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Requirements to submit AOI:

A comprehensive review of previously published data has been completed.: Yes

The specific aims are clear and focused.: Yes

The investigator has appropriate experience and expertise to develop the concept proposal; if not, has identified a mentor or senior co-investigator.: Yes

The investigator agrees to develop an initial draft of the concept proposal within 6 weeks of approval of the AOI and to finalize the concept proposal within 6 months.: Yes

Project Title: Exposure-specific absolute risks of second primary cancer and cardiovascular disease for five-year survivors of childhood Hodgkin's lymphoma

Planned research population (eligibility criteria): Five-year survivors of Hodgkin's lymphoma diagnosed before age 21 who are participants of the Childhood Cancer Survivor Study

Proposed specific aims: Second primary cancers and cardiovascular events are some of the most frequent and serious late-effects experienced by survivors of childhood Hodgkin's lymphoma (HL) (1). A number of association studies have identified demographic and treatment-related risk factors for second cancers and cardiovascular disease in survivors of childhood HL (2-3).

Absolute risk is the probability that an individual with a specific health and exposure history will experience an adverse event within a defined time interval given the presence of competing events. Relative risk associations have limited clinical value because they are insufficient to determine a survivor's actual probability of experiencing an event. Some studies have reported cumulative incidence by childhood cancer diagnosis for specific second cancers and cause-specific mortality (4-7). These represent the average absolute risk over combinations of risk factors in the given subpopulation of survivors. Absolute risks as functions of risk factors for leading adverse outcomes in survivors have not been thoroughly considered. In this study, using data from the Childhood Cancer Survivor Study, we will quantify absolute risks for second primary cancers and for cardiovascular disease of HL survivors (n~3,000), based on demographic, treatment characteristics, and modifiable factors, such as smoking, alcohol consumption, and physical activity, whose impact on risk is unclear. Both self-reported cardiovascular disease and cardiovascular-related mortality will be examined. The absolute risk framework is relevant for clinical decision-making because it provides an individualized

prediction of the probability of disease within a specified time interval. A further advantage of this framework is that, by assessing the risk of all outcomes on the same probability scale, it allows direct comparison of the risk of disparate outcomes. Thus, this study will provide a unique perspective on the exposure-specific risks of second cancer and cardiovascular morbidity/mortality that could thus be useful for the development of long-term management guidelines of HL survivors (8). References 1. Oeffinger KC, Hudson MM, Mertens AC, et al: Increasing Rates of Breast Cancer and Cardiac Surveillance Among High-Risk Survivors of Childhood Hodgkin Lymphoma Following a Mailed, One-Page Survivorship Care Plan. *Pediatric Blood & Cancer* 56:818-824, 2011. 2. Castellino SM, Geiger AM, Mertens AC, et al: Morbidity and mortality in long-term survivors of Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. *Blood* 117:1806-1816, 2011 3. Swerdlow AJ, Higgins CD, Smith P, et al: Second Cancer Risk After Chemotherapy for Hodgkin's Lymphoma: A Collaborative British Cohort Study. *Journal of Clinical Oncology* 29:4096-4104, 2011 4. Neglia JP, Friedman DL, Yasui Y, et al: Second malignant neoplasms in five-year survivors of childhood cancer: Childhood cancer survivor study. *Journal of the National Cancer Institute* 93:618-629, 2001 5. Mertens AC, Yasui Y, Neglia JP, et al: Late mortality experience in five-year survivors of childhood and adolescent cancer: The childhood cancer survivor study. *Journal of Clinical Oncology* 19:3163-3172, 2001 6. Armstrong GT, Liu Q, Yasui Y, et al: Late Mortality Among 5-Year Survivors of Childhood Cancer: A Summary From the Childhood Cancer Survivor Study. *Journal of Clinical Oncology* 27:2328-2338, 2009 7. Meadows AT, Friedman DL, Neglia JP, et al: Second Neoplasms in Survivors of Childhood Cancer: Findings From the Childhood Cancer Survivor Study Cohort. *Journal of Clinical Oncology* 27:2356-2362, 2009 8. Travis LB, Ng AK, Allan JM, et al: Second Malignant Neoplasms and Cardiovascular Disease Following Radiotherapy. *Journal of the National Cancer Institute* 104:357-370, 2012

Will the project require non-CCSS funding to complete?: Yes
If yes, what would be the anticipated source(s) and timeline(s) for securing funding?: The work will be supported by intramural funds of the National Cancer Institute.

Does this project require contact of CCSS study subjects for . . .

Additional self-reported information: No
Biological Samples: No
Medical record data: No
If yes to any of the above, please briefly describe.:

What CCSS Working Group(s) would likely be involved? (Check all that apply)

Second Malignancy: Primary
Chronic Disease: Secondary
Psychology / Neuropsychology:
Genetics:
Cancer Control: Secondary
Epidemiology / Biostatistics:

To describe the anticipated scope of the study, please indicate the specific CCSS data to be included as outcome (primary or secondary) or correlative factors. (Check all that apply)

Late mortality: Secondary
Second Malignancy: Primary

Health Behaviors

Tobacco: Correlative Factors
Alcohol: Correlative Factors
Physical activity: Correlative Factors
Medical screening:
Other:
If other, please specify:

Psychosocial

Insurance:
Marriage:
Education:
Employment:
Other:
If other, please specify:

Medical conditions

Hearing/Vision/Speech:
Hormonal systems:
Heart and vascular: Primary
Respiratory:
Digestive:
Surgical procedures:
Brain and nervous system:
Other:
If other, please specify:

Medications

Describe medications:

Pregnancy and offspring:
Family History:

Psychologic/Quality of Life

BSI-18:
SF-36:
CCSS-NCQ:
PTS:
PTG:
Other:
If other, please specify:

Chronic conditions (CTCAE v3):
Health status:

Demographic

Age: Correlative Factors
Race: Correlative Factors
Sex: Correlative Factors
Others:
If others, please specify:

Cancer treatment

Chemotherapy: Correlative Factors
Radiation therapy: Correlative Factors
Surgery:

Anticipated sources of statistical support

CCSS Statistical Center:
Local institutional statistician: Yes
If local, please provide the name(s) and contact information of the statistician(s) to be involved.:
Stephanie Kovalchik will be the lead statistician on this project.
Will this project utilize CCSS biologic samples?: No

If yes, which of the following?

Buccal cell DNA:
Peripheral blood:
Lymphoblastoid cell lines:
Second malignancy pathology samples:
Other requiring collection of samples:
If other, please explain:

Other general comments: