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Study Title:

CHRONIC HEALTH CONDITIONS AND FUNCTION AFTER NON-HODGKIN LYMPHOMA IN THE CHILDHOOD CANCER SURVIVOR STUDY:
Analysis Concept Form

Working Group and Investigators:

Elizabeth Bluhm, M.D., M.P.H.	bluhme@mail.nih.gov	Fax 301-402-0207
Robert Hayashi, M.D.	hayashi_r@kids.wustl.edu	
Charles A Sklar, M.D.	sklarc@MSKCC.ORG	
Kevin Oeffinger, M.D.	oeffingk@mskcc.org	
Anna Meadows, M.D.	MEADOWS@email.chop.edu	
Ann C. Mertens, Ph.D.	mertens@epi.umn.edu	
Les L. Robison, Ph.D.	robison@epi.umn.edu	
Sarah Donaldson, M.D.	sarah@reyes.stanford.edu	
Lillian Meacham, M.D	lmeacha@emory.edu	
Marilyn Stovall, Ph.D.	mstovall@mdanderson.org	
Leslie Segal-Kersun, M.D.	segall@email.chop.edu	
John Whitton, M.S.	jwhitton@fhcrc.org	
Peter Inskip, Sc.D.	inskippe@mail.nih.gov	

1.0 Background and rationale:

Although non-Hodgkin lymphoma (NHL) is most often a disease of older adults, the diagnosis accounts for 6% of cancers in children younger than age 20 in the United States (Ries, 1999). Five-year survival approaches 85-95% for limited-stage disease in children (Sandlund, 2000), while overall 5-year survival in children younger than age 19 diagnosed during 1992-1998 is estimated as 78.2% (Ries, 2002). The increasing number of young survivors approaching middle and late adulthood should prompt an exploration of late adverse health effects after treatment (Schwartz, 1999). Prior research in the Childhood Cancer Survivor Study (CCSS) has revealed an increased risk of dying from cardiopulmonary disease after NHL (Mertens, 2001), but incidence and prevalence of organ system dysfunction have only been described based on small studies. Specific late adverse effects reported in follow-up series after NHL include: left ventricular dysfunction (Haddy, 1998), gonadal dysfunction in men and women (Bokemeyer, 1994; Haddy, 1998), hepatitis C (Haddy, 1998), cognitive impairment, increased mean whole body percent fat (Nysom, 2003), avascular necrosis of bone (Ribeiro, 2001), endodontal disease (Oguz, 2004), and worse general health status versus siblings of children with cancer (Hudson, 2003).

Risk factors for adverse medical outcomes after NHL may relate to a combination of genetic predisposition and specific toxic exposures during chemotherapy and radiation therapy (RT), as seen in studies of late effects after other childhood cancers. Agents or

treatments associated with specific adverse late effects after NHL have not been identified. The mainstay of NHL treatment is systemic chemotherapy, but RT to bulk disease was an integral part of treatment regimens until the mid- to late-1990's (Link, 1990). Despite similarity to acute lymphoblastic leukemia (ALL) regimens, the late effects after NHL appear to be milder than after ALL. However, few studies of survivors of childhood NHL permit precise estimates of the occurrence of late or long-term effects or identification of risk factors (Haddy, 1998). A study of the 1082 patients treated for NHL from 1970 to 1986 and surviving 5 years until enrollment in the CCSS cohort would permit the largest and most comprehensive study of late effects after treatment with detailed exposure information available from medical records.

The CCSS cohort provides an opportunity to assess the prevalence of and risk factors for the following outcomes: 1) cardiopulmonary disease (cardiomyopathy/congestive heart failure (CHF), coronary artery disease, valvular heart disease, hypertension, cardiac arrhythmias, and pulmonary fibrosis); 2) neuropathy (peripheral neuropathy, symptoms of central neurologic dysfunction, and neurocognitive deficits); 3) gonadal dysfunction and infertility; 4) endocrine dysfunction (thyroid hormone abnormalities, diabetes mellitus, growth delay, obesity, avascular necrosis of bone); 5) hepatic disease; 6) renal insufficiency; 7) visual defects; 8) measures of functional adjustment; and 9) health-related behaviors among NHL survivors including usual source of health care. Understanding these late health effects and functioning is crucial to providing follow-up medical care to this population and avoiding harm in future patients who undergo cancer therapy. A previous study concept incorporated mortality and second malignant neoplasms after NHL, and these topics will not be covered in this proposal.

2.0 Overall objectives:

The Steering Committee in February, 2004, set forth objectives to evaluate survivorship issues for each original cancer diagnosed in CCSS. This proposal describes variables of interest in the overview of survivorship issues in individuals with the diagnosis of NHL. The Chronic Diseases Working Group in October, 2005, called for cohesive reporting of late effects after a single cancer diagnosis to serve as a reference for health care providers.

2.1 Specific aims:

- To assess the occurrence and timing of onset of self-reported dysfunction of the following organ systems after treatment for NHL: cardiopulmonary, neurologic, gonadal/reproductive, endocrine, hepatic, renal, and visual.

- To compare the hazard ratio (to be reported as relative risk (RR)) of each medical outcome among NHL survivors relative to the rate or proportion in siblings of childhood cancer patients (NHL survivor-sibling comparison) and as a function of treatment regimen (internal comparisons among NHL survivors).

- To evaluate measures of functional adjustment including employment, health insurance coverage, and living situation, in NHL survivors versus siblings.

- To describe interactions with health care providers, including insurance coverage, age- and risk-appropriate screening, and protective or risky health behaviors.

3.0 Hypotheses: Based on previous smaller series of NHL survivors and adverse late effects after other cancers, we anticipate that NHL survivors will experience an elevated risk of dysfunction of several organ systems relative to siblings, with treatment-specific effects hypothesized below. Pending review of the data, it is possible that there may be insufficient power to address some hypotheses. The initial strategy will be to look for any evidence of dysfunction in each organ systems using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (as described in detail in the analysis framework outcome variable section); subsequent examinations will pursue details of abnormal organ system function. Hypotheses of *a priori* interest are listed below.

3.1 Cardiopulmonary: Cardiomyopathy (CHF) will be increased after exposure to >200 mg/m^2 doxorubicin, mediastinal irradiation, or both, with an increased effect with younger age at therapy. Pericardial disease will be increased in NHL survivors relative to siblings. Coronary artery disease, hypertension, cardiac conduction defects/arrhythmias, and valvular heart disease will be increased in NHL survivors after mediastinal irradiation, enhanced by doxorubicin exposure, relative to unexposed NHL survivors and siblings. Pulmonary fibrosis and self-reported pulmonary disease will be increased in NHL survivors exposed to carmustine (BCNU), lomustine (CCNU), cytosine arabinoside (Ara-C), bleomycin, methotrexate, or mediastinal RT, relative to unexposed NHL survivors and siblings, and this effect will be enhanced in smokers.

3.2 Neurologic impairment: Peripheral neuropathy (self-reported) will be increased in NHL survivors exposed to vincristine versus unexposed NHL survivors and siblings. Neurocognitive deficits will be increased in NHL survivors exposed to high-dose intravenous (IV) and intrathecal (IT) methotrexate and cranial RT, especially RT received at younger age and higher doses, relative to unexposed NHL survivors and siblings. Symptoms of central neuropathy such as lack of coordination or motor problems will be increased in NHL survivors exposed to high-dose methotrexate and cranial RT relative to unexposed NHL survivors and siblings

3.3 Gonadal/reproductive: Gonadal failure and infertility will be increased in male and female NHL survivors relative to siblings, and increased in NHL survivors exposured to high cumulative cyclophosphamide doses and pelvic radiation relative to unexposed NHL survivors, and effects in women are expected to be enhanced by cranial RT. In women, both premature ovarian failure and premature menopause are anticipated.

3.4 Endocrine: Hypothyroidism will be increased in NHL survivors with exposure to thyroid RT without shielding. Short stature, obesity, and diabetes mellitus will be increased in cases exposed to cranial RT and total body irradiation versus unexposed NHL survivors and siblings. Avascular necrosis of bone will be increased in NHL survivors exposed to cranial RT, pelvic RT, high-dose methotrexate, and prednisone and other steroids, more so after continuous IV prednisone treatement, relative to unexposed NHL survivors and siblings.

3.5 Hepatic dysfunction: Viral hepatitis will be increased in NHL survivors who received blood products before 1983 relative to unexposed NHL survivors and siblings; other hepatopathy or cirrhosis will not be increased in NHL survivors relative to siblings.

3.6 Renal insufficiency: Renal insufficiency will not be increased in NHL survivors relative to siblings.

3.7 Visual defects: Visual deficits and cataracts will be increased in NHL survivors exposed to prednisone and cranial RT relative to unexposed NHL survivors and siblings.

3.8 Measures of functional adjustment: Psychosocial functioning will be mildly impaired among NHL survivors versus siblings, worse after cranial RT.

3.9 Interactions with the health care system: NHL survivors will underutilize screening and age- and diagnosis-specific health behaviors versus recommendations developed by the Children's Oncology Group (Hudson, 2004). NHL survivors will be more likely to hold health insurance coverage than siblings.

3.10 Additional risk factors and effect modifiers will be sought to explore the susceptibility of some patients to late effects, including age at treatment, gender, smoking, and combinations of therapeutic agents.

4.0 Analysis framework:

4.1 Study Population: Subjects will carry a confirmed diagnosis of non-Hodgkin lymphoma made during the years 1970-1986, will have survived 5 years from diagnosis, have provided informed consent to participate in the CCSS, and have responded to the baseline questionnaire (n=1082). Children under age 21 at diagnosis will be eligible. A sibling comparison group will include all siblings of CCSS subjects for whom questionnaire data are available, regardless of primary diagnosis.

4.2 Outcome Variables: Adverse medical outcomes will be assessed using the NCI CTCAE v3.0 (grades 1-5) for each organ system of interest. CTCAE organ system severity scores have been determined for all conditions reported by CCSS subjects through the efforts of a team of experts (verbal communication, Kevin Oeffinger, 10/19/2005). In all organ systems with a profile of toxicity based on CTCAE v3 measures, we will explore contributing factors. Additionally, hypotheses of a priori interest will be explored for identification of chemotherapy or RT exposures associated with specific symptoms or diagnoses. For psychosocial outcomes and measures of functional adjustment, aggregate or special variables created for the CCSS will be utilized, including health status variables and health care utilization variables. Frequency distributions will be computed for the most common outcomes. Those outcomes with low frequency will not be analyzed in detail. There will be limited power to address rare late events. Specific outcome variables are listed below.

4.2.1 Physical health conditions: Organ system-specific CTCAE v3 outcomes for cardiopulmonary, neurologic, gonadal/reproductive, endocrine, hepatic, renal, visual systems. Where the CTCAE summary outcome is abnormal, the contributing factors will be further explored. Gonadal failure in women will include acute ovarian failure (loss of function <5 years after diagnosis) and premature menopause (loss of function more than 5 years after diagnosis).

4.2.2 Health status: general health, mental health, limitations of activity, functional impairment, pain following cancer, anxiety following cancer.

4.2.3 Health care utilization: general medical contact, general physical exam, cancer-related visit, cancer center visit, emergency room (ER) visit, hospitalization. If available, variables describing basic and optimum risk-based care will be used.

4.2.4 Health insurance coverage, marital status, employment: as reported on most recent questionnaire.

4.2.5 Positive and risky health behaviors: Pap smear within 3 years (females), echocardiogram, colonoscopy, bone mineral density testing, mammography, testing for hepatitis B and C after blood transfusion; current smoking, binge drinking, heavy drinking, physical inactivity (as defined in Castellino, 2005).

4.3 Explanatory variables:

- Any anthracyclines (yes/no), doxorubicin cumulative dose (mg/m^2), duration of total therapy (number of cycles)
- Any epipodophyllotixins (yes/no), cyclophosphamide cumulative dose (mg/m^2), duration of total therapy (number of cycles)
- Other chemotherapy drug exposures, including: BCNU, CCNU, Ara-C, 6-mercaptopurine (6-MP), methotrexate (doses not available), steroids, bleomycin, vincristine (doses not available).

- Irradiation of the breast, thyroid, brain, mediastinum, abdomen, and pelvis within the RT treatment field using first pass coding. Irradiation of the heart, lungs, cranium, ovaries, testes, kidneys, and liver. Dose estimates will be established in collaboration with Marilyn Stovall, using most appropriate assessment of dose in Gy/site.
- CNS prophylaxis with RT (any/none, total radiation dose (Gy))
- Intrathecal chemotherapy (intrathecal methotrexate (mg/m^2))
- NHL relapse (yes/no)
- Surgery (ICD-9 code and date of specific procedure)
- History of blood products transfusion (F2 B6,7)

4.4 Potential confounders and effect modifiers:

- Age at diagnosis of NHL
- Calendar year of diagnosis of NHL
- Current attained age
- Time from NHL diagnosis to current age
- Gender
- Race/ethnicity
- Presence or absence of metastatic cancer at NHL diagnosis
- Cigarette smoking (F2 L1-4) (B N1)

5.0 **Statistical Methods:** Patterns of adverse health outcomes will be described in the cohort of NHL survivors in the CCSS. Symptoms and health outcomes will be assessed by self-report, and are not validated. However, CTCAE aggregate variables for toxicity by organ system exclude psychosomatic dysfunction, and include only physical symptoms, based on extraction of symptoms, diagnoses, and treatments reflecting a single underlying condition (verbal communication, Kevin Oeffinger, 10/18/2005). Frequency distributions will be computed for the most commonly reported medical conditions. Rates of adverse outcomes will be compared with those for siblings of childhood cancer patients using multivariate Cox proportional hazard models to obtain hazard rate ratios (presented as relative risks) (survivor-sibling comparison).

Where there are sufficient numbers, adverse health effects will be stratified by time of occurrence (between diagnosis and end of treatment; less than 5 years after diagnosis; 5 or more years after diagnosis). Where there are sufficient 10-year survivors, an additional category (10 or more years after diagnosis) will be added. Effects with onset less than five years following NHL diagnosis will be presented with the caveat that they are derived from patients who survived for at least five years following diagnosis. Where date of onset is not available, items will not be analyzed with respect to time of onset. Further analyses will seek to identify treatment exposures associated with adverse effects (internal analysis comparing NHL survivors).

Measures of functional adjustment will be assessed using health status variables. Interactions with the healthcare system and health maintenance activities will be evaluated using health care utilization variables and responses to the baseline and second follow-up (FU2) questionnaires. Health care practices will be compared with clinical guidelines developed by the Children's Oncology Group (Hudson, 2004).

Rates and relative hazard rates with associated 95% confidence intervals will be reported. Statistical analysis will be performed using SAS (SAS Institute, Cary, NC) and Epicure (Hirosoft, Seattle, WA). Analyses will be conducted at the National Cancer Institute.

Examples of specific tables and figures:

Table 1. Non-Hodgkin lymphoma patient and sibling characteristics:
(note that categories may be added or modified)

	NHL Survivors No. (%)	**Siblings No. (%)**
Gender		
Male	762 (70%)	
Female	320 (30%)	
Race/ethnicity		
White non-Hispanic	935 (86%)	
Black or African-American	46 (4%)	
Other (6 missing)	95 (9%)	
Age at diagnosis (years)		N/A
≤ 4	184 (17%)	
5-9	326 (30%)	
10-14	346 (32%)	
15-21	226 (21%)	
Mean time since diagnosis (or sibling's diagnosis) (years)		
Extent of disease at diagnosis		N/A
Not metastatic	483 (45%)	
Metastatic	268 (25%)	
Missing information	333 (31%)	
Site of disease		N/A
Lymph nodes/hematopoietic	531 (49%)	
GI	109 (10%)	
Head and neck	78 (7%)	
Bone	52 (5%)	
Heart/mediastinum	81 (7%)	
Unknown primary site	55 (5%)	
All others	176 (16%)	
Year of diagnosis		N/A
1970-78	410 (38%)	
1979-1986	672 (62%)	
Treatment regimen		N/A
RT, no chemotherapy	37 (4%)	
Chemotherapy, no RT	274 (30%)	
RT and chemotherapy	596 (64%)	
Others, missing data	19 (2%)	

Radiation for primary malignancy[a] Chest Abdomen Pelvis Head and/or neck Total body		N/A
Individual drugs Cyclophosphamide Vincristine Methotrexate Adriamycin BCNU Ara-C	 800 (87%) 836 (91%) 791 (86%) 295 (32%) 188 (20%) 413 (45%)	N/A
Classes of drugs Anthracyclines Alkylating agents Epipodophyllotoxins	 525 (57%) 814 (88%) 84 (9%)	
Relapse No Yes		N/A
NDI Vital status on 12/31/02 Alive Dead		
Smoking Never Former Current		

Table 2. Incidence of adverse medical outcomes in NHL survivors and relative risks compared to siblings. (Additional outcome categories will be contingent on data analysis. Rate and RR will also be presented by time period of first occurrence: diagnosis to end of treatment; end of treatment to 5 years after diagnosis; more than 5 years after diagnosis to end of follow-up)

Health outcome	**NHL survivors No.**	**Siblings No.**	**Rate**[b]	**RR (95% CI)**
Cardiopulmonary Any condition (grade 1-4)[c] Severe or life-threatening condition (grade 3 or 4)				

[a] Categories are not mutually exclusive.
[b] Number of events per 1,000 person-years following NHL.
[c] Severity grade refers to CTCAE v3.0 scores.

Coronary artery disease Arrhythmia Heart failure/CHF Hypertension Valvular heart disease Pericardian disease Pulmonary fibrosis				
Neurologic Any condition (grade 1-4) Severe or life-threatening condition (grade 3 or 4) Peripheral neuropathy Coordination/motor problem Neurocognitive deficits				
Gonadal/reproductive: women only Any condition (grade 1-4) Severe or life-threatening condition (grade 3 or 4) Acute ovarian failure Premature menopause Infertility				
Gonadal/reproductive: men only Any condition (grade 1-4) Severe or life-threatening condition (grade 3 or 4) Infertility				
Endocrine/Metabolic Any condition (grade 1-4) Severe or life-threatening condition (grade 3 or 4) Hypothyroidism Hyperthyroidism Short stature (<10th percentile at final height) Obesity Diabetes mellitus Avascular necrosis of bone				
Hepatic dysfunction Any condition (grade 1-4) Severe or life-threatening condition (grade 3 or 4) Cirrhosis Viral hepatitis				
Renal insufficiency Any condition (grade 1-4) Severe or life-threatening condition				

(grade 3 or 4) Need for supplements Dialysis				
Visual deficits Any condition (grade 1-4) Severe or life-threatening condition (grade 3 or 4) Visual difficulties Cataracts				

Table 3. Outcome of late events by treatment group and estimated risk compared to (selected) reference treatment group.

(Because of the multiplicity of factors to be considered, specific treatment exposures to be presented in tables and text will be contingent on data analysis. Dosage categories will be refined using drug scores.)

Outcome	**NHL survivors No.**	**RR (95% CI)**
Coronary artery disease No doxorubicin ≤ 200mg/m^2 doxorubicin > 200 mg/m^2 doxorubicin No mediastinal RT Mediastinal RT > 200 mg/m^2 doxorubicin and mediastinal RT		 1.0 1.0
Cardiomyopathy/CHF No doxorubicin ≤ 200mg/m^2 doxorubicin > 200 mg/m^2 doxorubicin No mediastinal RT Mediastinal RT > 200 mg/m^2 doxorubicin and mediastinal RT		 1.0 1.0
Valvular heart disease No mediastinal RT Mediastinal RT		 1.0
Pulmonary fibrosis No exposure to these 4 drugs Any bleomycin Any BCNU		 1.0

Any CCNU Any Ara-C Any methotrexate No mediastinal RT Mediastinal RT		1.0
Peripheral neuropathy No vincristine Any vincristine		1.0
Neurocognitive deficits No methotrexate Some methotrexate High-dose methotrexate Intrathecal methotrexate No CNS RT Any CNS RT		1.0 1.0
Gonadal failure, females No cyclophosphamide Low dose cyclophosphamide High dose cyclophosphamide No RT Pelvic RT with gonadal exposure CNS RT Both pelvic and CNS RT		1.0 1.0
Infertility, males No cyclophosphamide Low dose cyclophosphamide High dose cyclophosphamide No pelvic RT Pelvic RT with gonadal exposure		1.0 1.0
Infertility, females No cyclophosphamide Low dose cyclophosphamide High dose cyclophosphamide No pelvic RT Pelvic RT with gonadal exposure		1.0 1.0
Any thyroid disorder No thyroid RT Thyroid RT with shield Unshielded thyroid RT		1.0
Hypothyroidism No thyroid RT Thyroid RT with shield		1.0

Unshielded thyroid RT		
Growth delay/ short stature No RT Cranial RT Total body irradiation		1.0
Avascular necrosis of bone No prednisone Prednisone Continuous IV steroids Pulse IV steroids No methotrexate Low-dose methotrexate High-dose methotrexate No pelvic RT Pelvic RT No cranial RT Cranial RT Both cranial RT and prednisone Both cranial RT and methotrexate Both pelvic RT and methotrexate Both pelvic RT and prednisone		1.0 1.0 1.0 1.0
Diabetes mellitus No abdominal RT Abdominal RT No cranial RT Cranial RT		1.0 1.0
Cataracts No prednisone Prednisone No cranial RT Cranial RT Both prednisone and cranial RT		1.0 1.0

Table 4. Measures of functional adjustment after NHL treatment: marital and employment status according to sex

Sex	NHL survivors No.	Siblings No.	Rate in NHL survivors (95% CI)	Siblings No.	Rate in NHL survivors (95% CI)	Siblings No.	Rate in NHL survivors (95% CI)
		Married		Separated or divorced		Never married	
Female							
Male							
		Employed full-time		Employed part-time		Unemployed	
Female							
Male							

Table 5. Measures of functional adjustment in NHL survivors compared to sibling group: health status.

	NHL survivors No.	Siblings No.	RR (95% CI)
Adverse health status			
General health			
Mental health			
Limitations of activity			
Functional impairment			
Pain as a result of cancer			
Anxiety/fears as a result of cancer			
Any adverse health domain			

Table 6. Utilization of the health care system in NHL survivors compared to sibling group. (Additional outcome details will be contingent on data analysis.)

	NHL survivors No.	Siblings No.	RR (95% CI)
Health insurance coverage			
None			
Any			
Private or group health insurance			
Medicaid or Medicare coverage			
Medical care (within previous 2 years)			
General medical contact			
General physical exam			
Cancer-related medical visit			

Cancer center visit ER visit Hospitalization			
Protective health behaviors: After any anthracyclines or mediastinal radiation: Ever have an echocardiogram Echocardiogram within 2 yrs Ever see a cardiologist After mediastinal radiation: Ever mammogram (women only) Mammogram within 2 yrs Any subjects: Bone mineral densitometry Colonoscopy Among women: Pap smear within 3 years After any blood product transfusions: Hepatitis B or C testing			
Risky health behaviors:[d] Current smoking Binge drinking Heavy drinking Physical inactivity			

6.0 <u>Special consideration:</u> N/A

[d] Variables defined in Castellino, 2005.

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