Analysis Concept Proposal

***Title*:** Body Mass Index and Risk of Subsequent Neoplasms

***Working groups*:** Second Malignancy (primary), Chronic Disease (secondary), Biostatistics

Investigators:

Lenat Joffe, MD, MS	lv2351@cumc.columbia.edu
Lucie Turcotte, MD, MPH, MS	turc0023@umn.edu
Nina Kadan-Lottick, MD, MPH	nina.kadan-lottick@yale.edu
Joseph Neglia, MD, MPH	jneglia@umn.edu
Kevin Oeffinger, MD	kevin.oeffinger@duke.edu
Greg Armstrong, MD, MSCE	greg.armstrong@stjude.org
Kirsten K. Ness, PhD	kiri.ness@stjude.org
Philip Lupo, PhD	Philip.lupo@bcm.edu
Elena Ladas, PhD	ejd14@cumc.columbia.edu
Rebecca Howell, PhD	rhowell@mdanderson.org
Brent Weil, MD	brent.weil@childrens.harvard.edu
Yutaka Yasui, PhD	Yutaka.Yasui@stjude.org
Wendy Leisenring, ScD	wleisenr@fhcrc.org
Miriam Conces, MD	Miriam.Conces@nationwidechildrens.org
Michael Arnold, MD, PhD	Michael.Arnold@childrenscolorado.org

Background and Rationale:

Childhood cancer survivors have an up to 6-fold increased incidence of subsequent malignant neoplasms (SMNs) for more than 20 years following their primary disease.[1,2] Excess body weight and lower levels of physical activity are well-recognized risk factors for developing several primary cancers among adults in the general population;[3-6] and among children with cancer, high body mass index (BMI) is associated with higher rates of cancer relapse, as well as poorer overall and event-free survival.[7,8] The independent and/or concomitant contributions of excess body weight and low physical activity to the development of subsequent neoplasms (SNs) among long-term childhood cancer survivors are unknown.

In 2012, it was estimated that 3.6% of all new cancer diagnoses in adults were attributable to high BMI.[4] In a meta-analysis examining BMI and cancer incidence, *Reneha et al* showed that each 5-kg/m^2 increase in BMI conferred an increased risk of esophageal adenocarcinoma (RR=1.52; 95% CI: 1.33 to 1.74), colon cancer (RR=1.24; 95% CI: 1.20 to 1.28), and multiple myeloma (RR=1.11; 95% CI: 1.05 to 1.18) in men; and endometrial cancer (RR=1.59; 95% CI: 1.50 to 1.68), gallbladder cancer (RR=1.59; 95% CI: 1.02 to 2.47), esophageal adenocarcinoma (RR=1.51; 95%CI: 1.31 to 1.74), and postmenopausal breast cancer (RR=1.12; 95% CI: 1.08 to 1.16) in women.[3] Obesity has also been associated with increased meningioma risk (RR=1.45, 95% CI: 1.26-1.67).[9] The mechanistic relationship between excess fat and cancer risk has not yet been fully elucidated, but sex steroids, metabolic hormones, and inflammation are hypothesized contributors.[10] In a small, single-institution study (N=59), *Moke et al* demonstrated that survivors of pediatric cancer who were obese both at diagnosis and at the end of therapy had a four-fold increased risk of SMNs compared to those who were not obese [aOR, 4.44 (95% CI 1.37–14.34)]. Moreover, though not statistically significant, SMNs had increased association with higher BMI Z-score at diagnosis [OR 1.27 (95% CI 0.99–1.63)] as well as higher BMI categories at diagnosis [aOR overweight, 1.25 (95% CI 0.55–2.52); aOR obese, 2.51 (95% CI 1.00–6.29)].[8] These findings underscore the need to expand upon this highly understudied area of research.

Low physical activity levels in survivors are associated with elevated BMI and confer increased likelihood of all-cause mortality.[11-13] Additionally, higher physical activity levels have been suggested to reduce the risk of up to 13 adult-onset malignancies by 10-25%.[10] A pooled analysis of 12 prospective adult U.S and European cohorts reinforced these findings in 10 of the 13 malignancies, irrespective of patient BMI.[5] Childhood cancer survivors

are predisposed to being overweight or obese[13,14] and consistently report sub-optimal physical activity levels;[15,16] however the association with SNs is unknown.

Studies with large sample sizes and long follow-up periods are necessary to investigate the association between modifiable risk factors, such as overweight/obese BMI and physical activity, with the risk of SNs in childhood cancer survivors. The proposed study will leverage data from patients enrolled in the Childhood Cancer Survivor Study (CCSS) cohort to further investigate this critically understudied area in a large cohort with uniform, longitudinal ascertainment of these measures. These data are essential to informing intervention studies aimed at reducing the burden, and associated morbidity and mortality, of SNs among future patients.

Specific Aims:

Aim1: Determine the association between overweight or obese BMI during cancer survivorship and risk of SNs, adjusted for original cancer diagnosis, surgical intervention, radiation and chemotherapy exposures, and other lifestyle factors including smoking and alcohol use.

Aim 2: Determine the association between overweight or obese BMI at cancer diagnosis and risk of SNs, adjusted for original cancer diagnosis, surgical intervention, radiation and chemotherapy exposures, and other lifestyle factors including smoking and alcohol use.

Aim 3: Determine the association between lower physical activity levels during cancer survivorship and the risk of SNs, adjusted for original cancer diagnosis, surgical intervention, radiation and chemotherapy exposures, and other lifestyle factors including smoking and alcohol use.

Exploratory Aim: Determine if the association between low physical activity and SNs is mediated by elevated BMI or if these are 2 independent risk factors for SN risk.

Hypotheses:

1. Survivors who have an overweight or obese BMI for any length of time during CCSS follow-up will have increased risk of SNs compared to survivors who are normal or underweight throughout follow-up.
2. Survivors who have an obese BMI for any length of time during CCSS follow-up will have increased risk of SNs compared to those who are in the overweight BMI category for any length of time during follow-up.
3. Survivors who have overweight or obese BMI at time of childhood cancer diagnosis will have increased risk of SNs compared to survivors who have normal or underweight BMI at diagnosis.
4. Survivors who have obese BMI at time of childhood cancer diagnosis will have increased risk of SNs compared to those who are in the overweight BMI category at diagnosis.
5. Survivors who have overweight or obese BMI at time of childhood cancer diagnosis in addition to any time during CCSS follow-up, will have increased risk of SNs compared to survivors who have overweight or obese BMI at diagnosis or follow-up alone.
6. Survivors who do not meet national guideline recommendations for moderate or vigorous physical activity levels at any time during CCSS follow-up will have increased risk of SNs compared to those who meet these recommendations for any length of time during the follow up period.

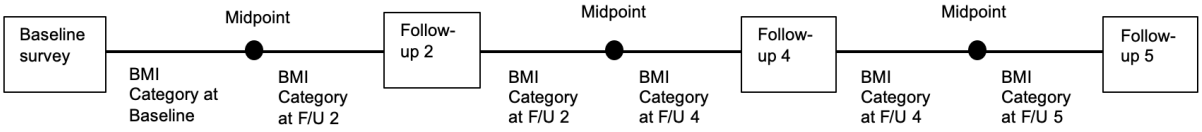
Analysis Framework:

1. Approach and Population of Interest: A retrospective analysis will be conducted on survivors enrolled in the CCSS cohort, diagnosed between 1970-1999, who have BMI data available at time of diagnosis as well as during the survivorship period, defined as 5 years from first childhood cancer diagnosis (N=24,362), and who also have physical activity levels available from follow-up surveys.

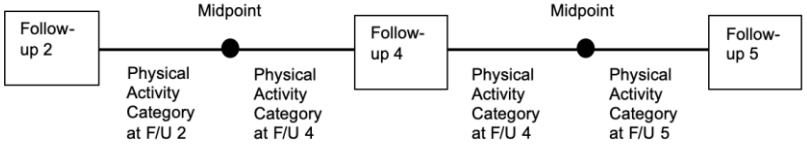
2. Outcome Measures: The primary outcome is development of SNs after childhood cancer. SNs will be identified via self- or proxy-reported surveys confirmed by pathological report consistent with previous CCSS methodology. If pathology report is unavailable, death certificate or medical records will be used for verification. SNs are coded by histology using the International Classification of Diseases for Oncology (ICD-O). Of interest for this study are SMNs, including invasive neoplasms as classified by ICD-O, 3rd

Edition, behavior code 3,[17] as well as ductal carcinoma in situ (DCIS) of the breast, nonmelanoma skin cancer (NMSC) and meningiomas. All other nonmalignant neoplasms will be excluded from the analysis.

3. Predictor Variables:
   3.1. BMI category at the time of cancer diagnosis for survivors will be calculated from height, weight, and body surface area (BSA) measures reported in the medical record abstraction form (MRAF), section D.1 - D.10. BMI categories will be determined as per CDC guidelines.[18] Each BMI category will be analyzed independently.
      3.1.1. Underweight < 18 years old: ≤ 5th percentile; ≥ 18 years old: BMI < 18.5 kg/m^2
      3.1.2. Normal < 18 years old: 6th - 84th percentile; ≥ 18 years old: BMI 18.5-24.9 kg/m^2
      3.1.3. Overweight < 18 years old: 85 - 94th percentile; ≥ 18 years old: BMI 25-29 kg/m^2
      3.1.4. Obese < 18 years old: ≥95th percentile; ≥ 18 years old: BMI ≥ 30 kg/m^2
   3.2. BMI category during the survivorship period will be calculated from self-reported heights and weights for survivors at each available CCSS survey follow-up time point. Height and weight data correspond to A.10 - A.11 in the Baseline survey, 7 - 8 in follow-up survey 2, and A.1 - A.2 in follow-up surveys 4 and 5. BMI categories will be determined by CDC guidelines, as outlined in section 3.1 above.
      3.2.1. Time spent in each BMI category will be calculated in years, as follows:



   3.3. Physical activity levels are ascertained as the average number of minutes per day (or week) of moderate or vigorous physical activity. Data available starting with follow-up 2 and corresponds to D.1 - D.7 in follow-up survey 2, N.15 - N.21 in follow-up survey 4, and N.15 - N.24 in follow-up survey 5.
      3.3.1. A binary variable for whether subjects meet the nationally recommended guidelines for physical activity will be generated at each available CCSS survey follow up time point.
         3.3.1.1. For individuals ≥ 18 years old: 150 minutes of moderate intensity physical activity or 75 minutes of vigorous physical activity weekly.
         3.3.1.2. For children and adolescents 6-17 years old: 60 minutes of moderate to vigorous physical activity daily.[19]
         3.3.1.3. Time spent in each physical activity level category will be calculated in years, as follows:



      3.3.2. Mean number minutes of physical activity per week will be will also be examined as a continuous variable.

4. Descriptive Characteristics of the Cohort:
   4.1. Demographics: age at diagnosis, sex, race/ethnicity, primary childhood malignancy, attained age, time from initial diagnosis, decade of diagnosis (1970s, 80s, 90s)
   4.2. Health behaviors:
      4.2.1. Smoking status/tobacco use (yes [ever]/no). Corresponds to N.1 - N.2 in the Baseline survey, L.1 - L.6 in follow-up survey 2, and N.7 - N.14 in follow-up surveys 4 and 5.
      4.2.2. Alcohol use (never/moderate/moderate-high/high-risk). Corresponds to question N.3 - N.8 in the Baseline survey, and N.1 - N.6 in follow-up surveys 4 and 5. Alcohol use categories will be defined as per the U.S. Department of Health and Human Services and U.S. Department of Agriculture.[20] For each individual the highest reported alcohol use category will be used for analysis.
         4.2.2.1. Moderate use - women: up to one drink per day, men: up to two drinks per day.
         4.2.2.2. Moderate-high – women: two to three drinks per day, men: three to four drinks per day.
         4.2.2.3. High-risk use - women: four or more drinks per day, men: five or more drinks per day.

4.2.2.4. One alcoholic drink-equivalent is described as containing 14 g (0.6 fluid oz) of pure alcohol. Reference beverages that are one alcoholic drink-equivalent: 12 fluid ounces of regular beer (5% alcohol), 5 fluid ounces of wine (12% alcohol), or 1.5 fluid ounces of 80 proof distilled spirits (40% alcohol).

4.3. Therapeutic exposures:
- 4.3.1. Therapeutic radiation (yes/no)
  - 4.3.1.1. Cranial radiation (yes/no)
    - 4.3.1.1.1. Brain segment 1 (infratentorial region) (yes/no)
    - 4.3.1.1.2. Brain segment 2 (surrogate for pituitary) (yes/no)
    - 4.3.1.1.3. Brain segment 3 (frontal supratentorial region) (yes/no)
    - 4.3.1.1.4. Brain segment 4 (posterior supratentorial region) (yes/no)
  - 4.3.1.2. Neck radiation (yes/no)
  - 4.3.1.3. Chest radiation (yes/no)
  - 4.3.1.4. Abdominal radiation (yes/no)
  - 4.3.1.5. Pelvis radiation (yes/no)
  - 4.3.1.6. Extremity radiation (yes/no)
  - 4.3.1.7. Spine (yes/no)
  - 4.3.1.8. Maximum dose to exposed body region (Gy), divided into 3-5 dose categories
  - 4.3.1.9. Age (years) at first radiation exposure
- 4.3.2. Chemotherapy agent class and cumulative doses
  - 4.3.2.1. Alkylating agents (yes/no/cumulative dose, reported as cyclophosphamide equivalents[21])
  - 4.3.2.2. Anthracyclines (yes/no/cumulative dose, reported as doxorubicin equivalents)
  - 4.3.2.3. Epipodophyllotoxins (yes/no/cumulative dose)
  - 4.3.2.4. Corticosteroids (yes/no)
- 4.3.3. Surgical intervention (yes/no)
  - 4.3.3.1. Lower limb amputation (yes/no)
  - 4.3.3.2. Lower limb joint replacement or other repair (yes/no)
  - 4.3.3.3. Upper limb amputation (yes/no)
  - 4.3.3.4. Upper limb joint replacement or other repair (yes/no)
  - 4.3.3.5. Procedures of the spine (yes/no)
  - 4.3.3.6. Other (limb shortening or lengthening) (yes/no)

Statistical Approach:

Descriptive statistics will be calculated for baseline demographics, health behaviors, and therapeutic exposures. These will include mean, standard deviation, median, minimum and maximum for continuous measures and frequency and proportion for categorical measures.

Aim1: Determine the association between overweight or obese BMI during cancer survivorship and risk of SNs, adjusted for original cancer diagnosis, surgical intervention (4.3.3 above), radiation exposure (4.3.1 above, site/maximum dose) whose effects are possibly modified by age at RT, and chemotherapy exposures including corticosteroids, and other lifestyle factors including smoking and alcohol use.

We will use the same time-to-event analysis approach that has been used in the previous CCSS SN papers, namely, the piecewise-exponential models. The analytic strategy will be to build a base clinical model with all relevant clinical and demographic factors and then evaluate BMI by adding it to the base clinical model. While BMI during survivorship may be a mediator between cancer treatment variables and SNs, we will adjust for cancer treatments' direct effects on SNs in the base clinical model and assess the influence of BMI during survivorship on SN risk. The challenging aspect will be the time-dependency of BMI (and lifestyle factors): we will employ the midpoint change method illustrated in 3.2.1 above. We will start the analysis at the baseline CCSS survey as the survivors' BMI information prior to the baseline is not available (except the BMI at cancer diagnosis).

Aim 2: Determine the association between overweight or obese BMI at cancer diagnosis and risk of SNs, adjusted for original cancer diagnosis, surgical intervention (4.3.3 above), radiation exposure (4.3.1 above,

site/maximum dose) whose effects are possibly modified by age at RT, and chemotherapy exposures including corticosteroids, and other lifestyle factors including smoking and alcohol use.

We will follow the same approach as Aim 1, but using the overweight and obese status at cancer diagnosis instead of BMI during survivorship. This analysis will start at the CCSS cohort entry (5 years since diagnosis).

Aim 3: Determine the association between lower physical activity levels during cancer survivorship and the risk of SNs, adjusted for original cancer diagnosis, surgical intervention (4.3.3 above), radiation exposure (4.3.1 above, site/maximum dose) whose effects are possibly modified by age at RT, and chemotherapy exposures including corticosteroids, and other lifestyle factors including smoking and alcohol use.

We will follow the same approach as Aim 1, but using the physical activity levels, instead of BMI, during survivorship.

Exploratory Aim: Determine if the association between low physical activity and SNs is mediated by elevated BMI or if these are 2 independent risk factors for SN risk.

The concept of this mediation analysis is that the physical activity level at the CCSS follow-up 2 survey influences the subsequent SN risk via changes in BMI from the CCSS follow-up 2 survey. We will categorize the BMI change from the follow-up 2 BMI into several categories. The analysis will start the statistical model of Aim 3 but additionally adjusted for BMI at follow-up 2: the association of the physical activity level with SN risk in this model is the non-mediated association of interest. Then we add the BMI change to this model to assess the attenuation of the association of interest. Power of this analysis is limited: thus, we consider this an exploratory aim.

Proposed Tables and Figures:

Table 1. Participant Characteristics

Characteristic	N	%	P
Age at baseline, years			
<18			
18-29			
30-39			
40-54			
Sex			
Male			
Female			
Race			
White			
Black			
Other			
Unknown			
Ethnicity			
Hispanic			
Non-Hispanic			
Age at diagnosis, years			
0-3			
4-9			
10-14			
15-20			
Original Cancer diagnosis			
Leukemia			
CNS malignancy			
Hodgkin lymphoma			
Non-Hodgkin lymphoma			
Kidney tumors			
Neuroblastomas			
Soft tissue sarcoma			
Bone tumors			
Treatment era			
1970-1979			
1980-1989			
1990-1999			
Chemotherapy			

Anthracycline (mg/m2) None 0-100 101-300 >300 Epipodophyllotoxin (mg/m2) None 1-1000 1001-4000 >4000 Alkylating agent (CED) (mg/m2) None 1-3999 4000-7999 8000+ Corticosteroids Yes No			
Radiation None Cranial -Segment 1 -Segment 2 -Segment 3 -Segment 4 Neck Chest Abdomen Pelvis Extremity Spine Maximum dose to any region (Gy) Age at first radiation exposure			
Surgery None Lower limb amputation Lower limb joint replacement or other repair Upper limb amputation Upper limb joint replacement or other repair Procedures of the spine Other (limb shortening or lengthening)			
BMI at diagnosis Underweight Normal Overweight Obese			
Max BMI at follow-up Underweight Normal Overweight Obese			
Physical activity (meeting DOH guidelines) Yes No			
Tobacco use Yes/ever No			
Alcohol use Never Moderate Moderate-high High-risk			
Type of Subsequent Neoplasm None Malignant Nonmelanoma skin cancer Meningioma Other benign neoplasm			
Vital Status Alive			

Deceased			

Table 2. Comparing SN development among childhood cancer survivors, by BMI category at cancer diagnosis

SN Category	Underweight			Normal			Overweight			Obese		
	N	%	P	N	%	P	N	%	P	N	%	P
All												
Hematologic Leukemia Lymphoma												
Solid Organ Breast Bone GI STS Thyroid Other												
CNS Glial Medulloblastoma PNET Meningioma Other												
Skin Melanoma NMSC												

Table 3. Comparing SN development among childhood cancer survivors, by maximum BMI category at survivorship follow-up

SN Category	Underweight			Normal			Overweight			Obese		
	N	%	P	N	%	P	N	%	P	N	%	P
All												
Hematologic Leukemia Lymphoma												
Solid Organ Breast Bone GI STS Thyroid Other												
CNS Glial Medulloblastoma PNET Meningioma Other												
Skin Melanoma NMSC												

Table 4. Comparing SN development among childhood cancer survivors, by lowest physical activity level

SN Category	Low Physical Activity Level			Moderate – Vigorous Physical Activity Level		
	N	%	P	N	%	P
All						
Hematologic Leukemia Lymphoma						
Solid Organ Breast Bone GI STS Thyroid						

Other						
CNS Glial Medulloblastoma PNET Meningioma Other						
Skin Melanoma NMSC						

Table 5. Association of patient and treatment factors with development of SNs among childhood cancer survivors: univariate analysis

Patient or Treatment Domain	**Any SMNs**				**Hematologic SMNs**				**Solid Organ SMNs**				**CNS SNs**				**Skin SNs**			
	N (%)	SIR	95% CI	P	N (%)	SIR	95% CI	P	N (%)	SIR	95% CI	P	N (%)	SIR	95% CI	P	N (%)	SIR	95% CI	P
Age at baseline, years <18 18-29 30-39 40-54																				
Sex Male Female																				
Race White Black Other Unknown																				
Ethnicity Hispanic Non-Hispanic																				
Age at diagnosis, years 0-3 4-9 10-14 15-20																				
Original Cancer diagnosis Leukemia CNS malignancy Hodgkin lymphoma Non-Hodgkin lymphoma Kidney tumors Neuroblastomas Soft tissue sarcoma Bone tumors																				
Chemotherapy Anthracycline (mg/m2) None 0-100 101-300 >300 Epipodophyllotoxin (mg/m2) None 1-1000 1001-4000 >4000 Alkylating agent (CED) (mg/m2) None 1-3999 4000-7999 8000+ Corticosteroids Yes																				

No																				
Radiation None Cranial -Segment 1 -Segment 2 -Segment 3 -Segment 4 Neck Chest Abdomen Pelvis Extremity Maximum dose to any region (Gy) Age at first radiation exposure																				
Surgery None Lower limb amputation Lower limb joint replacement or other repair Upper limb amputation Upper limb joint replacement or other repair Procedures of the spine Other (limb shortening or lengthening)																				
BMI at diagnosis Underweight Normal Overweight Obese																				
Max BMI at follow-up Underweight Normal Overweight Obese																				
Physical activity (meeting DOH guidelines) Yes No																				
Tobacco use Yes/ever No																				
Alcohol use Never Moderate Moderate-high High-risk																				

Table 6. Association of BMI and physical activity levels with development of SNs among childhood cancer survivors: multivariate analysis

Patient or Treatment Domain	**Any SMNs**				**Hematologic SMNs**				**Solid Organ SMNs**				**CNS SNs**				**Skin SNs**			
	N (%)	SIR	95% CI	P	N (%)	SIR	95% CI	P	N (%)	SIR	95% CI	P	N (%)	SIR	95% CI	P	N (%)	SIR	95% CI	P
Age at baseline, years <18 18-29 30-39 40-54																				
Sex Male Female																				
Race White Black Other																				

Unknown																				
Ethnicity Hispanic Non-Hispanic																				
Age at diagnosis, years 0-3 4-9 10-14 15-20																				
Original Cancer diagnosis Leukemia CNS malignancy Hodgkin lymphoma Non-Hodgkin lymphoma Kidney tumors Neuroblastomas Soft tissue sarcoma Bone tumors																				
BMI at diagnosis Underweight Normal Overweight Obese																				
BMI at follow-up Underweight Normal Overweight Obese																				
Physical activity (meeting DOH guidelines) Yes No																				
Chemotherapy Anthracycline (mg/m2) None 0-100 101-300 >300 Epipodophyllotoxin (mg/m2) None 1-1000 1001-4000 >4000 Alkylating agent (CED) (mg/m2) None 1-3999 4000-7999 8000+ Corticosteroids Yes No																				
Radiation None Cranial -Segment 1 -Segment 2 -Segment 3 -Segment 4 Neck Chest Abdomen Pelvis Extremity Maximum dose to any region (Gy) Age at first radiation exposure																				

Surgery None Lower limb amputation Lower limb joint replacement or other repair Upper limb amputation Upper limb joint replacement or other repair Procedures of the spine Other (limb shortening or lengthening)																				

**Please note that this table will be constructed with backwards-stepwise regression, and additional variables significant at p<0.10 in Table 4 will be added.*

Table 7. Relative risk of SNs among childhood cancer survivors, by BMI category at cancer diagnosis

	Any SMNs				**Hematologic SMNs**				**Solid Organ SMNs**				**CNS SNs**				**Skin SNs**			
	N (%)	RR	95% CI	P	N (%)	RR	95% CI	P	N (%)	RR	95% CI	P	N (%)	RR	95% CI	P	N (%)	RR	95% CI	P
Underweight																				
Normal																				
Overweight																				
Obese																				

* adjusted for baseline age, age at diagnosis, sex, race/ethnicity, original cancer diagnosis, surgical history, chemotherapy, and radiation site/max dose as well as age at RT exposure

Table 8. Relative risk of SNs among childhood cancer survivors, by maximum BMI category at survivorship follow-up

	Any SMNs				**Hematologic SMNs**				**Solid Organ SMNs**				**CNS SNs**				**Skin SNs**			
	N (%)	RR	95% CI	P	N (%)	RR	95% CI	P	N (%)	RR	95% CI	P	N (%)	RR	95% CI	P	N (%)	RR	95% CI	P
Underweight																				
Normal																				
Overweight																				
Obese																				

* adjusted for baseline age, age at diagnosis, sex, race/ethnicity, original cancer diagnosis, surgical history, chemotherapy, and radiation site/max dose as well as age at RT exposure

Table 9. Relative risk of SNs among childhood cancer survivors, by lowest physical activity level

	Any SNs				**Hematologic SMNs**				**Solid Organ SMNs**				**CNS SMNs**				**Skin SMNs**			
	N (%)	RR	95% CI	P	N (%)	RR	95% CI	P	N (%)	RR	95% CI	P	N (%)	RR	95% CI	P	N (%)	RR	95% CI	P
Low Physical Activity Level																				
Moderate/ Vigorous Physical Activity Level																				

* adjusted for baseline age, age at diagnosis, sex, race/ethnicity, original cancer diagnosis, surgical history, chemotherapy, and radiation site/max dose as well as age at RT exposure

Figure 1. Cumulative incidence of any SNs at 30 years after cancer diagnosis, by BMI category at cancer diagnosis

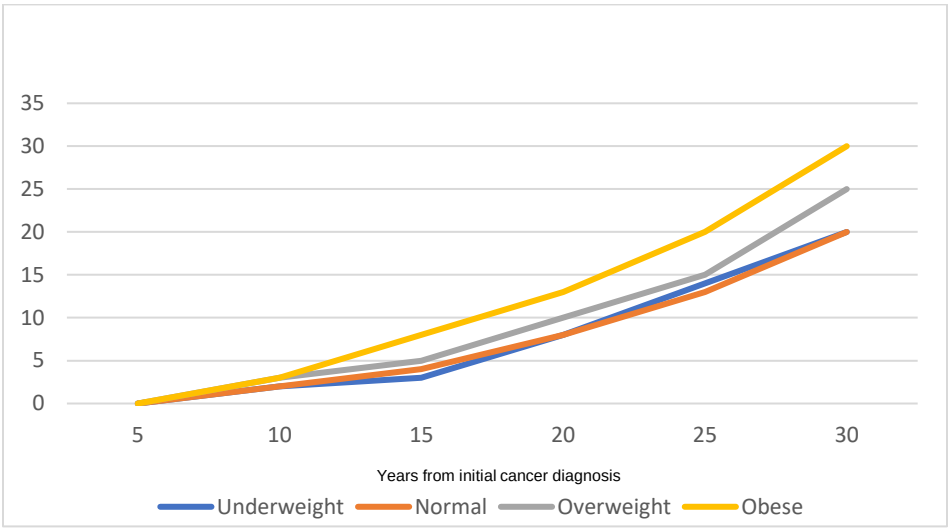


Figure 2. Cumulative incidence of any SNs at 30 years after cancer diagnosis, by BMI category at survivorship follow-up

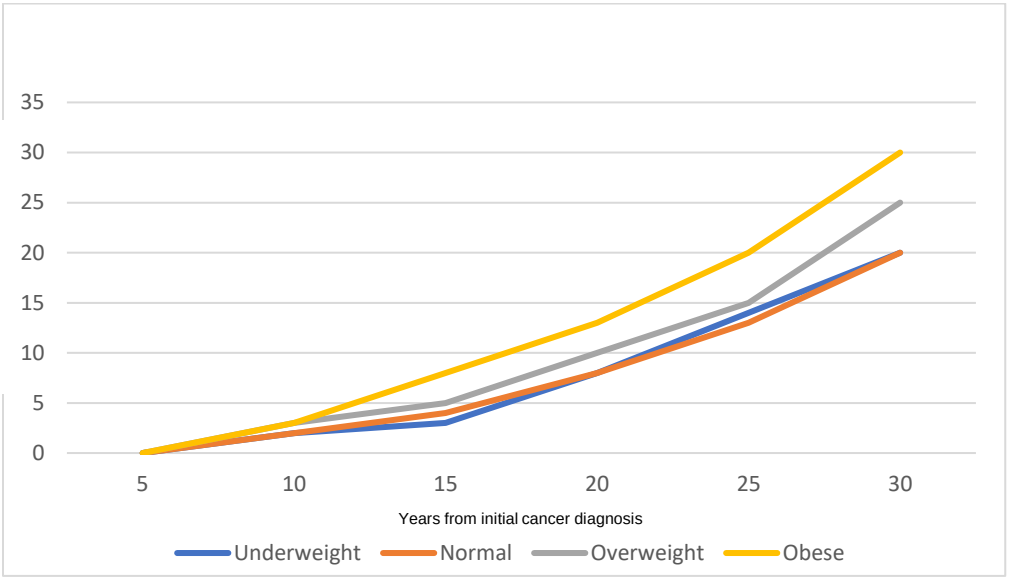


Figure 3. Cumulative incidence of any SNs at 30 years after cancer diagnosis, by physical activity level

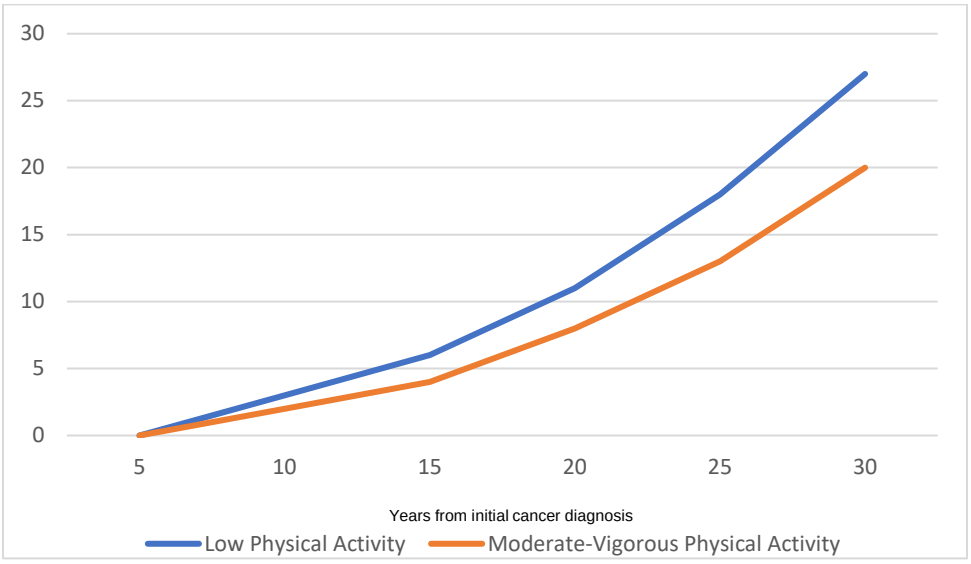
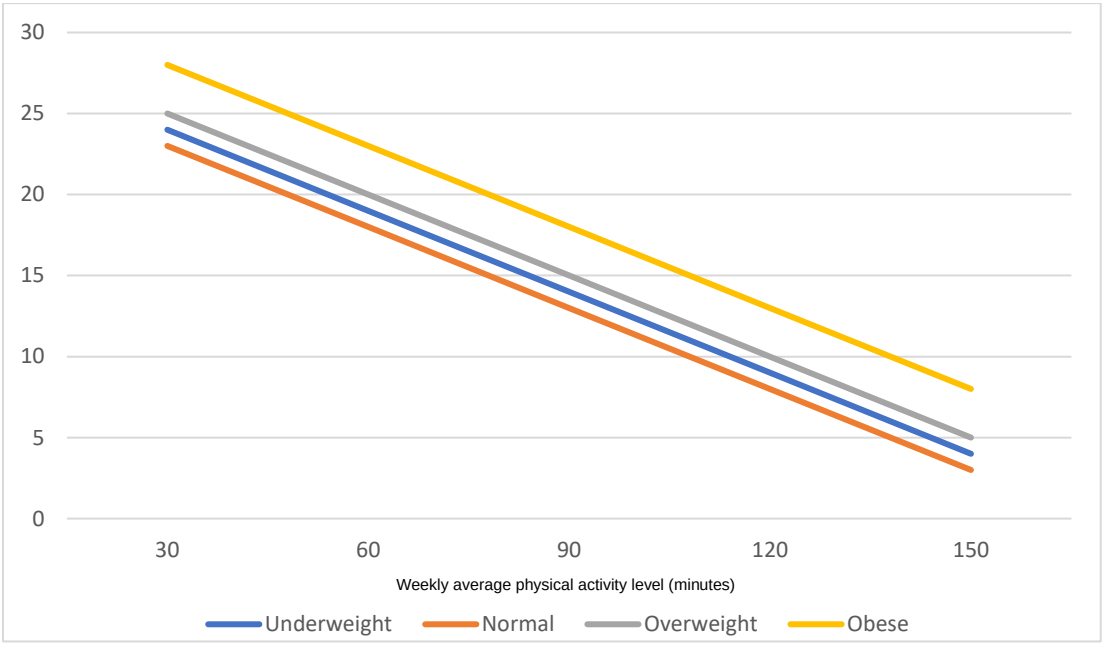


Figure 4. Cumulative incidence of second malignancy at with increased physical activity level, by BMI at survivorship follow-up



References:

1. Gramatges MM, Liu Q, Yasui Y, et al. Telomere content and risk of second malignant neoplasm in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2014;20(4):904-911.
2. Turcotte LM, Liu Q, Yasui Y, et al. Temporal Trends in Treatment and Subsequent Neoplasm Risk Among 5-Year Survivors of Childhood Cancer, 1970-2015. *JAMA.* 2017;317(8):814-824.
3. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet.* 2008;371(9612):569-578.
4. Goodwin PJ, Chlebowski RT. Obesity and Cancer: Insights for Clinicians. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2016;34(35):4197-4202.
5. Moore SC, Lee IM, Weiderpass E, et al. Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults. *JAMA internal medicine.* 2016;176(6):816-825.
6. Rezende LFM, Sa TH, Markozannes G, et al. Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770 000 cancer cases. *British journal of sports medicine.* 2018;52(13):826-833.
7. Joffe L, Ladas EJ. Nutrition during childhood cancer treatment: current understanding and a path for future research. *Lancet Child Adolesc Health.* 2020;4(6):465-475.
8. Moke DJ, Hamilton AS, Chehab L, Deapen D, Freyer DR. Obesity and Risk for Second Malignant Neoplasms in Childhood Cancer Survivors: A Case-Control Study Utilizing the California Cancer Registry. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.* 2019.
9. Shao C, Bai LP, Qi ZY, Hui GZ, Wang Z. Overweight, obesity and meningioma risk: a meta-analysis. *PloS one.* 2014;9(2):e90167.
10. Giovannucci E. An Integrative Approach for Deciphering the Causal Associations of Physical Activity and Cancer Risk: The Role of Adiposity. *J Natl Cancer Inst.* 2018;110(9):935-941.
11. Scott JM, Li N, Liu Q, et al. Association of Exercise With Mortality in Adult Survivors of Childhood Cancer. *JAMA Oncol.* 2018;4(10):1352-1358.
12. Cox CL, Nolan VG, Leisenring W, et al. Noncancer-related mortality risks in adult survivors of pediatric malignancies: the childhood cancer survivor study. *Journal of cancer survivorship : research and practice.* 2014;8(3):460-471.
13. Green DM, Cox CL, Zhu L, et al. Risk factors for obesity in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2012;30(3):246-255.
14. Oeffinger KC, Mertens AC, Sklar CA, et al. Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2003;21(7):1359-1365.
15. Devine KA, Mertens AC, Whitton JA, et al. Factors associated with physical activity among adolescent and young adult survivors of early childhood cancer: A report from the childhood cancer survivor study (CCSS). *Psycho-oncology.* 2018;27(2):613-619.
16. Ness KK, Leisenring WM, Huang S, et al. Predictors of inactive lifestyle among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer.* 2009;115(9):1984-1994.
17. World Health Organization: International classification of diseases for oncology. https://apps.who.int/iris/bitstream/10665/96612/1/9789241548496_eng.pdf?ua=1. Accessed July, 2020.
18. Centers for Disease Control and Prevention. Healthy Weight, Body Mass Index (BMI). https://www.cdc.gov/healthyweight/assessing/bmi/index.html.

19. *U.S. Department of Health and Human Services. Physical Activity Guidelines for Americans, 2nd edition.* Washington, DC: U.S Department of Health and Human Services2018.
20. U.S. Department of Health and Human Services, U.S. Department of Agriculture. Dietary Guidelines for Americans 2015-2020, eighth edition. https://health.gov/our-work/food-nutrition/2015-2020-dietary-guidelines/guidelines/. Accessed August, 2020.
21. Green DM, Nolan VG, Goodman PJ, et al. The cyclophosphamide equivalent dose as an approach for quantifying alkylating agent exposure: a report from the Childhood Cancer Survivor Study. *Pediatric blood & cancer.* 2014;61(1):53-67.