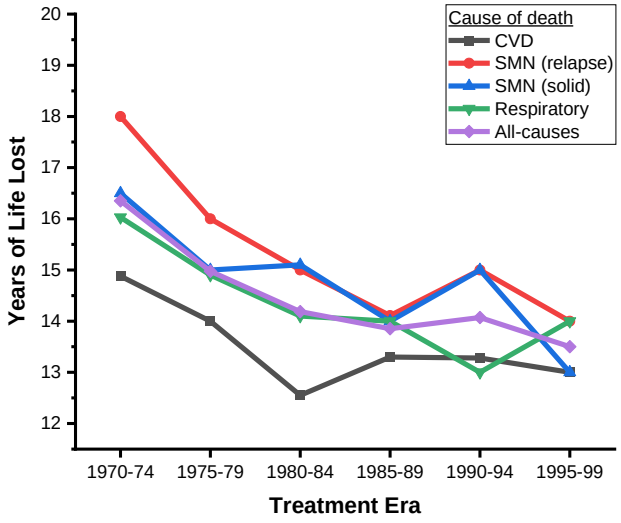
*Comparison will include non-treatment related covariables.

Table 3. Comparison of DALY, YLL, $YLD_{isability,}$ $YLD_{isutility}$ between survivors and siblings

	DALY			YLL			$YLD_{isability}$			$YLD_{isutility}$		
Variable	β	SD	p-value	β	SD	p-value	β	SD	p-value	β	SD	p-value
Age at study enrollment												
Female												
BMI (avg/min/max over follow-up)												
Study enrollment year (continuous)												
Treatment												
None/Surgery only (survivors)												
Chemotherapy only												
Radiotherapy only												

Chemo+radiation												
Sibling												
Highest education attained												
Did not complete HS												
Completed HS/GED												
Some college/training after HS												
College grad/post-graduate												
Smoking												
Never												
Ever												
Drinking												
Never												
Ever												
Average # days exercised/did sports for at least 20 minutes (across questionnaires)												

Figure 1. Adjusted YLL by treatment era (similar plots for DALY, $YLD_{isability,}$ $YLD_{isutility}$ will be made)



6. SPECIAL CONSIDERATIONS

Once the data are provided by the CCSS Statistical Center, F.L. Wong's group at City of Hope (COH) will estimate the mortality and incidence functions and, depending on the CCSS statistical resources, possibly the QOL/utility functions. A similar project is ongoing at COH based on 1577 adult recipients of allogeneic Hematopoietic Cell Transplantation. Mortality functions were estimated using the COD from deceased patients, which were applied to alive patients in microsimulation to project their (future) date of death and COD. Lacking disease incidence data, the age of disease onset was estimated using the incidence rates in GHDE. Disability weights from GHDE were also used. Microsimulation in has been programmed in R which will be modified for the CCSS cohort.

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