

**Cause-Specific Mortality and Second Cancer Incidence after Non-Hodgkin Lymphoma: A Report from the Childhood Cancer Survivor Study.**

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**Abstract**

*Background:* Second primary malignancies and premature death are a concern for patients surviving treatment for childhood lymphomas. Despite in-depth reports on second cancer risk after Hodgkin lymphoma, there is limited published information on clinical, demographic, and treatment risk factors for second malignant neoplasms (SMNs) or deaths after non-Hodgkin lymphoma (NHL).

*Methods:* We assessed mortality and SMNs among 1,082 five-year survivors of NHL in the Childhood Cancer Survivor Study, a multi-institutional North American retrospective cohort study of pediatric cancer survivors diagnosed between 1970 and 1986 before age 21. We searched the National Death Index for dates and causes of death and inquired about SMNs in periodic questionnaires, with confirmation of all reported SMNs by a study pathologist. We calculated standardized mortality ratios (SMRs) and standardized incidence ratios (SIRs) based on United States population rates. We calculated relative risks (RRs) for death and SMNs by demographic, clinical, and treatment characteristics using proportional hazards modeling. Medical physicists determined organ exposure to radiation therapy (RT) based on clinical RT records.

*Results:* There were 87 deaths among 5-year survivors (SMR=4.2, 95% confidence interval (CI): 1.8, 4.1). Leading causes of death were NHL ( $n=21$ ), solid tumors ( $n=17$ ), circulatory diseases ( $n=12$ ), and leukemia ( $n=10$ ). There were elevated rates of mortality due to NHL, solid tumor SMNs, leukemia, cardiac disease, and pneumonia. The mortality rate remained elevated beyond 20 years after NHL. Risk factors for death included NHL relapse (RR=8.5), doxorubicin (RR=1.8), bleomycin (RR=4.1), platinum agents (RR=4.0), and cardiac RT exposure (RR=1.8). There were 31 SMNs, including 27 solid tumor SMNs (SIR=3.9, 95%.CI: 2.6, 5.7), specifically SMNs of the breast ( $n=6$ , SIR=9.1), thyroid ( $n=6$ , SIR=9.4), oral cavity and pharynx ( $n=3$ ), brain and nervous system ( $n=3$ ), bone ( $n=2$ ) and urinary bladder ( $n=2$ ). Risk factors for solid tumor SMNs were female sex (RR=3.1), mediastinal NHL disease (RR=5.2), and breast RT exposure (RR=4.3). Overall cumulative incidence of solid tumor SMNs from 5 to 20 years after NHL diagnosis was 0.03 (95% CI: 0.02, 0.05).

*Conclusions:* We identified a four-fold risk of mortality and three-fold risk of SMNs in a large cohort of pediatric NHL survivors relative to the general U.S. population. Survivors of childhood NHL, particularly those treated with chest RT, may be at continued increased risk of early mortality and solid tumor SMNs. Health care providers responsible for this population should remain alert to second cancers and other severe late health outcomes.

# Cause-specific mortality and second cancer incidence after non-Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study



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## Introduction

- NHL accounts for 6% of cancers age <20 in US, with 78.2% 5-year survival (for those diagnosed 1992-1998) (Fies LAG et al, U.S. SEER Program, 1975-1998).
- Second primary malignancies (SMNs) and premature death are a concern for the growing population of children surviving treatment for childhood lymphomas.
- Late effects after treatment for non-Hodgkin lymphoma (NHL) are not well characterized, but have appeared to be less severe than after other primary cancers, including Hodgkin lymphoma (HL).

## Study Aims

- To estimate standardized incidence rates (SIR) for occurrence of SMNs and cause-specific standardized mortality rates (SMR) among 5-year survivors of NHL.
- To investigate treatment exposures and demographic and clinical characteristics as predictors of SMNs and death.

## Methods

- Retrospective cohort study of 1,082 five-year survivors of a diagnosis of childhood NHL.
- Eligibility: cancer diagnosis 1970-86 age <21
- Exposure and clinical data: medical records abstraction; organ-specific radiation therapy (RT) exposure classification (breast, thyroid, brain)
- Questionnaires: self-reported second (not subsequent) cancer outcomes with pathologic confirmation.
- Vital status assessment 12/31/2002 via National Death Index search. Underlying cause of death determined from death certificate (79 of 87 deaths).
- SMR, SIR analyses versus U.S. SEER data, standardized by age, sex, and race.
- Poisson regression modeling (SAS PHREG).

## Results

### Study subjects

Participation: 1082 of 1532 eligible subjects (71%).

Figure 1. Demographics and presenting characteristics of NHL patients

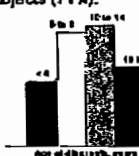
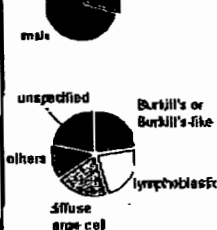
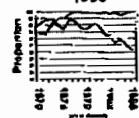


Figure 2. Proportion of subjects treated with chemotherapy or RT, 1970-1995



### Mortality

87 deaths with known date of death, mean age 26 years at death. Mean 17 (range 0-27) years' follow-up: 10,261 person-years to death or study close.

Table 1. Observed (O) and expected (E) overall and cause-specific mortality rate ratios (SMRs).

Cause of death	NHL diagnoses		
	O	E	SMR (95% CI)
All causes	87	21.0	4.2 (3.2, 5.4)
All cancers	48	1.8	26.7 (19.7, 35.4)
NHL	21	0.2	131 (81.4, 200)
Solid nonhematologic tumors	17	1.5	13.3 (7.7, 21.3)
Leukemias	10	0.1	37.2 (17.8, 68.4)
Cardio disease	9	1.3	6.8 (3.1, 13.0)
Cardiomyopathy	6	0.2	24.8 (8.0, 57.8)
Pneumonitis	3	0.2	16.4 (3.1, 45.1)
External causes	10	12.9	0.8 (0.4, 1.4)

## Results

Figure 3. Causes of death after NHL

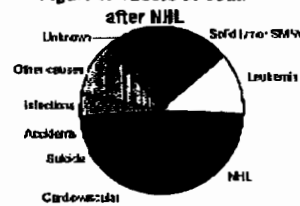


Table 2. Predictors of death from all causes except NHL.

Treatment	O	RR (95% CI)
Female sex (vs. male)	22	3.1 (1.8, 5.0)
Cardiac RT (vs. no cardiac RT)	15	8.1 (1.0, 3.6)
Doxorubicin (vs. no doxorubicin)	21	1.3 (1.0, 3.1)
Bleomycin (vs. no bleomycin)	7	2.4 (1.0, 5.0)

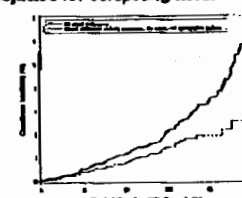
## Second malignancies

Elevated SIRs for cancers of the breast ( $n=6$ , SIR=9.1 (95% CI: 3.3, 19.7)), thyroid ( $n=6$ , SIR=8.4 (95% CI: 3.5, 21.5)), oral cavity and pharynx ( $n=3$ , SIR=4.4 (95% CI: 2.0, 42.1)), bone ( $n=2$ , SIR=11.6 (95% CI: 1.3, 41.8)), brain ( $n=3$ , SIR=5.8 (95% CI: 1.2, 16.8)), and bladder ( $n=2$ , SIR=14.5 (95% CI: 1.6, 52.2)); and for all solid tumors ( $n=21$ , SIR= 3.9 (95% CI: 2.6, 5.7)) and all SMNs ( $n=31$ , SIR=3.5 (2.4, 5.0)).

Table 3. Risk factors for solid tumor SMNs after NHL.

NHL histopathology	years after NHL (n=27)	
	O	RR (95% CI)
Female sex (vs. male)	17	3.1 (1.4, 7.0)
NHL histopathology		
Burkitt's	0	Not determined
Lymphoblastic (vs. unspecified)	6	2.3 (0.7, 9.1)
Diffuse large cell (vs. unspecified)	10	3.4 (1.1, 11.0)
NHL primary site		
Mediastinum (vs. lymph nodes)	7	5.2 (1.0, 33.0)
Treatment exposures		
Breast RT (vs. no breast RT)	12	4.3 (1.6, 11.5)
Thyroid RT (vs. no thyroid RT)	10	1.2 (0.9, 1.5)

Figure 4. Cumulative incidence of second neoplasms after NHL, adjusted for competing risks.



- 3% cumulative incidence of second cancers 20 years after NHL diagnosis
- Non-melanoma skin cancer contributes substantially beyond 20 years

## Conclusions

- Three-fold overall risk of SMNs and four-fold risk of mortality relative to the age-, sex-, race-standardized U.S. population.
- Elevated death rate for deaths from NHL, solid tumor SMNs, leukemia, cardiac disease, pneumonia, and after cardiac RT, doxorubicin, and bleomycin.
- Increased incidence of cancers of the breast, thyroid, oropharynx, bone, brain, and bladder. Increased incidence of solid tumor SMNs for female sex and after mediastinal NHL or breast exposure to RT.
- Limitations: few individual cases of each outcome for evaluation of predictors; did not assess SMNs occurring during first 5 years after NHL.
- Strengths: large dataset with detailed medical records exposure data, for a rare group of pediatric cancers.
- Health care providers should be aware of the persistent risks among NHL 5-year survivors, particularly after chest RT.

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The Childhood Cancer Survivor Study is an NCI-funded initiative (U24 CA55727) to provide and facilitate research among long-term survivors of cancer diagnosed during childhood and adolescence. Investigators interested in potential uses of the resource are encouraged to visit [www.nccs.org](http://www.nccs.org).