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Lina Inagaki, MD Date

Survival After Second Primary Lung Cancer Following Non-Hodgkin Lymphoma:

A U.S. Population-Based Study

By

Lina Inagaki, MD

Master of Public Health

Global Epidemiology

_____

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By

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M.D., University of Tsukuba, 2006

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Abstract

Survival After Second Primary Lung Cancer Following Non-Hodgkin Lymphoma: A U.S. Population-Based Study

By

Lina Inagaki, MD

Background: Cancer survivors are known to have a higher risk of developing second primary cancer (SPC). While Hodgkin lymphoma attracts more attention, non-Hodgkin lymphoma (NHL) survivors account for a larger population of those who develop SPC, and lung cancer accounts for the largest risk of SPC among NHL-survivors. Although a follow-up care plan for cancer survivors has been recommended, concrete guidelines for screening for SPC have not been established.

Methods: Study patients were identified from the SEER program from 1990 through 2009. A total of 863 NHL survivors who developed second primary lung cancer and 3,452 patients among 232,202 first primary lung cancer patients without a history of malignancy were randomly sampled and included in the analysis. The overall survival (OS) between the two groups were compared using a Log-rank test, followed by subset analysis for estimated survival among patients with localized stage lung cancer, in which OS was significantly different, using Cox proportional hazard regression, controlling for sex, race, year of diagnosis, age at diagnosis, histology, tumor grade and marital status.

Results: NHL survivors experienced significantly inferior survival after lung cancer compared to patients without a history of malignancy at localized stage disease: 5-year OS was 33.0% vs. 44.8% ($p < 0.001$), whereas the survival did not differ significantly for regional stage: 13.9% vs. 19.2% ($p = 0.38$), and distant stage: 0% vs. 2.9% ($p = 0.10$). The subset analysis for patients with localized stage showed that the adjusted Hazard Ratio for death among NHL survivors was 1.38 (95% CI, 1.10-1.73; $p = 0.005$).

Conclusion: NHL survivors were shown to have inferior survival when diagnosed with localized stage lung cancer compared to the general population. Because NHL survivors may not benefit from screening, the promotion of lung cancer screening to reduce mortality among NHL survivors warrants careful assessment.

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Table of Contents

List of Tables

List of Figure

Introduction

Due to advances in medical treatments over the past few decades, there are more cancer survivors in society. The number of survivors in the United States was 11.7 million in 2007, while there were only 9.8 million in 2001 and 3 million in 1971 (1). As a consequence of this trend, the incidence of subsequent primary cancer has increased. It has been estimated that among those cancer survivors alive as of January 2002, at least 750,000 (nearly 8%) had multiple primary cancers between 1975 and 2001(2). Thus, an emerging issue in public health is elucidating the epidemiology and mechanisms of subsequent malignancies to estimate their effects on society. In clinical settings, questions remain regarding the best practices for screening and treating second primary cancers, considering the cumulative effect of prior therapies.

Cancer survivors may face issues specific to their prior therapy, especially the long-term effects of treatment on their physical and psychosocial health. It is recommended that cancer survivors have a survivorship care plan after successful treatment for their first cancer. Clinicians should be able to provide patients with a summary of treatment and plan of aftercare, including follow-up schedules for visits and testing, screening for early detection of subsequent cancer, as well as management of treatment-related effects and other health problems (3).

The survivorship care plan, however, lacks scientific evidence for establishing concrete recommendations: who needs to be screened for which cancer and at what intervals.

Current follow-up plans for cancer survivors at oncology clinics are usually up to five or ten years, based on cancer type, followed by regular visits to a primary care physician. A more desirable follow-up plan in cancer survivorship has not been identified.

It is speculated that survivors have a higher risk of developing second primary cancer and that the prognosis is poorer compared to the general population. For instance, many previous studies focusing on the risk of second primary cancer among Hodgkin lymphoma survivors found an elevated risk (4-6). Because Hodgkin lymphoma is characterized by its outstandingly good prognosis, decades after treatment, cumulative mortality from second primary cancers exceeds mortality from Hodgkin lymphoma (6). Hodgkin lymphoma survivors are shown to be at elevated risk of solid cancers (7).

Non-Hodgkin lymphoma (NHL), on the contrary, affects a larger population. The incidence rate was 19.6/100,000 per year for NHL, while it was 2.8/100,000 per year for HL based on cases diagnosed in 2005-2009 from 18 SEER geographic areas. The number of patient who developed subsequent solid cancer was 5,490 among NHL survivors, whereas it was 1,336 among HL survivors, according to the SEER program database between 1973 and 2000 (4). Though considerable attention has been paid to the population of HL survivors, few studies have focused on NHL survivors' risk of second primary cancer. More attention to NHL survivors is essential in order for lymphoma clinics to follow up their patients.

Successful cancer screening reduces the incidence rate of advanced disease, which eventually leads to a reduction in cancer mortality and incidence (8). Screening for breast, cervical, and colorectal cancer all resulted in a decrease in mortality, whereas PSA screening for prostate cancer was proved to have insufficient efficacy in reducing mortality without increasing complications. While current screening programs for the three cancers above have proven effective in the general population, screening programs for other cancers may have efficacy in reducing mortality, depending on a different expected risk. Since lymphoma survivors are presumed to be at high-risk for subsequent cancers, screening programs for this population should be considered.

Given the possible future implications of new screening programs for NHL survivors, this study focuses on lung cancer. Also, this research aims to compare survival after second primary cancer between NHL survivors and the general population based on the SEER program data, in hopes of contributing to cancer survivorship.

Second Primary Cancer among Non-Hodgkin Lymphoma Survivors

NHL is the seventh most common cancer among males in the U.S. and the sixth among females (9). The incidence has been increasing in the last few decades, although the cause of this rise is unknown (10). NHL is comprised of a clinically and pathologically diverse complex of disease subtypes. Standard treatment for a common but aggressive type of NHL is usually chemotherapy with or without radiotherapy. The indolent type of NHL can be followed by just "watch and wait." The prognoses vary, depending on subtype

and individual, but 5-year overall survival in 2009 was 68.2% (11). Survival greatly improved after the development of monoclonal antibody therapy.

From 1973 to 2000, 5,490 NHL patients developed subsequent malignancies in the SEER cancer registry, which evaluated more than 100,000 lymphoma or myeloma patients (4). (Latency between diagnosis of NHL and subsequent cancer was two months in the SEER program, whereas latency was set as 12 months in the current study to reflect clinical practice.) There was a 14% elevated risk of subsequent malignancies compared with the general population, and excess absolute risk was 19 excess cancers per 10,000 person-years.

Many studies have found an elevated risk of subsequent hematologic malignancies. Cyclophosphamide, or alkylating agent, has now been identified as causing therapy-related myeloid leukemia and myelodysplastic syndrome in a dose-dependent manner (12, 13). However, the evidence was not consistent for the risk of subsequent cancer overall after NHL (14-17), presumably due to the era and age of study cohorts with different follow-up durations that reflect different susceptibilities of toxicity by age, historical change of NHL therapy and latency until development of a second cancer. Recent large cohort studies, however, have been successful in capturing excess risk (4, 18).

The largest excess risk was observed for lung cancer in the SEER data as well as in a British cohort study: the risk ratio of lung cancer was 1.6 and the absolute excess risk was

5.8/10,000 person-years in British studies (18). Also, the cumulative dose of cyclophosphamide has been revealed to raise the risk of bladder cancer (19). Although an increased risk has been reported for subsequent breast cancer in Hodgkin lymphoma survivors (6), NHL survivors are less likely to develop breast cancer compared to the general population because of ovarian toxicity with radiotherapy for NHL (12).

Epidemiology of Lung Cancer

Though lung cancer is a highly preventable disease, it has been a leading cause of death. The incidence and mortality rates are 62.6/100,000 and 50.6/100,000 per year, respectively (11). Lung cancer remains a lethal malignancy with 5-year overall survival (OS) being 15.9% for 2002-2008 from 18 SEER geographic area (11).

A very strong causal association between lung cancer and tobacco smoking has been confirmed. The geographic pattern and temporal change of lung cancer incidence are determined primarily by consumption of tobacco worldwide. Growing tobacco consumption is followed by an increasing incidence rate of lung cancer with decades of latency, and vice versa (10). In the U.S., successful tobacco cessation campaigns reduced mortality among men after 1990, while incidence continued to increase among women until 2003(11). The role of amount and duration of cigarette smoking have been evaluated in British cohort studies (20) and case-control studies (21). The excess risk increased in proportion to the square of the amount of cigarettes consumed per day, whereas excess risk rose to the fourth power of the duration of smoking (10). Therefore,

tobacco cessation programs play an important role in the primary prevention of lung cancer. After five years of cessation, the excess risk decreases significantly.

Lung Cancer Screening

Cough and hemoptysis are usually initial symptoms of lung cancer. Although symptoms tend to develop earlier for the tumor that is located closer to the central bronchus rather than at the peripheral lung, they are usually silent at the early stage. For the large portion of lung cancer patients, cancer has already developed to an advanced stage by the time patients develop symptoms. Only 15% of lung cancer patients are identified at the localized stage (11). Sputum cytology and imaging studies with chest X-ray and computed tomography (CT) are common forms of diagnostic modality.

Successful cancer screening is defined as leading to a reduction in cancer mortality that is lead by a reduction in the incidence rate of advanced disease (8). Currently, no lung cancer screening is provided as an organized screening program. In recent years, efficacy of newly proposed low-dose CT screening has been evaluated in the National Lung Screening Trial. It has been suggested that low-dose CT screening of high-risk patients for lung cancer has played a significance role in reducing mortality compared to chest X-ray screening, although the implementation of routine low-dose CT screening warrants further evaluation due to a high false positive rate (22).

Methods

Patients

This cohort study compares survival after lung cancer between exposed and unexposed groups of patients with and without prior history of NHL, respectively. All subjects were obtained from the U.S. population-based cancer registry of the SEER program operated by the National Cancer Institute.

Patients were recruited using the following criteria: (i) NHL-LC group – patients who were diagnosed with first primary NHL between 1989 and 2008, and who survived at least 12 months, and who subsequently developed second primary lung cancer at least 12 months after the diagnosis of NHL; (ii) LC1 group – patients who were diagnosed with first primary lung cancer between 1990 and 2009.

i. NHL-LC

Among patients registered as first primary NHL, 926 survivors were identified who developed second primary lung cancer. After exclusion of patients with unknown cancer stage, 863 patients were included in the initial analysis. A total of 258 patients with localized stage were included in the subset analysis.

ii. LC1

Of 232,202 patients registered as first primary lung cancer, 4 times the number of patients in NHL-LC were randomly sampled stratified by cancer stage. A total of 3,452 patients, comprised of 1,032 patients with localized stage, 932 with regional stage and 1,488 with

distant stage were included in the initial analysis. Sampling was by "proc surveyselect" procedure with an algorithm for systematic random sampling in SAS9.3 software (SAS Institute Inc., Cary, NC).

The study cohort was obtained from the multiple primary cancer database of the SEER9 (23) for NHL-LC and the SEER18 (24) for LC1, setting identical inclusion criteria for both cohorts. The SEER areas included in the analyses were San Francisco, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah and Metropolitan Atlanta.

Populations with unspecified race and unknown race were excluded from the study. NHL and lung cancer only includes malignant behavior. All diagnoses of NHL and lung cancer were confirmed by microscopic study or by a positive laboratory marker. Diagnosis only by imaging study was excluded. Diagnosis only by autopsy or death certificate was also excluded. In the NHL-LC group, history of NHL was confined to cases of first malignant disease a patient developed in his/her life, whereas lung cancer after NHL was confined to second primary lung cancer. Subsequent primary lung cancer after second primary lung cancer was excluded.

Measurement / variables

Following are the variables included in the analysis.

i. Outcome variable

Survival time

Survival time was calculated from the month of lung cancer diagnosis until the month of death or the month of last follow-up. The study endpoint for follow-up was December 31, 2009.

Survival status

Deaths from all causes were considered as events. Survival was censored for patients who were not known to be deceased as of the last follow-up.

ii. Predictor variables

NHL-survivor status

Patients with a history of NHL who developed second primary lung cancer, or NHL-LC, were the exposed population, whereas patients with first primary lung cancer, or LC1, were the unexposed population. This variable was a main effect of interest.

Sex Sex was classified as male and female.

Age at diagnosis of lung cancer

Age at diagnosis of lung cancer was categorized into three age groups: 0-64, 65-74, 75 and after. This is based on tertiles derived from a distribution of 5-year age

classification in the SEER program. Also, this classification corresponds to NCCN's classification in clinical cancer guidelines for the elderly in which young old patients are 65-75 years of age; old patients are 76-85 years of age; and oldest old patients are more than 85 years of age.

Year of diagnosis of lung cancer

Lung cancer diagnosis made from 1990 to 1999 and from 2000 to 2009 was grouped as 1990s and 2000s, respectively, so that the advance of medical treatment in the past two decades could be detected.

Histology

Lung cancer was classified into two categories of Small Cell Lung Cancer (SCLC), and Non-Small Cell Lung Cancer (NSCLC), based on clinical and pathological classification that reflected difference in prognosis and treatment.

Tumor grade

Tumor grade is a system for classifying the degree of malignancy according to pathological examination. Grade 1 is low grade, Grade 2 is intermediate grade, Grade 3 is high grade, and Grade 4 or anaplastic type is high(er) grade. The grading system reflects both histological findings and clinical prognosis in which higher grade has the worst prognosis. In this study, grade was dichotomized, so that Grade 1 and Grade 2 were in one group, and Grade 3 and anaplastic were in the other group.

Race

The race variable used the same categorization as the SEER Multiple Primary-Standardized Incidence Ratios (MP-SIR) session employed. Race was categorized into three groups of "white," "black," and "other." The "other" racial group includes American Indian/Alaskan Native and Asian/Pacific Islander. Populations with unspecified or unknown race were not included in the dataset.

Marital status

Utilizing the classification employed in the SEER program, marital status at diagnosis was classified into four categories: "Single (never married)," "Married (including common law)," "Separated and Divorced," and "Widowed." Marital status was re-categorized into two groups of "Widowed" versus "Not Widowed."

SEER registry

The SEER registry was the referral source for the individual data and the residential area at the time of cancer diagnosis. This study database is derived from nine SEER registries: San Francisco-Oakland SMSA, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah and Metropolitan Atlanta. The variable, SEER registry, corresponds to the nine databases in the SEER9 Regs Research Data.

iii. Stratification variable

Cancer stage

This analysis used the staging system of the "SEER historic stage A," and lung cancer was classified into "localized," "regional" and "distant" stages. Because cancer stage was a significant predictor of survival a priori, stage was used as a stratification variable.

Statistical Analysis

Patient characteristics of the NHL-LC group were compared to that of LC1 group by chi-square statistics.

i. Survival analysis for all stages

Kaplan Meier curves by lung cancer stage and by NHL-survivor status, NHL-LC and LC1, were drawn to evaluate survival. Median survival time and 5-year OS was calculated. Log-rank tests were used to assess difference in survival between NHL-LC and LC1.

ii. Subset analysis for localized stage lung cancer

Next, according to the result of log-rank test, only patients with localized stage were focused on for the further analysis. This subset analysis was to evaluate time to death using a Cox proportional hazard regression model.

Proportional hazard assumptions were initially evaluated by a graphical method. Plots of log negative log survival against log of survival time stratified by each predictor variable, one at a time, were examined. If plots were clearly parallel, the variables were considered to satisfy proportional hazard assumption, and were included in the modeling. For the variables that plots were not confirmed parallel by the graphical method, an extended Cox model was used to test the significance of time-dependent covariates. If the time-dependent covariate, created as an interaction term with the main predictor of NHL-survivor status, was significant, the covariate was considered not to meet the proportional hazard assumption. SEER registry variables were not employed in the Cox proportional hazard regression due to violation of proportional hazard assumption.

After screening of variables with p value of less than 0.2 in the univariate analysis, the initial Cox model included NHL-survivor status, sex, age at diagnosis, calendar year of diagnosis, histology, tumor grade, race and marital status if widowed. The variables in the model were tested for collinearity using a collinearity SAS macro. All of the possible variables were included in the model. The condition index (CI) was confirmed sufficiently small not to cause collinearity. Following the evaluation of collinearity, interaction was assessed through a likelihood ratio test. Interaction terms between the main effect of NHL-survivor status and all other covariates were created. A likelihood ratio test was performed between a full model with all interaction terms and a no-interaction reduced model. As a result, interaction terms were not included in the model.

Confounding and model precision was evaluated next. Cox proportional hazard regression through "PHREG" procedure in SAS was used to calculate the hazard ratio (HR) and its 95% confidence interval for NHL-survivor status, the main predictor variable of interest. Categorical variable that had more than two categories were dealt with the "CLASS" statement to create dummy variables to see simultaneous effect. The effect of the control variable on the HR of the initial model was individually examined by removing the control variable. HR, width of confidence interval and ratio of confidence interval were compared to those of the initial model to evaluate the validity and precision to select the final model. Again, collinearity was assessed controlling for covariates in the final model.

All p-values were two-sided, with $p < 0.05$ defined as statistically significant. All analyses were carried out by SAS 9.3 software. This study was reviewed and approved by the Emory University IRB.

Results

Patients and Tumor Characteristics

Patients and tumor characteristics at the time of lung cancer diagnosis grouped by cancer stages and by patients with and without history of prior NHL are shown in Table 1.

Among 926 NHL survivors who developed lung cancer, stage information was available for 258 (28%) patients with localized stage, 233 (25%) patients with regional stage and 372 (40%) patients with distant stage. Of 232,202 LC1 patients who developed first primary lung cancer, 4 times the number of NHL-LC patients in each stage were randomly sampled. A total of 4,315 patients were included in the analysis.

Patients in NHL-LC were significantly older than patients in LC1 (mean age 70.7 years vs. 67.4 years; $p = 0.01$), diagnosed as lung cancer in recent years (74% vs. 51%; $p < 0.001$) and were more often white (94% vs. 84%; $p < 0.001$) among those with localized stage disease.

30% of patients with localized stage were missing information on tumor grade. Model fit was evaluated with and without the variable of tumor grade later in the Cox proportional hazard regression, which found to increase model fit by keeping the variable in a model.

There was no significant difference in frequency of tumor histology when classified into two groups of NSCLC and SCLC between patients in NHL-LC and LC1 with localized stage (NSCLC was 97% vs. 95%; $p = 0.15$), while there was significant difference in

patients with regional or distant stage between NHL-LC and LC1 (86% vs. 83%; p = 0.04).

Survival Analysis for All Stages

Stage specific time to death after lung cancer among 258 patients in NHL-LC and 1,032 patients in LC1 was tested with log-rank test, and Kaplan-Meier survival curves were plotted (Figure 1). Kaplan-Meier curves represent survival stratified by three stages and by NHL-survivor status. OS was compared within each stage by a log-rank test (Table 2). It is notable that patients in NHL-LC experienced significantly inferior survival after lung cancer compared to patients in LC1 at localized stage: 5-year OS was 33.0% vs. 44.8% (p < 0.001), whereas the survival did not differ significantly at regional stage: 13.9% vs. 19.2% (p = 0.38) and at distant stage: 0% vs. 2.9% (p = 0.10).

Subset Analysis for Localized Stage Lung Cancer

Because only patients with localized stage lung cancer had a significant difference in survival between NHL-LC and LC1, further assessment to examine predictors of survival was limited to a subset of patients with localized stage.

Initially, 9 potential predictor variables from the SEER program were examined if they satisfy proportional hazard assumption by log negative log plots of survival estimates. Among the variables of calendar year of diagnosis, histology, race, marital status and SEER registry that were not confirmed parallel, an extended Cox model showed the

variable SEER registry violated the proportional hazard assumption and marital status met the assumption after recategorization into two groups of widowed or not widowed.

After screening of variables with p value of less than 0.2 in the univariate analysis (Table 3), the initial Cox model included NHL-survivors status, and all possible covariates of tumor grade, race, age at diagnosis, sex, calendar year of diagnosis, histology and marital status if widowed or not. This model was describes as follows.

Initial model:

$$h(t,X) = h_0(\mathrm{t}) \exp\{\beta_1(NHLsurvivor) + \gamma_1(TumorGrade) + \gamma_2(Race(black)) + \gamma_3(Race(other)) + \gamma_4(Age\ at\ diagnosis(65to74)) + \gamma_5(Age\ at\ diagnosis(75+)) + \gamma_6(Sex) + \gamma_7(Year\ of\ diagnosis) + \gamma_8(Histology) + \gamma_9(Widowed)\}$$

Collinearity was tested for the initial model. The largest condition index (CI) was 2.139, which was small enough to conclude that there was no collinearity among variables in the model.

Interaction between the main effect of NHL-survivor status and the other variables were evaluated. Simultaneous interaction effect was tested through a likelihood ratio test, comparing a full model, in which all covariates and interaction terms with NHL-survivor status were included, and a reduced model without interaction terms. Since the effect was not significant (p = 0.14), these interaction effects were removed from the model.

Next, assessment of confounding was carried out. The HR and corresponding 95% confidence intervals (95% CI) were compared to the initial model to determine if any models were valid and had increased precision after dropping a variable. The results of the analyses indicated that the only model that excluded variable of tumor grade from the initial model was invalid, because change in HR from the initial model was more than 10%. Hence, tumor grade needed to stay in the model as a confounder. There was not meaningful gain in precision by removing any other predictor variable.

As all predictor variables other than widowed were significant in the initial model, and they remained significant in a model after removing widowed, they were included in a final model as predictor variables. Therefore, the final model included NHL-survivor status as the main effect, and tumor grade, race, age at diagnosis, sex, calendar year of diagnosis and histology as other predictor variables (Table 4). The fit of the final model was evaluated using -2log likelihood function (-2logL) and the Akaike's information criterion (AIC). Both of them took the smallest value for the final model, suggesting the best fit when dropping the variable widowed.

Final model:

$$h(t,X) = h_0(\mathrm{t}) \exp\{\beta_1(NHLsurvivor) + \gamma_1(TumorGrade) + \gamma_2(Race(black)) + \gamma_3(Race(other)) + \gamma_4(Age\ at\ diagnosis(65to74)) + \gamma_5(Age\ at\ diagnosis(75+)) + \gamma_6(Sex) + \gamma_7(Year\ of\ diagnosis) + \gamma_8(Histology)\}$$

In the final model, NHL-survivor status was a significant predictor of survival after lung cancer in patients with localized stage disease (HR = 1.38; 95%CI, 1.10-1.73; p = 0.005), after controlling for tumor grade, race, age at diagnosis, sex, calendar year of diagnosis and histology, indicating a 38% increase in mortality for patients in NHL-LC compared to patients in LC1.

Discussion

A significant finding in this study is inferior prognosis of lung cancer among non-Hodgkin lymphoma (NHL) survivors compared to the general population when lung cancer stage is limited to localized stage. The median survival time at localized stage was 28 months and 49 months ($p < 0.001$) among NHL survivors (NHL-LC) and the general population (LC1), respectively. The survival differences diminished with regional and distant stages lung cancer.

There are at least three possible reasons accounting for the inferior OS: influence from prior therapy; more elderly patients in NHL-LC; and deaths from other causes among NHL survivors. Also, a reason for the diminished survival differences might be the highly aggressive nature of lung cancer after advanced stage.

The standard treatment for the majority of localized stage lung cancer has been lung resection, such as lobectomy and pneumectomy. In contrast, standard treatment for the NHL has been chemotherapy with/without radiotherapy. Lower respiratory function, lower physical performance status, or subclinical lowered organ function due to NHL treatment may have limited lung resection and other options for standard treatment.

The distribution of patients' age at diagnosis was different between NHL survivors and the general population who developed lung cancer, and the survivors were older. The log-rank test included the negative effect of the older population among NHL survivors on

survival, thereby resulting in poorer prognosis. However, the adverse effect on hazard did not disappear after adjusting for age at diagnosis in the Cox proportional hazard model.

NHL survivors are more likely to die from other causes, including other malignancies and benign diseases, as elevated risk has been shown by other studies for NHL and Hodgkin lymphoma survivors. Moreover, because the study population for NHL-LC consisted of 12-months survivors and longer, persons with active lymphoma and those who experienced lymphoma relapse would be included. Thus, it is estimated that NHL survivors with localized stage lung cancer experienced worse survival, while aggressiveness of lung cancer after advanced stage surpassed aggressiveness of NHL and other causes of deaths.

Strength

To the best of my knowledge, this is the first study that has shown the overall survival after second primary lung cancer among NHL survivors. Most publications on second malignancy focus on survivors from Hodgkin lymphoma and on the elevated risk. This study fills a gap between published studies and everyday practice where the incidence rate is 24.5 times and the number of survivor is about 2.8 times for NHL compared to HL, according to the SEER program as of 2009.

Weaknesses

There are five aspects of the current study that need further consideration. First, the SEER program does not have information about how cancer cases were detected, such as

by screening, follow-up clinic, or symptom. Hence, it reduces the impact on future directions in discussions on applying newly emerging lung cancer screening by low-dose CT for NHL survivors as a high-risk population. Second, about 30% of the predictor variable of tumor grade was unknown status. Although the model fit by likelihood ratio test improved with the variable, the result may be biased. Third, LC1 group was a sample of study subjects, rather than all of the 232,202 control cases in order to reduce the sample size for manageable analyses. Sensitivity analysis is desirable. Last, a cause-specific survival analysis would provide better understanding.

Future Direction

Lung cancer is the leading cause of second primary solid cancer among NHL survivors and it is technically detectable by low-dose CT screening when closely followed up. Although the key for better survival from solid cancer is always early detection, the worse prognosis at localized stage lung cancer casts doubt on a current assumption that cancer survivors would benefit from closer follow-up and more cancer screenings. First, NHL survivors are a high-risk population for lung cancer. Second, the early detection of lung cancer still seems to be the only effective method for better survival. Third, as this study found, survival after lung cancer among NHL survivors is worse than that of first primary lung cancer in the general population. Hence, the efficacy of screening in the reduction of mortality is not predictable due to contradictory factors. Evaluation of the efficacy of applying low-dose CT screening for subsequent primary lung cancer among cancer survivors at elevated risk is warranted in establishing a follow-up care plan.

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Table 1. Patients and Tumor Characteristics at Time of Lung Cancer Diagnosis Among 863 NHL Survivors and Sampled 3452 First Primary Lung Cancer Patients by Stage, SEER program, 1990-2009

	Localized							Regional/Distant						
	NHL-LC		LC1		χ^2	p-value		NHL-LC		LC1		χ^2	p-value	
	n	%	n	%				n	%	n	%			
Total	258		1032					605		2420				
Sex					0.61	0.44						0.1	0.73	
Female	130	50	492	48				264	44	1037	43			
Male	128	50	540	52				341	56	1383	57			
Age at diagnosis					10.50	0.01	*					74.8	<0.001	*
0-64	65	25	366	35				145	24	973	40			
65-74	100	39	367	36				221	37	856	35			
75+	93	36	299	29				239	40	591	24			
Year of diagnosis					47.45	<0.001	*					117.8	<0.001	*
2000s	192	74	522	51				456	75	1231	51			
1990s	66	26	510	49				149	25	1189	49			
Histology					2.05	0.15						4.1	0.04	*
NSCLC	250	97	978	95				520	86	1997	83			
SCLC	8	3	54	5				85	14	423	17			
Tumor grade					2.87	0.09						17.6	<0.001	*
Grade1 & Grade2	107	41	362	35				107	18	342	14			
Grade3 & Anaplastic	79	31	354	34				177	29	1003	41			
Unknown[a]	72	28	316	31				321	53	1075	44			
Race					20.27	<0.001	*					23.6	<0.001	*
White	243	94	862	84				537	89	1944	80			
Black	7	3	114	11				37	6	280	12			
Other	8	3	56	5				31	5	196	8			
Marital status					10.26	0.02	*					15.3	0.002	*
Married	161	62	568	55				332	55	1305	54			
Single	14	5	117	11				42	7	279	12			
Separated	30	12	102	10				63	10	319	13			
Widowed	45	17	205	20				133	22	450	19			
Unknown[a]	8	3	40	4				35	6	67	3			
SEER registry					8.82	0.36						24.6	0.002	*
San Francisco	29	11	134	13				79	13	348	14			
Connecticut	54	21	166	16				105	17	375	16			
Detroit	53	21	224	22				106	18	486	20			
Hawaii	5	2	44	4				15	2	108	4			
Iowa	39	15	132	13				98	16	336	14			
New Mexico	9	3	56	5				20	3	111	5			
Seattle	40	16	157	15				129	21	382	16			
Utah	8	3	32	3				18	3	71	3			
Atlanta	21	8	87	8				35	6	203	8			

Abbreviations: NHL-LC, non-Hodgkin lymphoma survivors who developed second primary lung cancer; LC1, lung cancer patients without history of malignancy; NSCLC, non-small cell lung carcinoma; SCLC, small cell lung carcinoma.

a Patients with unknow values were excluded from the calculation.

Table 2. Comparison of Overall Survival After Lung Cancer Between Patients in NHL-LC (n = 863) and LC1 (n = 3452) by Disease Stage, SEER program, 1990-2009

Stage of lung cancer and NHL-survivor status	MST (month)	5-year OS (%)	Log-rank test p-value[a]
Localized stage			< 0.001*
LC1	49	44.8	
NHL-LC	28	33.0	
Regional stage			0.38
LC1	15	19.2	
NHL-LC	14	13.0	
Distant stage			0.10
LC1	4	2.9	
NHL-LC	4	0.0	

Abbreviations: NHL-LC, non-Hodgkin lymphoma survivors who developed second primary lung cancer; LC1, lung cancer patients without history of malignancy; NHL, non-Hodgkin lymphoma, MST, median survival time; OS, overall survival.
a Log-ranke test was conducted within each disease stage to compare difference by NHL-survivor status.

Table 3. Examination of Univariate Association Between Potential Predictor Variables and Time to Death Among NHL-LC (n = 258) and LC1(n = 1032), SEER program, 1990-2009

Variable	Hazard Ratio	95% CI	p-value
NHL-survivor status			
LC1	Reference		
NHL-LC	1.47	(1.23 , 1.75)	<.001 *
Sex			
Female	Reference		
Male	1.29	(1.12 , 1.48)	<.001 *
Year of birth			<.001 *
1890-1924	Reference		
1925-1939	0.64	(0.55 , 0.75)	<.001 *
1940 and after	0.38	(0.31 , 0.47)	<.001 *
Age at diagnosis			<.001 [a]
0-64	Reference		
65-74	1.67	(1.40 , 1.98)	<.001 *
75+	2.28	(1.90 , 2.73)	<.001 *
Year of diagnosis			
2000s	Reference		
1990s	1.05	(0.91 , 1.22)	0.50
Histology			
NSCLC	Reference		
SCLC	1.94	(1.46 , 2.57)	<.001 *
Tumor grade			
Grade1 & Grade2	Reference		
Grade3 & Anaplastic	1.50	(1.27 , 1.78)	<.001 *
Race			0.002 [a]
White	Reference		
Black	1.47	(1.18 , 1.84)	<.001 *
Other	0.86	(0.61 , 1.20)	0.36
Widowed			
No	Reference		
Yes	1.373	(1.2 , 1.61)	<.001 *

Abbreviations: NHL-LC, non-Hodgkin lymphoma survivors who developed second primary lung cancer; LC1, lung cancer patients without history of malignancy; NSCLC, non-small cell lung carcinoma; SCLC, small cell lung carcinoma.
a Wald chi-square test for simultaneous effect of multiple categories.

Table 4. Estimated Hazard Ratios from Cox Proportional Hazard Models Examining the Association Between Status of NHL-LC and That of LC1 Among Patients with Localized Stage Lung Cancer, SEER program, 1990-2009

Variables	References	Initial Model[a] (n = 902)		Final Model[b] (n = 902)	
		HR	95% CI	HR	95% CI
NHL-LC	**LC1**	**1.39**	**(1.11 , 1.74)**	**1.38**	**(1.10 , 1.73)**
Tumor Grade3& Anaplastic	Grade1&Grade2	1.44	(1.21 , 1.72)	1.44	(1.21 , 1.72)
Race (Black)	Race (White)	1.59	(1.19 , 2.12)	1.60	(1.20 , 2.13)
Race (Other)	Race (White)	0.90	(0.60 , 1.36)	0.91	(0.60 , 1.37)
Age at diagnosis (65-74)	Age at diagnosis (0-64)	1.44	(1.17 , 1.78)	1.46	(1.19 , 1.80)
Age at diagnosis (75+)	Age at diagnosis (0-64)	2.06	(1.63 , 2.61)	2.13	(1.70 , 2.67)
Male	Female	1.28	(1.07 , 1.53)	1.25	(1.05 , 1.48)
Year of diagnosis in 1990s	in 2000s	1.30	(1.08 , 1.57)	1.30	(1.08 , 1.57)
Histology (SCLC)	NSCLC	1.78	(1.17 , 2.71)	1.80	(1.18 , 2.73)
Widowed	Not widowed	1.11	(0.89 1.38)		

Abbreviations: NHL-LC, non-Hodgkin lymphoma survivors who developed second primary lung cancer; LC1, lung cancer patients without history of malignancy; HR, hazard ratio; SCLC, small cell lung carcinoma; NSCLC, non-small cell lung carcinoma.

a Model fit of the initial model was -2Log(Likelihood) = 5152.04 and AIC = 5172.04

b Model fit of the final model was -2Log(Likelihood) = 5152.88 and AIC = 5170.88

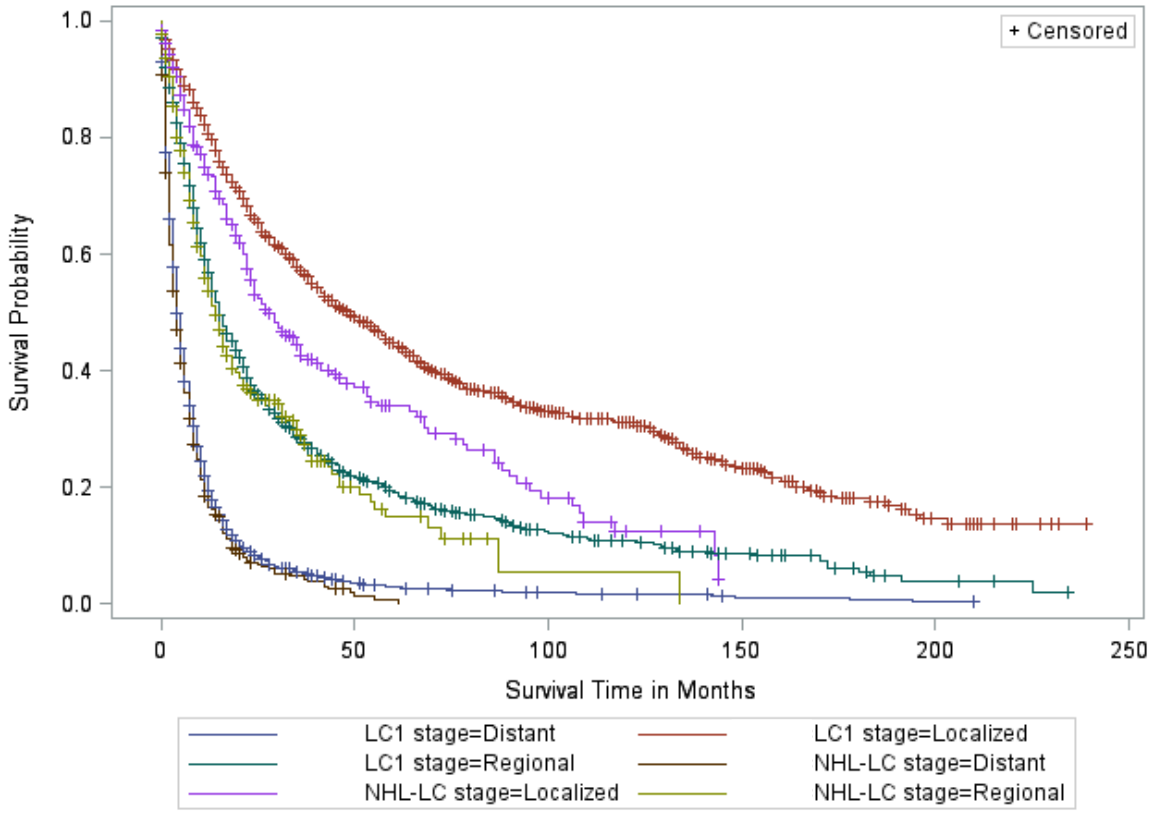

Figure 1. Kaplan-Meier overall survival curves for the 4315 lung cancer patients with disease stages localized, regional and distant. Comparison of patients with non-Hodgkin lymphoma survivors who developed second primary lung cancer (NHL-LC) and lung cancer patients without history of prior malignancy (LC1).

i. Comparison of patients with localized stage lung cancer by the NHL-survivor status. The uppermost curve (in red color) shows patients of LC1 (n = 1032; events = 649). The curve second from the top (in purple color) shows patients of NHL-LC (n = 258; events = 159).Log-rank p value is less than 0.001.

ii. Comparison of patients with regional stage lung cancer by the NHL-survivor status. The curve drawn in dark green color shows patients of LC1 (n = 932; events = 762). The curve drawn in light green color shows patients of NHL-LC (n = 233; events = 160). Log-rank p value equals 0.38.

iii. Comparison of patients with distant stage lung cancer by the NHL-survivor status. The lowermost and longer curve (in blue color) shows patients of LC1 (n = 1488; events = 1394). The lowermost and shorter curve (in brown color) shows patients of NHL-LC (n = 372; events = 343). Log-rank p value equals 0.10.