Identifying Risk Factors for Second Malignancies after Non-Hodgkin Lymphoma

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Dedication

The author wishes to thank her family and friends for their love and support throughout the dissertation process. In particular, the author wishes to thank her husband, Thanh. Your unconditional love, support, and endless encouragement were the reasons I was able to complete my dissertation. I am forever grateful to my wonderful best friend.

Abstract of Dissertation

Identifying Risk Factors for Second Malignancies after Non-Hodgkin Lymphoma

Purpose: To develop a better understanding of the risks of developing second malignancies after non-Hodgkin lymphoma (NHL).

Methods: To examine the potential associations between NHL treatments, autoimmune conditions, and selected infections and second lung cancer, melanoma, and acute myeloid leukemia/myelodysplastic syndrome (AML/MDS) after first primary NHL we conducted an analytic study using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. Hazard ratios (HR) and 95% confidence intervals (CI) for the associations between the specific risk factors and second malignancy risks were estimated using Cox proportional hazards regression models.

Results: Fludarabine-containing chemotherapy with or without rituximab increased melanoma risk after chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (HR=1.86, 95% CI=1.06-3.27; N=10, HR=2.72, 95%CI=1.33-5.56, respectively), whereas melanoma risk was not associated with specific treatments among patients with other NHLs. Lung cancer risks were also significantly increased among CLL/SLL patients who received fludarabine-containing chemotherapy without rituximab (HR=2.28, 95% CI=1.48-3.52). Significantly elevated lung cancer risks were also observed among diffuse large B-cell lymphoma (DLBCL) survivors who received cyclophosphamide-containing chemotherapy without rituximab (HR=2.13, 95%CI=1.01-4.47). AML/MDS risk was significantly elevated among NHL survivors who received any fludarabine-, cyclophosphamide-, and rituximab-containing chemotherapy compared with those who did not receive any infused chemotherapy (HR=3.52, 95% 1.96-6.33). Risks were highest for survivors who received fludarabine- and rituximab-containing chemotherapy without cyclophosphamide (HR=4.72, 95% CI 2.53-8.84) as well as for those who received fludarabine-containing chemotherapy alone (HR=5.95, 95% CI 2.27-15.58).

T-cell activating autoimmune diseases diagnosed prior to (HR=1.76, 95%CI=1.06-2.93) or after CLL/SLL (HR=2.32, 95%CI=1.34-4.03) increased second melanoma risks, whereas melanoma risk was not associated with T-cell/B-cell activating autoimmune diseases among patients with other NHLs. Increased second lung cancer risks were observed for B-cell activating autoimmune conditions occurring after DLBCL (HR=1.63, 95%CI=1.00-2.66), with strongest associations for rheumatoid arthritis (HR=1.89, 95%CI=0.91-3.65), and for T-cell activating autoimmune conditions diagnosed after other NHL subtypes (HR=1.56, 95%CI=1.07-2.27), with strongest associations for asthma (HR=2.00, 95%CI=1.34-2.97). In contrast, T-cell activating autoimmune conditions were significantly inversely associated after FL (HR=0.57, 95%CI=0.34-0.96), likely driven by skin autoimmune conditions, particularly localized scleroderma (HR=0.25, 95%CI=0.08-0.81). AML/MDS risks were increased 1.5- to 2.0-fold for autoimmune diseases occurring prior to NHL diagnosis for nearly all conditions we evaluated. Few associations were observed for diagnoses of autoimmune diseases occurring after NHL, with the exception of pernicious anemia (HR=2.24, 95% CI 1.46-3.42) and asthma (HR=1.98, 95% CI 1.22-3.19).

After accounting for history of smoking, lower airway respiratory infections, particularly pneumonia, were associated with increased risks of second lung cancer before and after CLL/SLL (before CLL/SLL: HR=1.53, 95%CI=1.10-2.12; after CLL/SLL: HR=2.21, 95%CI=1.65-2.96), and after DLBCL (HR=1.90, 95%CI=1.26-2.87) and follicular lymphoma [FL](HR=1.98, 95%CI=1.31-3.00). Upper airway respiratory infections were associated with increased second AML/MDS risk (before NHL HR=1.47, 95% CI 1.01-2.12, after NHL HR=1.74, 95% CI 1.10-2.76), particularly sinusitis (after NHL HR=2.18, 95% CI 1.44-3.31). Additionally, subsequent AML/MDS was also associated with pneumonia (after NHL HR=1.69, 95% CI 1.16-2.46). Other infections increased AML/MDS risks including skin infections likely driven by herpes zoster (HR=1.91, 95% CI 1.18-3.10), and urinary tract infections, particularly prostatitis (before NHL HR=1.71, 95% CI 1.05-2.76, after NHL HR=2.32, 95% CI 1.21-4.45) and cystitis/pyelonephritis (after NHL HR=1.68, 95% CI 1.07-2.62). Gastroenteritis was associated with second AML/MDS when

diagnosed after NHL (HR=1.76, 95%CI=1.11-2.79). Generally, infections were not associated with melanoma risk, except for urinary tract infections among CLL/SLL survivors, and pneumonia and gastrohepatic infections among survivors of other NHLs.

Conclusion: We have shown that specific chemotherapeutic agents, namely fludarabine and to a lesser extent cyclophosphamide, are associated with increased risk of second melanoma, lung cancer, and AML/MDS. We also identified numerous autoimmune conditions and infections that were associated with increased risk of second malignancies after NHL, particularly T-cell mediated diseases and melanoma, respiratory infections and lung cancer, and B-cell and T-cell mediated autoimmune conditions and various infections and AML/MDS. In addition, we were able to evaluate differences in risk by NHL subtype, especially for CLL/SLL. Our studies have provided valuable information regarding risks that can be considered when evaluating the risks and benefits of screening, particularly for melanoma and lung cancer, and can be used to better inform clinicians and their patients about treatment options and follow-up monitoring for their first cancers to improve long term health outcomes for these patients.

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List of Abbreviations

Abbreviation	Definition
AML	Acute Myeloid Leukemia
CI	Confidence Intervals
CLL	Chronic Lymphocytic Leukemia
COPD	Chronic Obstructive Pulmonary Disease
CPT	Current Procedural Terminology
DLBCL	Diffuse Large B-cell Lymphoma
EBV	Epstein-Barr Virus
HCPCS	Healthcare Common Procedure Coding System
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
HM	Hematologic Malignancy
HMO	Health Maintenance Organization
HR	Hazard Ratio
ICD-9	International Classification of Diseases 9th Edition
ICD-O-3	International Classification of Diseases Oncology 3rd Edition
MDS	Myelodysplastic syndromes
MEDPAR	Medicare Provider Analysis and Review
MM	Multiple Myeloma
NCI	National Cancer Institute
NCH	National Claims History
OUTPAT	Outpatient
PTLD	Post-transplant Lymphoproliferative Disorder

SEER	Surveillance, Epidemiology, and End Results
SLL	Small Lymphocytic Lymphoma
SMAHRT	SEER-Medicare Assessment of Hematopoietic Risk Traits
WHO	World Health Organization

Chapter 1: Introduction

Approximately 14 million people are living with cancer in the United States.[1] Because of advances in early stage detection and treatment of cancer, relative survival rates for all cancers combined have increased steadily in recent decades, with 5-year relative survival rates improving from 50% in 1975-1979 to 66% in 1996-2002 among adults in the US. Approximately 16% of newly diagnosed cancer cases occur in individuals with a prior cancer diagnosis,[2] and subsequent malignancies are a leading cause of morbidity and mortality among cancer survivors.

Most studies of second cancers to date have been descriptive, providing important evidence that cancer survivors have higher risk of subsequent malignancy than the general population and generating hypotheses to be pursued in analytic studies. Previous analytic studies of second cancer etiology conducted to date have primarily focused on quantifying the late effects of cancer treatments, with few investigations of shared environmental, lifestyle, and genetic risk factors. Because of the increasing population of cancer survivors, improving our understanding of the various contributors to second cancer risk can provide important insight into carcinogenesis as well as critical information for cancer survivors and their physicians.

Chapter 2: Background/Significance

Primary Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) is the 5th most common malignancy in the US, representing an estimated 4.3% of new malignancies.[1] The 5-year relative survival rate for overall NHL is 67%.[3] NHL embodies a group of heterogeneous diseases distinguished by specific clinical, morphologic, genetic, and immunophenotypic characteristics. The most common subtypes include diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). DLBCL is the most common NHL subtype and constitutes approximately 40% all NHL diagnoses.[3] FL is the second most commonly diagnosed NHL subtype at roughly 20%.[3] Overall, the combination of DLBCL, FL, and CLL/SLL make up about two-thirds of all NHL diagnoses. The NHL subtypes can divided into two prognostic groups, indolent lymphomas and aggressive lymphomas. Aggressive lymphomas, such as DLBCL, grow rapidly and tend to have shorter natural histories, but can be successfully treated with intensive combination chemotherapy regimens.[4,5] FL and CLL/SLL are considered indolent lymphomas which are slow-growing, incurable lymphomas that present few symptoms in early stages.[4,5] The 5-year relative survival rate ranges dramatically for specific subtypes, from approximately 60% for DLBCL to 85% for FL and CLL/SLL.[3]

The etiology of NHL is largely unknown, but immune dysfunction is the strongest and most well-established risk factor. Inherited or iatrogenic immune suppression of varying forms confers striking risk of NHL as observed in previous studies investigating congenital immunodeficiency and inherited immune deficiency syndromes,[6,7] bone marrow and organ transplants and immunosuppressive drugs,[8-10] and HIV infection and highly active antiretroviral therapy (HAART).[11,12] Immune stimulation and chronic inflammatory response also strongly increases risk of NHL. Infectious agents can have a direct oncogenic effect as observed with Epstein-Barr virus (EBV) or they can involve chronic antigenic stimulation such as hepatitis C virus (HCV).[13] Previous studies have shown increased NHL risk associated with autoimmune diseases such as

Sjögren syndrome and rheumatoid arthritis[14-17] and tumor necrosis factor single nucleotide polymorphisms (TNF SNPs).[18] Additional information regarding immune dysfunction will be discussed in a later section of this dissertation.

NHL survivors have reported to be at higher risk compared to the general population of developing a number of second malignancies, including cancers of the lung, bladder, kidney, head and neck, stomach, liver, colon, thyroid, bone, and soft tissues, as well as melanoma, leukemia, and Hodgkin lymphoma.[19-41] A recent study demonstrated significant differences of risks by NHL subtype, with higher risk of developing second primary lung cancer and melanoma after primary CLL/SLL and FL but not DLBCL, and acute non-lymphocytic leukemia (ANLL) after DLBCL and FL but not CLL/SLL.[40] Previous studies have hypothesized that NHL treatments (chemotherapy, radiotherapy), underlying immune dysfunction (including immune defects, susceptibility to infections, and inflammation), lifestyle factors (e.g., tobacco use, alcohol consumption), and genetic susceptibility likely contribute to the increased risks of second malignancies after NHL.[9,12,24,30,32,34-36,42-48] Because immune perturbation is the strongest known risk factor for NHL and also plays a key role in the development of other malignancies, this study will use cancer patient information derived from SEER-Medicare to quantify second malignancy risks after NHL in relation to NHL treatments, autoimmune conditions, and selected infections.

NHL Treatment

NHL can be treated with chemotherapy and/or radiotherapy, and standard treatment options are based largely on stage and histology.[5,49] Current treatment options have expanded to include monoclonal antibodies, biologic response modifiers, and antimicrobial agents in addition to alkylating agents, topoisomerase II inhibitors, and nucleoside analogs.[30,32,34,38,49] Radiotherapy is not as commonly used as chemotherapy for NHL but may still contribute to

second cancer risk because ionizing radiation has been shown to be an established risk factor for a wide range of malignancies.[50-52]

The initial treatment of DLBCL depends on the extent of the disease. Approximately 30 to 40 percent of DLBCL patients have limited stage disease. Limited stage disease (stage I or II) can be contained within one irradiation field and is treated with a combination of chemotherapy, rituximab, and radiotherapy.[53] This treatment approach has been associated with 5- and 10-year overall survival rates of 95 and 75 percent, respectively.[54-60] The remaining 60 to 70 percent of DLBCL patients are diagnosed with advanced stage disease (stage III or IV) and are treated with the current standard initial therapy known as R-CHOP.[53] R-CHOP includes a combination of alkylating agents, anthracyclines, glucocorticosteroids, and plant alkaloids, specifically cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) combined with rituximab. Rituximab is a monoclonal antibody targeting CD20 antigen which is present in benign and malignant B-cells. The use of R-CHOP for advanced stage DLBCL has been associated with 2- and 5-year survival rates of approximately 70 and 60 percent, respectively.[61,62]

Approximately 15 to 30 percent of patients diagnosed with FL have clinical stage I/II disease and less than 10 percent have pathologic stage I/II disease.[63] Radiotherapy is the main treatment for limited stage FL (stage I or II) with a 10-year overall survival rate range of 60 to 80 percent.[64] However, majority of patients with stage I FL in the United States do not receive radiotherapy, and observation of the tumor is an alternative choice of treatment, especially if the tumor is located in an area that is difficult to treat, or the patient refuses radiotherapy, or if significant morbidity/toxicity is expected from the radiotherapy.[63] Patients with advanced stage FL (stage III or IV) represent 70 to 85 percent of all FL diagnoses.[63] Asymptomatic patients are not treated initially, but once treatment is necessary, immunotherapy-based treatment, specifically combinations of chemotherapy and rituximab including R-CVP

(cyclophosphamide, vincristine, prednisone),[65,66] BR (bendamustine),[67] R-CHOP,[68,69] FR (fludarabine),[70] and R-FMD (fludarabine, mitoxantrone, dexamethasone)[71] are the preferred regimens with clinical results showing better response rates and survival.[32,49,63,72] Patients with FL who cannot tolerate rituximab can be treated with oral low dose single agent chlorambucil or cyclophosphamide.[72]

CLL/SLL is an extremely heterogeneous disease and not all patients require treatment at the time of diagnosis. Currently the treatment recommendation for early stage CLL/SLL is observation. A recent meta-analysis found that patients diagnosed with CLL/SLL who are not treated have similar survival rates to the general population and there was no difference in response between immediate versus delayed chlorambucil-based chemotherapy.[73] Localized radiotherapy can also be used as treatment for localized, stage I and stage II SLL with 10-year relapse-free rates of 80 and 62 percent, respectively.[74] There have been no prospective trials comparing chemotherapy to radiotherapy or observation in patients with early stage CLL/SLL to date. Fludarabine-based chemotherapy regimens are recommended for patients diagnosed with advanced stage CLL/SLL with overall response rates of 90 percent for FR (fludarabine with rituximab) combinations and 95 percent for FCR (fludarabine, cyclophosphamide, rituximab) combinations.[75-81] Patients can also be treated with alemtuzumab[82,83] and bendamustine,[84] both of which demonstrated better response rates when compared with chlorambucil.

Previous studies have shown that chemotherapy for first primary NHL is an established risk factor for subsequent leukemia and myelodysplastic syndromes.[21,22,24,30-32,34,35,38,40,85-97] Travis et al. found the pattern was similar to that observed for radiogenic leukemia and suggested that prednimustine, along with either mechlorethamine or procarbazine, with or without radiotherapy for first primary NHL led to increased risks of second AML/MDS.[98]

Evidence increasingly suggests that chemotherapy may also contribute to non-hematologic malignancies after treatment for first primary NHL.[20,22,23,31,35,89,99] Among NHL survivors, bladder cancer has been clearly linked to chemotherapy. Risk of second bladder cancer remains significantly elevated among 15- and 20-year NHL survivors which may reflect the high cumulative doses of alkylating agents, particularly cyclophosphamide which is commonly used in NHL treatment.[20,99] Acrolein is a major toxic metabolite of cyclophosphamide and has been shown to initiate bladder carcinogenesis in rats.[23,100]

A number of studies have speculated that NHL survivors also have higher risk of developing second malignancies after chemotherapy for first primary NHL based on patterns in descriptive studies, but evidence from analytic studies is lacking.[41] Previous descriptive studies[31,35,89] suggested increased risks of second lung cancer after treatment for a primary NHL and CLL and some analytic studies showed excesses of second lung cancer.[30,34,101] Other studies have hypothesized that chemotherapy for patients with NHL also have higher risk of developing second Hodgkin lymphoma compared to the general population.[31,34,40] The cytotoxic and immunosuppressive effects of chemotherapy for NHL may explain higher risk for second melanoma.[29,31,36] Some studies have observed possible increased risk of second colorectal cancer after first primary NHL CHOP treatment,[34,35] but other studies did not.[22,25,89]

Although only a few analytic studies investigating NHL and chemotherapy have been conducted, chemotherapy has been shown to affect subsequent cancer risks in survivors of cancers other than first primary NHL. Alkylating-agent containing chemotherapy and radiotherapy for Hodgkin lymphoma have been associated with increased lung cancer risk.[43] Among survivors of testicular cancer or Hodgkin lymphoma, chemotherapy has been shown to be a risk factor for increased second stomach cancer.[102]

Radiotherapy after NHL has been linked to ANLL in some studies,[24,34,35,85,86,103] but not others.[88,98] Analytic studies of other second cancer risks after radiotherapy for NHL are lacking, though hypotheses can be derived from both descriptive studies and studies of patients treated with radiotherapy for other reasons.

Previous descriptive studies have suggested increased risk of certain radiosensitive second malignancies after radiotherapy for first primary NHL, including cancers of the bladder, lung, and stomach.[22,50,51,88,104,105] It has been hypothesized that radiation can be an initiating agent in carcinogenesis and that the risk of treatment induced bladder cancer may be greater when chemotherapy, particularly cyclophosphamide, and radiotherapy are used in combination.[23] Additionally, cyclophosphamide induced proliferation might contribute to an earlier expression of radiation injury.[23,106]

Descriptive studies have implicated radiation as a possible risk factor for developing subsequent lung cancer with long latent periods;[51,88,107,108] however another study observed increased lung cancer risk in the first four years after NHL diagnosis,[31] and other studies did not find excesses of lung cancer.[22,88] Similar latency patterns were observed for lung cancer after Hodgkin lymphoma, where the initial increased risk was due to chemotherapy but the increased risk after longer latency was related to radiotherapy.[43] Increases in stomach cancer risk were mainly observed at least 10 years after initial NHL diagnosis and was suggested to be related to initial radiotherapy treatment since radiation has been shown to increase the risk of stomach cancer.[109]

Radiotherapy has been linked to risks of many subsequent malignancies among the most extensively studied patient populations including children, adolescent, and young adult survivors of other first primary cancers including cervical cancer,[105,110,111] brain cancer,[112,113] testis cancer,[114,115] and Hodgkin lymphoma,[28,116,117] as well as patients receiving radiotherapy

for specific benign conditions including peptic ulcer disease,[118] ankylosing spondylitis,[119,120] and gynecologic disorders.[104,121-123] Particularly radiosensitive second malignancies including female breast, bone, soft-tissue sarcoma, thyroid, leukemia, stomach, pancreas, lung, and central nervous system tumors have been observed after radiotherapy for childhood cancer.[91-93,95,96,124-129] Overall radiotherapy has been shown to cause second cancers in other populations; however, analytic studies looking at the association between radiotherapy for first primary NHL and second malignancy development have not been conducted.

A recent meta-analysis of 23 previous descriptive and analytic studies conducted by Pirani et al. showed that NHL survivors are at higher risk for second primary malignancies than the general population with a pooled relative risk of 1.88 and a 95% confidence interval of 1.58-2.22.[41] The principal meta-analysis covered 19 studies that included a total of 208,643 NHL survivors who developed 13,878 second primary malignancies from 1935 to 2004.[41] Twelve studies reported positive associations between first primary NHL and subsequent malignancies,[24,31,35,36,38,108,130-135] whereas 7 studies did not show an association.[21,30,38,64,88,136,137] Of the 19 studies in the main meta-analysis, 4 studies included current data from clinical trials,[30,34,35,38] 9 were hospital-based studies,[21,24,88,130,131,133-136] and 5 were population-based studies.[31,36,37,108,138] Additionally, they evaluated the effects of various NHL treatments on the relative risks and found that radiotherapy alone did not increase the risks for second primary malignancies, but chemotherapy and combination NHL treatments did increase the relative risks. The findings from the meta-analysis provided an extensive overview of estimating the risk of second primary malignancies among NHL survivors and suggested that chemotherapy, alone or in combination with radiotherapy, increased second malignancy risks. However, this descriptive meta-analysis cannot account for differing study designs, NHL subtypes, periods of study recruitment, various durations of follow-up, geographical and genetic variations, classification of NHL, and detailed treatment information.[41] This dissertation will provide the

first analytic study of subsequent malignancies after first primary NHL looking at detailed treatment information in the current treatment era.

Immunity

The etiology of many NHLs remain largely unknown, but previous studies have established immune dysfunction as the strongest risk factor for NHL.[9] Immune dysfunction can arise from various sources including inherited or iatrogenic immune suppression to immune stimulation and chronic inflammation. Approximately 25% of patients with congenital immunodeficiency will develop tumors during their lifetime, and NHL accounts for about 50% of all of the tumors diagnosed.[6] Previous studies have shown an increased risk of lymphoma in individuals who have undergone a bone marrow organ transplant or are infected with HIV.[8,9] Subsequent cancer risk after solid organ transplant may reflect the loss of immune surveillance or the effects of chronic inflammation or immune activation.[10,139] The development and increased use of immunosuppressive drugs in organ transplants can increase NHL risk.[10] Viruses can deplete lymphocytes leading to immune deficiencies as shown by HIV infection leading to reduced CD4 T lymphocytes and AIDS.[13] Patients infected with HIV have a 60- to 100-fold higher risk of developing NHL compared to the general population.[11,12] Among individuals exposed to long periods of highly active antiretroviral therapy (HAART) leading to longer survival, about 10% will eventually develop NHL.[6] Chemotherapy and radiotherapy can also contribute to immune dysfunction, and various hypotheses have provided possible explanations for the increased risk of subsequent malignancies after NHL including intrinsic susceptibility,[85] impairment of cellular immunity which can be exacerbated by therapy,[140] and the potential mitogenic effects of chemotherapy and radiation.[141] In studies that have considered NHL subtypes, DLBCL has shown increased risks associated with bone marrow transplant,[8] solid organ transplant,[142] and HIV AIDS.[11]

Immune stimulation has also been shown to increase risk of NHL. A number of infectious agents have been associated with NHL development including Epstein Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-cell lymphotropic virus type 1 (HTLV-1), human herpesvirus 8 (HHV8), and helicobacter pylori (H. pylori).[6] Infections associated with immune dysfunction appear to be related to poor immune control of known oncogenic viruses.[10] Viruses such as EBV, HHV8, and HTLV-1 can directly infect and transform lymphocytes causing disruptions in normal cell functions and have been implicated in NHL and specific NHL subtypes.[13] Some infections can increase NHL risk through chronic immune stimulation and persistent activation of lymphocytes or reactivation of latent oncogenic viruses.[13] Previous studies have shown that the chronic inflammatory response and/or immune activation caused by autoimmune conditions are responsible for an increased risk of NHL.[14-17] Changes in immunity and inflammatory response genes caused by common genetic variants in single nucleotide polymorphisms, specifically TNF and IL10, can also increase the risk of developing NHL.[18] In addition to being a key risk factor for the development of NHL, the natural history of NHL is associated with immune dysfunction, particularly for CLL/SLL survivors.[143] It has been hypothesized that the intrinsic immune deficiencies in patients with CLL/SLL may put them at higher risk of developing subsequent infections and potentially second malignancies.[143] Other studies have observed specific NHL subtype differences in risks, particularly regarding increased risks of DLBCL associated with HCV infection,[144] autoimmune diseases,[14] and TNF and IL10 polymorphisms.[18]

Immune dysfunction is also a key risk factor for a number of other malignancies as well. Studies of bone marrow and solid organ transplant recipients and patients with HIV/AIDS demonstrate increased risks for HL, NHL, Kaposi sarcoma, and cancers of the liver, stomach, cervix, vulva and vagina, penis, anus, oral cavity and pharynx, and larynx.[9] Increased risks in lung cancer have been hypothesized in descriptive studies to be related to altered immunity,[22,26,31,89,145,146] infections,[13] and therapeutic immunosuppression.[40,147] Previous

analytic studies have observed immunological alterations associated with lymphomas and increased risk of lung cancer.[9,47,48] Excesses of melanoma have also been observed in previous descriptive studies. Various hypotheses for reasons for increased risks of melanoma have suggested infections,[148,149] immune defects resulting from altered immunity,[22,26,27,29,31,89,146] therapeutic immunosuppression,[26,31,150,151] and interactions between ultraviolet radiation and NHL immune defects.[22,26,27,29,89,146]

A recent meta-analysis compared cancer incidence in population-based cohort studies of two known immunosuppressed populations, people with HIV/AIDS and people who were immunosuppressed after receiving solid organ transplantation.[9] Seven studies[152-158] of people with HIV/AIDS including 444,172 people over a follow-up period of 1980-2002 and five studies[159-163] of transplant recipients including 31,977 people over a follow-up period of 1970-2003 were included in the meta-analysis.[9] There were significantly increased incidences in cancer risk in both populations in 20 of the 28 specific cancers that were examined including the three types of AIDS-defining cancers (Kaposi's sarcoma, NHL, and cervical cancer).[9] The findings of the meta-analysis suggest that immune dysfunction plays an important role in the development of numerous cancers;[9] however, no previous analytic study has investigated immune deficiency as a risk factor for second primary malignancies.

Second Primary Malignancies

Previous research has found excess risks of second lung cancer after first primary NHL with SIRs ranging from 1.19 to 1.36.[39,40,89] Increased risks were also seen in specific NHL subtypes including FL (SIR=1.28, 95% CI 1.07-1.53) and CLL/SLL (SIR=1.42, 95% CI 1.26-1.60) but not DLBCL.[40] Various descriptive studies have hypothesized an association between treatment for NHL and second lung cancer.[30,31,34,40,88,89,101,108] It is plausible that NHL treatment could increase risk of subsequent lung cancer since other studies have found increased lung cancer risks after radiotherapy and chemotherapy for Hodgkin lymphoma.[43,164] Immune dysfunction

has also been hypothesized as a major risk factor for second lung cancer,[22,26,31,89,146] and previous studies have shown increased lung cancer risks with certain infections causing chronic inflammatory responses and tissue damage,[145] and altered immunity observed in immunosuppressed populations.[9,47,48] Second lung cancer excesses have also been suggested to be associated with therapeutic immunosuppression.[40,147] Treatment effects and immune dysfunction in NHL have been hypothesized to combine with the effects of smoking to increase the risk of lung cancer.[22,26,89,146]

Risks of AML/MDS are strongly elevated (SIR 3.22-4.65) after first primary NHL,[39,40] with higher risks for DLBCL and FL than for CLL/SLL.[40] Numerous studies have linked chemotherapy and radiotherapy to increased risk of AML/MDS;[21,22,24,30-32,34,35,38,85-89,98,103] however, AML/MDS has not been definitively associated with autoimmune conditions or infectious diseases.

Various studies have identified an excess of melanoma after first primary NHL,[39] particularly for CLL/SLL and FL but not DLBCL.[40] Based on previous descriptive studies, chemotherapy has been hypothesized to increase risk of developing a second melanoma.[26,29,31,36,150,151] Melanoma excesses have been associated with therapeutic immunosuppression;[26,31,150,151] however, patients with NHL exhibit a variety of immunological defects that may increase their risk of melanoma in the absence of any treatment effect.[165] Previous studies have shown excesses of second melanomas in immunosuppressed patients attributed to immune dysfunction due to immunological alterations associated with lymphomas.[9,48] Melanoma risk is strongly increased among patients who experience extreme immune suppression which indicates a potential infectious etiology.[148,149] It has been suggested that the immune defects in NHL may combine with ultraviolet radiation to increase the risk of melanoma.[22,26,27,29,89,146]

Justification

The previous background information emphasizes the importance and relevance of the specific hypotheses and aims of this dissertation. Previous studies have shown that non-Hodgkin lymphoma survivors are at increased risk of developing second primary malignancies compared to the general population and have provided descriptive information and several hypotheses regarding potential associations between NHL treatments, infections, and autoimmune conditions. Although chemotherapy and radiotherapy are well-established risk factors for developing subsequent malignancies in several different populations, the evidence of increased risks of second lung, AML/MDS, and melanoma remain inconclusive. Immune disturbances are the strongest known risk factors for NHL; however, there are no previous studies to date investigating immune dysfunction increasing risks of second malignancies. There is a need for additional analytic studies that can integrate treatment in the current era as well as include some immune-related risk factors that have not been previously studied. This dissertation will allow us to explore these potential associations in the SEER-Medicare dataset.

Importance of Current Project

With the increasing number of cancer survivors, as well as the improvements in chemotherapy and radiotherapy and additional knowledge regarding the relationship between immune dysfunction and NHL, it is important to develop a better understanding of associations between NHL treatment and specific medical conditions and the risk of developing second malignancies. This dissertation is the first analytic study to investigate NHL treatment and immune dysfunction risk factors associated with subsequent malignancies after first primary NHL. We also had the ability to explore whether second cancer immune-related risk factors may differ by NHL subtype. Additionally, our study results are generalizable to the elderly population in the US since we are using a population-based cohort that represents this population. The cohort study design also provides long-term follow-up for exposure assessment and second malignancy ascertainment, as well as eliminates selection bias since all subjects in the cohort

developed a first primary NHL and there is no opportunity to decline to participate since it is a records-based study.

The findings from this dissertation will help us develop a better understanding of the risk factors most strongly associated with second malignancy development and may provide further clues to the etiology of second malignancies as well as lymphomas. Additionally, this dissertation may provide important information for NHL survivors and their physicians regarding balancing the risks of developing a treatment-related subsequent malignancy with the known benefits achieved from treatment.

Chapter 3: Specific Aims

General Purpose

The purpose of this project was to develop a better understanding of the risks of developing second primary malignancies, specifically second lung, acute myeloid leukemia/myelodysplastic syndromes (AML/MDS), and melanoma, after non-Hodgkin lymphoma. Non-Hodgkin lymphoma survivors are at increased risk of developing a range of subsequent malignancies when compared with the general population. Previous studies have mainly provided descriptive information and various hypotheses regarding potential associations between NHL treatments and specific medical conditions and increased risk of subsequent malignancies after primary NHL. Chemotherapy and radiotherapy are well-established risk factors for increased risk of second malignancies in several different populations including survivors of childhood cancer and other first primary malignancies, but aside from some observed increased risks of second AML/MDS, bladder/kidney cancer, and possibly lung cancers, the evidence of increased risks of subsequent malignancies in NHL survivors remains inconclusive. Immune perturbation is the strongest known risk factor for NHL and also plays a significant role in the development of other malignancies; however, previous studies have not investigated immune dysfunction (e.g., autoimmune conditions, infectious diseases) as potential risk factors for second malignancies. Therefore, additional analytic studies investigating subsequent malignancies after first primary NHL are needed that can integrate treatment in the current era as well as include some immune-related risk factors that have not been previously studied. **Based on the previous research, it was hypothesized that NHL treatments, autoimmune conditions, and infections increase the risk of certain subsequent malignancies after NHL. Specifically, it was hypothesized that infections, autoimmune conditions, and chemotherapy increase the risk of subsequent melanoma. It was also hypothesized that autoimmune conditions, infections, radiotherapy, and chemotherapy all increase the risk for second lung cancer. Lastly, the third hypothesis stated that**

chemotherapy and radiotherapy for first primary NHL is related to second AML/MDS. This dissertation will use the Surveillance, Epidemiology, and End Results (SEER)-Medicare dataset to obtain information on initial, current NHL treatments, possible subsequent NHL treatments, NHL subtypes, and immune-related risk factors which will be incorporated into an analytic study investigating the associations between those risk factors and second malignancies for a large population-based cohort.

Specific Aims

There were two major aims of this project. **The first was to assess the association between specific risk factors (e.g. chemotherapy, radiotherapy, autoimmune conditions, and infections) and development of second malignancies after first primary NHL in the U.S. elderly population.** To accomplish this aim we conducted a population-based cohort study using data from the linkage of the SEER-Medicare database. Cases included incident cases of NHL reported to SEER between 1992 and 2009 for persons aged 66 years and older. Medicare claims included specific information regarding patient demographics, dates of diagnosis for various medical conditions, dates of treatment, and information on follow-up. The primary analysis tested for associations between chemotherapy, radiotherapy, autoimmune conditions, and infectious diseases and the diagnosis of a subsequent malignancy using Cox proportional hazards regression models to compute hazard ratios (HR) and 95% confidence intervals (CI).

The second major aim was to evaluate whether second malignancy risk factors differed among survivors of the most common NHL subtypes in the U.S. elderly population. To accomplish this aim we compared the exposure prevalence by NHL subtype and presented the results as descriptive analyses. Additionally, we evaluated the differences in risk factors by NHL subtype by including an interaction term between subtype and the risk factor of interest using a likelihood ratio p-value<0.05. Lastly, we used SEER-Medicare to conduct a population-based cohort study with stratified analyses from Aim 1 by first primary NHL subtype,

specifically diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

Chapter 4: Results

Risk factors for melanoma among survivors of non-Hodgkin lymphoma

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Running head: Risk factors for melanoma after CLL/SLL and NHL

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Abstract

Purpose: Previous studies have reported that non-Hodgkin lymphoma (NHL) survivors have increased risk of developing cutaneous melanoma, however, risks associated with specific treatments and immune-related risk factors have not been quantified.

Patients and Methods: We evaluated melanoma risk among 44,870 1-year survivors of first primary NHL diagnosed at ages 66-84 years during 1992-2009 and included in the Surveillance, Epidemiology and End Results-Medicare database. Information on NHL treatments, autoimmune diseases, and infections was derived from Medicare claims.

Results: A total of 202 second melanomas occurred among NHL survivors, including 91 after chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and 111 after other NHL subtypes. Melanoma risk after CLL/SLL was significantly increased among patients who received infused fludarabine-containing chemotherapy with or without rituximab (N=18, hazard ratio [HR]=1.86, 95% confidence interval [CI]=1.06-3.27; N=10, HR=2.72, 95%CI=1.33-5.56, respectively). Significantly elevated risks also were associated with T-cell activating autoimmune diseases diagnosed prior to (HR=1.76, 95%CI=1.06-2.93) or after CLL/SLL (HR=2.32, 95%CI=1.34-4.03). In contrast, among patients with other NHLs, melanoma risk was not associated with specific treatments or T-cell/B-cell activating autoimmune diseases. Generally, infections were not associated with melanoma risk, except for urinary tract infections among CLL/SLL survivors, and pneumonia and gastrohepatic infections among survivors of other NHLs.

Conclusion: We provide the first evidence that infused fludarabine-containing chemotherapy and T-cell activating autoimmune conditions significantly increase cutaneous melanoma risk among older adults with CLL/SLL, but not among those with other NHL subtypes. Our findings support the importance of regular dermatologic screening and education of patients and clinicians regarding these risks.

Introduction

Advances in treatment have substantially improved the prognosis following a diagnosis of non-Hodgkin lymphoma (NHL), with the 5-year relative survival increasing from 47% to 71% over the last four decades.[3] However, the occurrence of a second malignancy is an important cause of morbidity and mortality among the more than 700,000 NHL survivors in the US today.[1] Compared with the general population, NHL survivors have an increased risk of developing melanoma, with particularly elevated risks among survivors of more indolent NHLs, specifically chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and, to a lesser extent, follicular lymphoma (FL).[40]

Factors that may explain the elevated risk of melanoma after NHL remain unknown. In addition to immune deficits inherent to NHL, NHL treatments – particularly the immunosuppressive effects of chemotherapy – have been implicated, but previous studies have lacked detailed treatment data or sufficient numbers of second melanoma cases to investigate associations with specific chemotherapeutic agents.[22,26,27,29,31,36,37,40,41,89,146,166-173] The observation of increased melanoma risk in immunosuppressed patients [9,10,48,138,148,150] supports a potential role for immune dysfunction in the development of melanoma after NHL, either independently or in conjunction with ultraviolet radiation via sun exposure – a major risk factor for melanoma.[22,26,27,29,89,146,172,173] However, no previous study has had available data on these factors to investigate the hypothesized associations. We therefore used the Surveillance, Epidemiology and End Results-Medicare (SEER-Medicare) linkage to quantify second cutaneous melanoma risks after NHL in relation to NHL treatments and immune-related medical conditions (autoimmune diseases and selected infections) among 44,870 first primary NHL survivors in the US older adult population.

Methods

Study Population

The patient cohort for this analysis was identified through SEER-Medicare, described in detail previously.[174] For this analysis, eligible patients included males and females diagnosed with first primary NHL between ages 66-84 years during 1992-2009. First primary NHL cases were identified in the SEER database according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) (see Table 1 footnote).[4,175,176] Patients must have had continuous fee-for-service Medicare Parts A and B coverage at least 12 months before NHL diagnosis through the first 12 months following NHL diagnosis for ascertainment of treatment and medical condition exposures. NHL diagnoses and follow-up time at age ≥85 years were excluded because of under-ascertainment of second malignancies at older ages.[39] Patients who survived <1 year after NHL diagnosis (N=1,549) or who had Medicare claims for HIV (N=219) or solid organ transplantation (N=124) prior to NHL diagnosis were excluded from the study population. Second primary invasive cutaneous melanomas that developed ≥1year after first primary NHL also were identified through SEER (ICD-O-3 8720-8790 [primary site C44.0-C44.9], behavior code=3, sequence code=2), and classified according to site and thickness (Table 1).[177]

Ascertainment of NHL treatments and medical conditions

Information on NHL treatments (infused chemotherapy, radiotherapy, and hematopoietic stem cell transplant) and history of immune-related medical conditions (autoimmune diseases and infections) was derived from Medicare claims from hospital inpatient, physician, and outpatient services (see Supplementary Tables 1-3 for more details). For the analysis of infused chemotherapy, we focused on the most commonly used agents (cyclophosphamide, rituximab, and fludarabine), because other treatments (e.g., other alkylating agents, epipodophyllotoxins) were received by few cases (N<5). Data on chemotherapeutic agents given orally (e.g., chlorambucil, oral cyclophosphamide) were not available in Medicare files for the majority of the study period and thus were not included. Patients who did not receive therapy (i.e., followed with observation) or who received oral chemotherapy agents exclusively were

included in our referent group. Data on radiotherapy consisted of whether patients did or did not receive radiotherapy.

Occurrences of autoimmune diseases and infections were defined as having ≥1 Medicare claim at any time during follow-up, considering diagnoses occurring prior to NHL separately from those occurring after NHL. Diagnoses of these conditions occurring prior to 1992 (the start of the study period) or prior to age 65 years (when individuals enrolled in Medicare) were not captured. We evaluated all specific autoimmune conditions and infections with at least ten second melanoma cases, either prior to or after NHL. Due to the rarity of many diagnoses, we grouped them based on the tissue and organ systems involved; we also grouped autoimmune conditions according to whether they activate B- or T-cells (see Table 3 footnotes).[178-182] Hematologic autoimmune conditions (e.g., autoimmune hemolytic anemia, thrombocytopenia) were excluded from consideration because of difficulty distinguishing these diagnoses from manifestations of chemotherapy toxicity.

Because sun exposure is a key melanoma risk factor, we grouped NHL survivors into three regions according to their residence at the time of NHL diagnosis based on SEER registry (Table 1).These categorizations, which are based on levels of ultraviolet B radiation flux, have been shown to be a valid proxy for recent sun exposure in a melanoma risk model.[183]

Statistical analysis

Follow-up for the study population began one year after the diagnosis of first primary NHL and continued until the earliest of: second cancer diagnosis, age 85 years, death, loss to follow-up, or end of study (December 31, 2009). We used Cox proportional hazards regression to compute hazard ratios (HRs) and 95% confidence intervals (CIs) to assess the association between specific risk factors and the development of second melanoma after first primary NHL. Analyses used age as the time scale, were adjusted for demographic factors [sex, race (white,

other), residence (North, Central, South), and follow-up time as a time-dependent covariate (1-1.9, 2-2.9, 3-3.9, 4-4.9, 5-6.9, and ≥7 years)], and were stratified by calendar year of NHL diagnosis to account for differing exposure periods. Time-dependent covariates were used to indicate receipt of any radiotherapy or infused chemotherapy during follow-up based on the timing of initiation of therapy. For investigation of melanoma risks associated with autoimmune conditions/infections occurring before NHL diagnosis, we defined the follow-up period from age 65 or age at enrollment into Medicare to age of NHL diagnosis. Autoimmune conditions and infections diagnosed after NHL were evaluated as time-dependent covariates based on the timing of diagnoses of these conditions. Because treatment patterns for CLL/SLL differ substantially from other NHL subtypes[184] and because CLL/SLL survivors have higher risk for developing subsequent melanoma,[40] we calculated risks separately for CLL/SLL and all other NHL subtypes combined (excluding CLL/SLL).

Melanoma risk factors were identified as those with a two-sided Wald chi-square $P<0.05$ comparing models with and without the factor of interest. For all melanoma risk factors we identified in our primary analyses, exploratory analyses investigated differences in risks by residence due to the hypothesized interaction between immune dysfunction and ultraviolet radiation.[22,26,27,29,89,146,172,173] To evaluate if increased melanoma risk was influenced by increased medical surveillance, we also investigated differences by melanoma thickness.[185] Analyses were conducted using SAS 9.3 (Cary, NC).

Results

Our study population of 44,870 one-year survivors of first primary NHL included 13,950 individuals with CLL/SLL, 10,311 with DLBCL, 7,437 with FL, 3,516 with marginal zone lymphoma, and 9,656 with other lymphoma subtypes (Table 1). Median age at diagnosis was 74 years, and most survivors (91%) were white. Over half of CLL/SLL survivors were male (54%),

whereas 54% of DLBCL and 57% of FL survivors were female. At the time of NHL diagnosis, 45% of survivors resided in northern regions, 29% in central regions, and 26% in southern regions.

During 247,883 total person-years of follow-up, 202 second melanomas were diagnosed. Median interval from NHL to melanoma diagnosis was 3 years (range=1-14.8 years). Melanoma risks were higher among males, non-Hispanic Caucasians, those residing in southern regions, and survivors of CLL/SLL (Supplementary Table 4). Nearly half (N=91, 45%) of melanomas were diagnosed after CLL/SLL, with 40.7% of these occurring on the face, head, or neck and 42.9% with ≥1mm thickness (Table 1). In contrast, among survivors of all other NHL subtypes combined, melanomas with specified site and depth occurred most frequently on the trunk (29.7%), and 27.9% were ≥1mm thick.

A total of 5,051 (36.3%) CLL/SLL survivors received infused chemotherapy during follow-up, of whom 2,712 (53.7%) initiated chemotherapy within 12 months of diagnosis and 2,339 (46.3%) initiated chemotherapy >12 months after diagnosis. The most commonly received infused agents were rituximab (26.8%), fludarabine (21.2%), and cyclophophosphamide (17.2%)(Table 2, Supplementary Table 1). Initial analyses showed second melanoma risk was significantly increased among 2,958 patients who were treated with any fludarabine-containing chemotherapy for CLL/SLL (HR=1.87, 95%CI=1.07-3.27) compared with patients not recorded as receiving infused chemotherapy or who received oral agents alone (Table 2, Model A). Further analyses showed significantly elevated melanoma risks among CLL/SLL patients who received infused fludarabine-containing chemotherapy with (HR=1.86, 95%CI=1.06-3.27) or without rituximab (HR=2.72, 95%CI=1.33-5.56) (Table 2, Model B). Treatment of CLL/SLL with radiotherapy was not associated with melanoma risk.

Among survivors of other NHL subtypes, 20,880 (67.5%) patients received infused chemotherapy during follow-up. Of those, 18,694 (89.5%) began chemotherapy within the first 12 months of

NHL diagnosis, and 2,186 (10.5%) initiated chemotherapy >12 months after diagnosis. Rituximab (50.9%) and cyclophosphamide (54.3%) were the most commonly received agents (Table 2, Supplementary Table 1). Melanoma risks were not significantly increased after treatment with any rituximab-, fludarabine-, or cyclophosphamide-containing chemotherapy (Model A), or after radiotherapy (Model B). In more detailed models, non-significantly elevated risks were observed among patients who received cyclophosphamide-containing chemotherapy without rituximab (HR=1.68, 95%CI=0.93-3.04) (Model B).

Diagnosis of T-cell activating autoimmune diseases before and after CLL/SLL was associated with significantly increased risk of melanoma when compared with patients without T-cell activating autoimmune diseases (before CLL/SLL: HR=1.76, 95%CI=1.06-2.93; after CLL/SLL: HR=2.32, 95%CI=1.34-4.03), whereas non-significant decreases in melanoma risk were observed for B-cell activating conditions occurring before and after CLL/SLL (Table 3). Among T-cell activating autoimmune conditions melanoma risks were particularly elevated for individuals diagnosed prior to CLL/SLL with Graves' disease (HR=2.27, 95%CI=1.03-4.99) or psoriasis (HR=2.60, 95%CI=1.19-5.69), and after CLL/SLL diagnosis with chronic rheumatic heart disease (HR=1.93, 95%CI=1.03-3.61), skin-related autoimmune conditions (HR=1.85, 95%CI=1.01-3.37), and asthma (HR=2.22, 95%CI=1.22-4.01). Although a number of CLL/SLL patients were diagnosed with infections during follow-up, only the occurrence of cystitis/pyelonephritis urinary tract infections after CLL/SLL diagnosis was associated with significantly elevated melanoma risk (HR=1.81, 95%CI=1.05-3.13).

In contrast to CLL/SLL, among non-CLL/SLL survivors, the diagnosis of B- or T-cell activating autoimmune conditions as a group was not significantly related to subsequent melanoma risk (Table 3). In analyses of specific conditions, the occurrence of localized scleroderma (T-cell activating condition) prior to non-CLL/SLL diagnosis was associated with an increased melanoma risk (HR=1.73, 95%CI 1.07-2.82). Among infections, a heightened melanoma risk was

linked to pneumonia diagnosed before non-CLL/SLL (HR=1.71, 95%CI 1.08-2.71) and gastrohepatic infections (mainly gastroenteritis) diagnosed after non-CLL/SLL (HR=1.92, 95%CI 1.13-3.26). Significant decreases in melanoma risk were not observed for any specific autoimmune conditions or infections.

Risk estimates for the associations described above were materially unchanged in multivariate analyses that included all chemotherapeutic agents as well as autoimmune conditions and infections with $P<0.05$ in the same model. Risk estimates also were similar for melanomas <1 and ≥1 mm thick, and regardless of area of residence. Although our sample size was small, risk estimates for chemotherapeutic agents and for autoimmune conditions and infections generally were similar when we evaluated melanoma risks occurring after the two most common non-CLL/SLL NHL subtypes, namely DLBCL and FL.

Discussion

In a large-scale, population-based study, we show for the first time that patients with CLL/SLL who were treated with fludarabine-containing chemotherapy (with or without rituximab) or who were diagnosed with T-cell activating autoimmune conditions have approximately two-fold elevated risk of cutaneous melanoma. In contrast, survivors of other NHL subtypes combined (non-CLL/SLL NHL) had no evidence of heighted melanoma risk associated with either T-cell or B-cell autoimmune diseases, and specific chemotherapy regimens did not appear to strongly raise the risk of melanoma. In general, most infections did not appear to be related to melanoma risks, with the possible exceptions of urinary tract infections occurring after CLL/SLL and pneumonia or gastrohepatic infections occurring in patients with non-CLL/SLL NHL. Our study results provide direct evidence for the importance of immune perturbation in explaining the excess of melanoma observed in CLL/SLL survivors.

CLL/SLL is an indolent lymphoma with a five-year relative survival rate of nearly 85%.[3] Patients with CLL/SLL experience profound and prolonged immune dysfunction characterized by defective B- and T-cell function, which contributes to increased incidence of infections and autoimmune diseases.[143,186,187] In the first quantification of second melanoma risk associated with specific infused chemotherapy agents for CLL/SLL, including both initial and subsequent chemotherapy, we demonstrated that fludarabine-containing regimens, with or without rituximab, are linked to a significant excess risk of melanoma after CLL/SLL. Elevated secondary malignancy risks – including treatment-related acute myeloid leukemia and solid malignancies, particularly skin cancers – have been reported in fludarabine-treated CLL/SLL cohorts,[45,167,170,188-193] but no previous study has directly compared melanoma risks in patients treated with and without fludarabine. The exact mechanism of action of fludarabine in the induction of cutaneous melanoma is unclear, but may be due to the inherent predisposition to malignancy among CLL/SLL patients coupled with the broad immunosuppressive and DNA-damaging effects of fludarabine.[188,194,195]

Elevated melanoma risks also have been observed in other immunosuppressed populations, such as solid organ and bone marrow transplant recipients, particularly those who received T-cell depleting therapies,[10,48] as well as in persons with HIV/AIDS.[9,196] Additionally, T-cells are a critical component of the anti-tumor response in melanoma patients,[197-199] the importance of which is supported by recent evidence showing that immunotherapy directed at T-cell checkpoints is effective in treating metastatic melanoma. In our study, the melanomas occurring after CLL/SLL were more likely to be ≥1mm thick than those occurring after other NHL subtypes, which is consistent with previous studies reporting these melanomas as more advanced and more aggressive than melanomas that arise in the general population.[138,200-203] Patients with CLL/SLL are commonly diagnosed with hematologic autoimmune conditions, most frequently autoimmune hemolytic anemia and thrombocytopenia; however, non-hematologic autoimmune diseases are reportedly rare.[204,205] In a new finding, we show that melanoma risk

is approximately two-fold increased for patients with T-cell activating autoimmune conditions, including Graves' disease, psoriasis, chronic rheumatic heart disease, localized scleroderma/psoriasis, and asthma. Combined with previous literature, our findings support the importance of T-cell dysfunction as a contributor to melanoma risk after CLL/SLL.

NHL subtypes other than CLL/SLL comprises a heterogeneous group of lymphomas, with the most common subtypes including DLBCL, an aggressive NHL with five-year relative survival of 60%, and FL, a more indolent lymphoma with five-year relative survival of 87%.[3] Although cutaneous melanoma has been reported in excess after all NHLs combined in numerous studies,[22,26,27,29,31,36,37,40,41,89,146,166-173] limited data by NHL subtype have suggested a modestly elevated melanoma risk after FL , whereas risk following DLBCL did not exceed unity.[40] In contrast to our results for CLL/SLL, we found no significant associations between melanoma risk and treatment for the combined group of other NHL subtypes, although a 70% non-significant elevation in risk was seen among those treated with cyclophosphamide-based regimens without rituximab. Although cyclophosphamide has been associated with immunosuppression at higher doses and can increase the risk of bacterial infections, the association is due to ensuing neutropenia and not reduced T-cell function.[206-208] Our investigation had small numbers of melanoma cases following specific NHL subtypes other than CLL/SLL, thus future studies with larger numbers will be needed to evaluate treatment and immune related risk factors for DLBCL, FL and other major NHL subtypes.

We found little evidence that T- or B-cell activating autoimmune conditions were related to subsequent melanoma after non-CLL/SLL NHL, raising the possibility that these conditions may only contribute to the development of second melanoma after NHL in the context of profound and prolonged immunosuppression such as that seen in CLL/SLL survivors. As the single exception, melanoma risk was significantly elevated among individuals who developed localized scleroderma prior to non-CLL/SLL NHL. We also observed increased risks for melanoma among

individuals diagnosed with pneumonia and gastrohepatic infections after non-CLL/SLL NHL – a different pattern of infections than observed for CLL/SLL survivors, in whom melanoma risk only was significantly associated with urinary tract infections. While it is plausible that these infections could be markers of immune perturbation, and T-cell dysfunction in particular for pneumonia,[209,210] our data overall could not demonstrate strong associations with the occurrence of infections.

The primary strength of this study was the analysis of a large population-based cohort to identify specific risk factors for second melanoma development by NHL subtype. Additionally, this was one of the first analytic studies to consider detailed treatment as well as non-treatment risk factors for second melanoma after first primary NHL. The cohort, records-based study design also provided long-term follow-up for exposure assessment and second melanoma occurrence, and eliminated selection bias. Despite these strengths, several key limitations should be considered in the interpretation of our results. Most notably, information on oral chemotherapy agents was not available for the duration of follow-up, thus we could not ascertain receipt of chlorambucil or other oral alkylators.[190] Chlorambucil is myelosuppressive but does not typically result in profound T-cell depletion; nevertheless, our fludarabine-related risk estimates are likely to be conservative since patients who received only oral chemotherapy are included in our referent group. Additionally, due to the nature of the Medicare claims database, some exposures may have been misclassified, for example due to missing information on infections and autoimmune diseases diagnosed in patients before entry into Medicare at age 65 years, as well as for mild infections for which the patient did not seek medical care. We also were restricted to assessing potential risk factors that generate a medical claim, which excluded key melanoma risk factors such as genetic susceptibility or a direct measure of sun exposure. However, our analyses were adjusted for residence (a proxy for sun exposure).[183]

We provide the first evidence that specific chemotherapeutic agents and immune-related medical conditions are related to subsequent melanoma risk among older CLL/SLL survivors, but not among patients with other NHL subtypes. Our findings identify high-risk NHL survivors that may benefit most from regular full skin examinations in order to maximize opportunities for early detection of cutaneous melanoma. Further research is needed to understand the biological mechanisms behind the immune perturbations that lead to melanoma development and to determine if similar risks extend to younger NHL survivors.

Table 1. Selected characteristics of 44,870 1-year survivors of first primary NHL, overall and by NHL subtype, diagnosed at ages 66-84 years, 16 SEER registries, 1992-2009

	Total NHL		First primary NHL subtype*									
			CLL/SLL		DLBCL		FL		MZL		Other	
	N	%	N	%	N	%	N	%	N	%	N	%
Total number of 1-year survivors	44,870		13,950		10,311		7,437		3,516		9,656	
Age at NHL diagnosis (years)												
65-69	9,673	21.6	2,901	20.8	2,169	21.0	1,828	24.6	767	21.8	2,008	20.8
70-74	13,120	29.2	3,982	28.5	3,038	29.5	2,243	30.2	988	28.1	2,869	29.7
75-79	12,754	28.4	4,030	28.9	2,934	28.5	1,985	26.7	958	27.3	2,847	29.5
80-84	9,323	20.8	3,037	21.8	2,170	21.1	1,381	18.6	803	22.8	1,932	20.0
Sex												
Male	22,097	49.3	7,590	54.4	4,725	45.8	3,229	43.4	1,439	40.9	5,114	53.0
Female	22,773	50.8	6,360	45.6	5,586	54.2	4,208	56.6	2,077	59.1	4,542	47.0
Race												
White	40,752	90.8	12,841	92.1	9,222	89.4	6,888	92.6	3,090	87.9	8,711	90.2
Other/unknown	4,118	9.2	1,109	7.9	1,089	10.6	549	7.4	426	12.1	945	9.8
Year of NHL diagnosis												
1992-1997 †	8,127	18.1	2,755	19.8	1,798	17.4	1,345	18.1	233	6.6	1,996	20.7
1998-2003	15,978	35.6	5,002	35.9	3,680	35.7	2,618	35.2	1,317	37.5	3,361	34.8
2004-2009	20,765	46.3	6,193	44.4	4,833	46.9	3,474	46.7	1,966	55.9	4,299	44.5
Residence at time of NHL diagnosis ‡												
North	20,348	45.4	6,691	48.0	4,473	43.4	3,206	43.1	1,511	43.0	4,467	46.3
Central	12,778	28.5	3,727	26.7	3,107	30.1	2,260	30.4	1,041	29.6	2,643	27.4
South	11,744	26.2	3,532	25.3	2,731	26.5	1,971	26.5	964	27.4	2,546	26.4
Median age at NHL (years)	74.0		75.0		74.0		74.0		75.0		74.0	
Mean person-years at risk	5.5		5.6		5.4		5.8		5.6		5.3	
Total number of second melanomas	202		91		34		34		10		33	
Median interval from NHL to melanoma (years)	3.0		3.3		2.9		2.8		3.0		2.6	
Site of melanoma §												
Face/head/neck	73	36.1	37	40.7	<10	~	11	32.4	<10	~	14	42.4
Trunk	56	27.7	23	25.3	13	38.2	<10	~	<10	~	<10	~
Upper extremities	52	25.7	22	24.2	<10	~	<10	~	<10	~	<10	~
Lower extremities	13	6.4	<10	~	<10	~	<10	~	<10	~	<10	~
Other/unspecified	<10	~	<10	~	<10	~	<10	~	<10	~	<10	~
Thickness (mm) of melanoma												
< 1.0	104	51.5	41	45.1	25	73.5	16	47.1	<10	~	16	48.5
1.0-3.9	55	27.2	31	34.1	<10	~	10	29.4	<10	~	<10	~
≥ 4.0	15	7.4	<10	~	<10	~	<10	~	<10	~	<10	~
Unknown	28	13.9	11	12.1	<10	~	<10	~	<10	~	<10	~

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); International Classification of Diseases for Oncology, 3rd edition (ICD-O-3); marginal zone lymphoma (MZL); non-Hodgkin lymphoma (NHL); Surveillance, Epidemiology and End Results (SEER).

~ Counts and percentages are not reported for less than 10 melanoma cases to protect patient confidentiality.

* First primary NHL subtype defined by ICD-O-3 as DLBCL (9678-9680, 9684 [B-cell]), FL (9690-9691, 9695, 9698), CLL/SLL (9670, 9823), MZL (9689, 9699) and other NHL (9590-9596, 9671, 9673, 9675, 9684 [non B-cell], 9687, 9700-9702, 9705, 9708-9709, 9714-9719, 9727-9729, 9827 [primary site=C.420-421, 424]).

† 1992-1997 includes 13 SEER registries, whereas 1998-2003 and 2004-2009 include 16 SEER registries.

‡ Residence defined by SEER registry areas, including north (Connecticut, Detroit, Iowa, Seattle, and New Jersey), central (San Francisco, Utah, San Jose, Greater California, and Kentucky), and south (Hawaii, New Mexico, Atlanta, Los Angeles, Rural Georgia, Greater Georgia, and Louisiana).

§ Melanoma site defined by ICD-O-3 as face/head/neck (C44.0-44.4), trunk (C.44.5), upper extremities (C.44.6), lower extremities (C.44.7), and other/unspecified (C44.8-44.9).

Table 2. Risk of melanoma after first primary NHL, by subtype, in relation to NHL treatments

	Total NHL		Melanoma cases			
NHL treatment *	N	%	N	%	HR †	95% CI
Patients diagnosed with first primary CLL/SLL						
Infused chemotherapy						
None recorded	8,899	63.8	52	57.1	1.00	Referent
Model A ‡						
Any rituximab	3,744	26.8	27	29.7	1.41	0.76-2.63
Any fludarabine	2,958	21.2	28	30.8	1.87	1.07-3.27
Any cyclophosphamide	2,402	17.2	19	20.9	1.07	0.57-2.01
Model B §						
Fludarabine without rituximab	917	6.6	10	11.0	2.72	1.33-5.56
Rituximab without fludarabine	1,703	12.2	<10	~	1.52	0.74-3.14
Fludarabine + rituximab	2,041	14.6	18	19.8	1.86	1.06-3.27
Radiotherapy						
No	12,925	92.7	85	93.6	1.00	Referent
Yes	1,025	7.3	<10	~	0.83	0.30-2.29
Patients diagnosed with first primary NHL other than CLL/SLL						
Infused chemotherapy						
None recorded	10,040	32.5	34	30.6	1.00	Referent
Model A ‡						
Any rituximab	15,726	50.9	53	47.8	1.06	0.62-1.82
Any fludarabine	2,518	8.1	<10	~	1.20	0.57-2.57
Any cyclophosphamide	16,786	54.3	68	61.3	1.40	0.87-2.26
Model B §						
Cyclophosphamide without rituximab	4,781	15.5	24	21.6	1.68	0.93-3.04
Rituximab without cyclophosphamide	3,721	12.0	<10	~	0.93	0.42-2.06
Cyclophosphamide + rituximab	12,005	38.8	44	39.6	1.23	0.74-2.02
Radiotherapy						
No	21,051	68.1	76	68.5	1.00	Referent
Yes	9,869	31.9	35	31.5	1.14	0.75-1.73

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); confidence interval (CI); hazard ratio (HR); non-Hodgkin lymphoma (NHL).

~ Counts and percentages are not reported for less than 10 melanoma cases to protect patient confidentiality.

* Treatments received by fewer than 10 melanoma cases are not reported here but are included in Supplementary Table 1 (e.g., other alkylating agents, epipodophyllotoxins, and hematopoietic stem cell transplantation).

† HR (95% CI) adjusted for sex, race, residence, and follow-up time (time-dependent covariate) and stratified by calendar year. Age was used as the time scale. Time-dependent covariates used to indicate receipt of any radiotherapy or chemotherapy during follow-up based on timing of initiation of therapy. The HRs for chemotherapy in Models A and B were additionally adjusted for receipt of other alkylating agents. The HR for radiotherapy was additionally adjusted for chemotherapy using Model B.

‡ Percentages do not add up to 100% because groups are not mutually exclusive.

§ Percentages do not add up to 100% because a small number of patients received other agents.

Table 3. Risk of melanoma after first primary NHL, by subtype, in relation to autoimmune conditions and infections

	Prior to NHL diagnosis						After NHL diagnosis *					
	Total NHL		Melanoma cases				Total NHL		Melanoma cases			
Autoimmune conditions †	**N**	**%**	**N**	**%**	**HR ‡**	**95% CI**	**N**	**%**	**N**	**%**	**HR ‡**	**95% CI**
Patients diagnosed with first primary CLL/SLL												
B-cell activating conditions	2,263	16.2	<10	~	0.58	0.26-1.26	3,637	26.1	13	14.3	0.78	0.39-1.58
T-cell activating conditions	5,488	39.3	36	39.6	1.76	1.06-2.93	6,749	48.4	49	53.9	2.32	1.34-4.03
Autoimmune conditions, by organ system												
Systemic/connective tissue	1,687	12.1	<10	~	0.74	0.32-1.70	1,912	13.7	<10	~	1.33	0.63-2.78
Cardiovascular	1,367	9.8	<10	~	1.30	0.62-2.73	2,370	17.0	15	16.5	1.68	0.90-3.15
Chronic rheumatic heart disease	1,219	8.7	<10	~	1.51	0.72-3.16	2,187	15.7	15	16.5	1.93	1.03-3.61
Endocrine	931	6.7	<10	~	2.15	1.02-4.52	1,213	8.7	<10	~	1.19	0.47-2.98
Graves' disease	783	5.6	<10	~	2.27	1.03-4.99	872	6.3	<10	~	1.57	0.63-3.95
Skin	2,222	15.9	18	19.8	1.54	0.90-2.63	2,402	17.2	21	23.1	1.85	1.01-3.37
Localized scleroderma	1,809	13.0	12	13.2	1.14	0.61-2.12	1,924	13.8	13	14.3	1.43	0.72-2.82
Psoraisis	445	3.2	<10	~	2.60	1.19-5.69	431	3.1	<10	~	2.44	0.88-6.75
Gastrointestinal	1,435	10.3	<10	~	0.63	0.26-1.58	2,926	21.0	<10	~	0.69	0.32-1.51
Nervous system	110	0.8	<10	~	0	0.0	180	1.3	<10	~	2.20	0.30-15.97
Asthma	1,919	13.8	13	14.3	1.46	0.80-2.67	2,484	17.8	18	19.8	2.22	1.22-4.01
Infections, by organ system												
Respiratory - upper airway	5,847	41.9	35	38.5	0.94	0.60-1.49	5,850	41.9	35	38.5	0.78	0.42-1.46
Pharyngitis	2,141	15.4	10	11.0	0.76	0.39-1.47	2,143	15.4	11	12.1	0.94	0.45-1.98
Sinusitis	4,074	29.2	24	26.4	1.06	0.65-1.74	4,238	30.4	29	31.9	1.20	0.67-2.15
Respiratory - lower airway	6,122	43.9	37	40.7	0.97	0.61-1.54	8,347	59.8	41	45.1	0.72	0.40-1.30
Acute bronchitis	4,526	32.4	27	29.7	1.10	0.68-1.77	5,081	36.4	34	37.4	1.18	0.66-2.09
Pneumonia	2,872	20.6	16	17.6	0.93	0.53-1.62	6,414	46.0	21	23.1	0.69	0.38-1.22
Skin	2,125	15.2	17	18.7	1.56	0.90-2.70	3,490	25.0	21	23.1	1.38	0.79-2.41
Cellulitis	1,191	8.5	11	12.1	1.71	0.90-3.25	1,948	14.0	11	12.1	1.25	0.62-2.53
Urinary tract	6,227	44.6	39	42.9	1.37	0.83-2.25	7,942	56.9	46	50.6	1.77	1.01-3.12
Cystitis/pyelonephritis, UTI	5,630	40.4	34	37.4	1.49	0.90-2.45	7,599	54.5	40	44.0	1.81	1.05-3.13
Prostatitis §	1,554	20.5	17	23.0	1.17	0.66-2.06	1,199	15.8	14	18.9	1.45	0.67-3.13
Gastrohepatic	2,084	14.9	11	12.1	0.91	0.48-1.74	2,594	18.6	12	13.2	1.08	0.55-2.14
Gastroenteritis	2,020	14.5	11	12.1	0.93	0.49-1.78	2,445	17.5	11	12.1	1.01	0.50-2.06

Table 3 continued. Risk of melanoma after first primary NHL, by subtype, in relation to autoimmune conditions and infections

	Prior to NHL diagnosis						After NHL diagnosis *					
	Total NHL		Melanoma cases				Total NHL		Melanoma cases			
Autoimmune conditions †	**N**	**%**	**N**	**%**	**HR ‡**	**95% CI**	**N**	**%**	**N**	**%**	**HR ‡**	**95% CI**
Patients diagnosed with first primary NHL other than CLL/SLL												
B-cell activating conditions	6,013	19.5	16	14.4	1.01	0.58-1.75	8,078	26.1	24	21.6	1.42	0.81-2.50
T-cell activating conditions	13,142	42.5	36	32.4	0.79	0.51-1.22	15,201	49.2	35	31.5	0.99	0.59-1.64
Autoimmune conditions, by organ system												
Systemic/connective tissue	4,798	15.5	<10	~	0.54	0.26-1.13	4,734	15.3	<10	~	0.64	0.26-1.60
Cardiovascular	3,212	10.4	<10	~	0.69	0.32-1.49	5,527	17.9	<10	~	0.45	0.18-1.11
Endocrine	2,419	7.8	<10	~	0.30	0.07-1.23	2,947	9.5	<10	~	1.08	0.47-2.50
Skin	5,648	18.3	23	20.7	1.28	0.79-2.06	5,394	17.5	18	16.2	1.17	0.61-2.24
Localized scleroderma	4,265	13.8	22	19.8	1.73	1.07-2.82	4,110	13.3	17	15.3	1.55	0.81-2.97
Gastrointestinal	3,458	11.2	10	9.0	1.01	0.52-1.96	6,043	19.5	15	13.5	1.25	0.68-2.31
Pernicious anemia	2,635	8.5	<10	~	1.37	0.68-2.76	5,068	16.4	15	13.5	1.53	0.83-2.83
Nervous system	194	0.6	<10	~	4.21	1.00-17.63	379	1.2	<10	~	1.81	0.25-13.24
Asthma	4,338	14.0	<10	~	0.72	0.36-1.44	5,133	16.6	13	11.7	1.39	0.72-2.70
Infections, by organ system												
Respiratory - upper airway	13,016	42.1	41	36.9	0.95	0.63-1.45	11,944	38.6	40	36.0	1.21	0.71-2.08
Otitis media	3,400	11.0	11	9.9	0.97	0.52-1.83	2,857	9.2	<10	~	1.06	0.46-2.45
Pharyngitis	4,800	15.5	18	16.2	1.16	0.69-1.94	4,299	13	12	10.8	0.83	0.40-1.74
Sinusitis	9,109	29.5	30	27.0	1.00	0.65-1.55	8,120	26.3	26	23.4	1.00	0.54-1.84
Respiratory - lower airway	13,047	42.2	41	36.9	1.07	0.69-1.66	16,711	54.1	46	41.4	1.28	0.78-2.09
Acute bronchitis	9,819	31.8	30	27.0	0.97	0.62-1.51	9,358	30.3	27	24.3	1.03	0.59-1.81
Pneumonia	5,667	18.3	27	24.3	1.71	1.08-2.71	12,383	40.1	25	22.5	0.96	0.57-1.64
Skin	4,501	14.6	13	11.7	0.92	0.51-1.66	7,025	22.7	15	13.5	0.93	0.52-1.66
Cellulitis	2,465	8.0	<10	~	0.62	0.25-1.53	3,762	12.2	11	9.9	1.42	0.75-2.68
Urinary tract	14,162	45.8	53	47.8	1.38	0.90-2.12	17,462	56.5	54	48.7	1.17	0.67-2.03
Cystitis/pyelonephritis, UTI	12,837	41.5	39	35.1	1.15	0.74-1.80	16,759	54.2	51	46.0	1.45	0.89-2.37
Prostatitis §	3,168	21.8	19	25.0	1.18	0.69-2.02	2,154	14.9	<10	~	0.65	0.23-1.84
Gastrohepatic	4,880	15.8	14	12.6	1.03	0.58-1.83	5,926	19.2	21	18.9	1.92	1.13-3.26
Gastroenteritis	4,689	15.2	13	11.7	0.98	0.54-1.77	5,556	18.0	19	17.1	1.70	0.98-2.95

Table 3 continued. Risk of melanoma after first primary NHL, by subtype, in relation to autoimmune conditions and infections

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); confidence interval (CI); hazard ratio (HR); non-Hodgkin lymphoma (NHL); urinary tract infections (UTI).

~ Counts and percentages are not reported for less than 10 melanoma cases to protect patient confidentiality.

* New claims occurring after NHL but prior to second cancer, death, end of study, or loss to follow-up, with no claims prior to NHL.

† B-cell activating conditions include rheumatoid arthritis, Sjogren's syndrome, discoid lupus erythematosus, reactive arthritis, Felty's syndrome, chronic thryoiditis, systemic/discoid lupus erythematosus, pernicious anemia, and myasthenia gravis. T-cell activating conditions include ankylosing spondylitis, dermatomyositis, polymyalgia rheumatica, sarcoidosis, systemic sclerosis, rheumatic fever, chronic rheumatic heart disease, giant cell arteritis, systemic vasculitis, Addison's disease, Graves' disease, primary biliary cirrhosis, alopecia areata, localized scleroderma, dermatitis herpetiformis, psoriasis, celiac disease, Crohn's disease, ulcerative colitis, amyotrophic sclerosis, multiple sclerosis, and asthma.

‡ Individuals with no history of the condition of interest comprise the referent group for each analysis. Hematologic autoimmune conditions (e.g., autoimmune hemolytic anemia, thrombocytopenia) were excluded from consideration because of difficulty distinguishing these diagnoses from manifestations of chemotherapy toxicity. HR (95% CI) adjusted for sex, race, residence, and follow-up time (time-dependent covariate) and stratified by calendar year. Age was used as the time scale.

§ Among males only.

Risk factors for second lung cancers among survivors of non-Hodgkin lymphoma

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ABSTRACT

Background

Non-Hodgkin lymphoma (NHL) survivors have increased risk of developing second lung cancer, but data on specific risk factors are lacking.

Methods

We assessed second lung cancer risk among 44,870 1-year survivors of first primary NHL diagnosed at ages 66-84 years during 1992-2009 from the Surveillance, Epidemiology, and End Results (SEER)-Medicare data linkage. Information on potential risk factors, including NHL treatments and immune-related medical conditions, was derived from Medicare claims.

Results

A total of 700 second lung cancers were diagnosed among NHL survivors. Lung cancer risks were significantly increased among chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) patients who received fludarabine-containing chemotherapy without rituximab (hazard ratio [HR]=2.28, 95% confidence interval [CI]=1.48-3.52). Significantly elevated lung cancer risks were also observed among diffuse large B-cell lymphoma (DLBCL) survivors who received cyclophosphamide-containing chemotherapy without rituximab (HR=2.13, 95%CI=1.01-4.47). After accounting for history of smoking, lower airway respiratory infections, particularly pneumonia, were associated with increased risks of second lung cancer before and after CLL/SLL (before CLL/SLL: HR=1.53, 95%CI=1.10-2.12; after CLL/SLL: HR=2.21, 95%CI=1.65-2.96), and after DLBCL (HR=1.90, 95%CI=1.26-2.87) and follicular lymphoma [FL](HR=1.98, 95%CI=1.31-3.00). Increased second lung cancer risks were observed for B-cell activating autoimmune conditions occurring after DLBCL (HR=1.63, 95%CI=1.00-2.66), with strongest associations for rheumatoid arthritis (HR=1.89, 95%CI=0.91-3.65), and for T-cell activating

autoimmune conditions diagnosed after other NHL subtypes (HR=1.56, 95%CI=1.07-2.27), with strongest associations for asthma (HR=2.00, 95%CI=1.34-2.97). In contrast, T-cell activating autoimmune conditions were significantly inversely associated after FL (HR=0.57, 95%CI=0.34-0.96), likely driven by skin autoimmune conditions, particularly localized scleroderma (HR=0.25, 95%CI=0.08-0.81).

Conclusion

Our findings support a role for specific chemotherapeutic agents and immune-related medical conditions in the development of lung cancer after NHL. Further research is needed to better understand the immune-related biological mechanisms that contribute to lung cancer.

INTRODUCTION

Prognosis following a diagnosis of non-Hodgkin lymphoma (NHL) – the 6th most common malignancy in the US – has improved substantially over the past four decades.[3] However, the ~700,000 NHL survivors in the US today face increased risks for developing another malignancy compared with individuals with no prior history of cancer.[1] Lung cancer is one of the most aggressive as well as one of the most commonly diagnosed second cancers among NHL survivors,[41] occurring 30-40% more frequently among survivors of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and follicular lymphoma (FL) compared with the general population.[40] Despite these documented excesses, however, data on specific risk factors are sparse.[21,30,31,34-38,40,41,89,101,135,166,167,169-172,211,212] A potential role for chemotherapy and radiotherapy has been hypothesized, as seen in survivors of Hodgkin lymphoma.[42,43] However previous studies have lacked detailed treatment data or sufficient numbers to assess the risks with specific chemotherapeutic agents. Immune dysfunction related to the development of NHL also has been hypothesized to play a role, an idea supported by elevated lung cancer risk in immunosuppressed populations such as persons with HIV/AIDS and solid organ transplant recipients.[9,10] Additionally, both NHL treatments and immune dysfunction could interact with cigarette smoking to contribute to lung cancer development.[152,213] Because previous studies have lacked the data necessary to investigate these possible associations, we used the Surveillance, Epidemiology, and End Results-Medicare (SEER-Medicare) data linkage to assess second lung cancer risks after NHL associated with NHL treatments, autoimmune disease, and selected infections among 44,870 first primary NHL survivors in the US elderly population.

METHODS

Study Population

Non-Hodgkin lymphoma survivors were identified through SEER-Medicare, which has been previously described elsewhere.[174] Briefly, SEER-Medicare is a data linkage between two large population-based data sources which provide specific demographic, clinical, cancer characteristics, and cause of death information for persons diagnosed with cancer. Since 1973, the National Cancer Institute funded the Surveillance, Epidemiology, and End Results (SEER) database, which provides cancer information on approximately 26% of the U.S. population.[177] Medicare provides federally funded health insurance for persons aged >65 years, accounting for approximately 45 million people. Together, SEER-Medicare matches 94% of SEER cancer cases over 65 years of age and includes all Medicare covered services for beneficiaries with fee-for-service coverage.

We used the SEER database to identify a cohort of individuals with first primary NHL according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) (see Table 1 footnote).[4,176] Patients included males and females diagnosed between 1992-2009 at ages 66-84 years who had continuous fee-for-service Medicare Parts A and B coverage at least 12 months before NHL diagnosis through the first 12 months following NHL diagnosis for ascertainment of treatment and medical condition exposures. NHL diagnoses and follow-up time at ages ≥85 years because of under-ascertainment of second malignancies at older ages.[39] We excluded patients with less than one year of survival time after NHL diagnosis (N=1,549) or Medicare claims for HIV (N=219) or solid organ transplantation (N=124). Second primary lung cancers that developed at least one year after first primary NHL were identified through SEER (ICD-O-3 primary site C34.0-34.9, excluding morphology codes 9050-9055, 9140, and 9590-9992; behavior code=3, sequence code=2).[177]

Ascertainment of NHL treatments and medical conditions

Information on NHL treatments (infused chemotherapy and radiotherapy) and medical history (autoimmune diseases and infections) was derived from Medicare claims from hospital

inpatient, physician, and outpatient services (see Supplementary Tables 1-3 for more details). For analyses of infused chemotherapy, we focused on the most commonly used specific chemotherapy agents (cyclophosphamide, rituximab, and fludarabine), grouping together other agents (e.g., other alkylating agents, epipodophyllotoxins) due to small numbers (N<10 exposed cases). Data on prescription drugs were not available during the study period; therefore, we were unable to capture information regarding oral chemotherapy, such as chlorambucil. Data on radiotherapy consisted of whether patients did or did not receive radiotherapy, with no detailed information available on radiotherapy fields or dose.

Occurrences of autoimmune diseases and infections were defined as having ≥1 Medicare claim at any time during follow-up, considering diagnoses occurring prior to NHL separately from those occurring after NHL diagnosis. Diagnoses of autoimmune conditions and infections occurring before the start of the study period in 1992 or prior to age 65 years (when individuals enrolled in Medicare) were not captured. Analyses considered individual conditions and infections with at least ten exposed lung cancer cases, diagnosed either before or after NHL. Due to the rarity of many diagnoses, we grouped them based on the tissue and organ systems involved; we also grouped autoimmune conditions according to whether they activate B- or T-cells (see Table 3 footnotes).[178-182] Hematologic autoimmune conditions (e.g., autoimmune hemolytic anemia, thrombocytopenia) were excluded from consideration because of difficulty distinguishing these diagnoses from manifestations of chemotherapy toxicity.

Although comprehensive data on tobacco use are not available in SEER-Medicare, medical claims for chronic obstructive pulmonary disease (COPD) and history of tobacco use before NHL diagnosis were combined as a proxy indicator variable to adjust for likely history of cigarette smoking.[11,214]

Statistical analysis

Follow-up began one year after first primary NHL diagnosis and continued until second lung cancer diagnosis, age 85 years, death, loss to follow-up, or end of study (December 31, 2009), whichever came first. Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) to assess the association between specific risk factors and risk of second lung cancer after NHL. Analyses used age as the time scale and were adjusted by sex, race (non-Hispanic Caucasian other), pre-NHL smoking status, and follow-up time (modeled as a time-dependent covariate: 1-1.9, 2-2.9, 3-3.9, 4-4.9, 5-6.9, and ≥7 years), with additional stratification by calendar year of NHL diagnosis to account for differing exposure periods.

Time-dependent covariates were used to indicate receipt of infused chemotherapy or radiotherapy during follow-up based on the timing of initiation of therapy. Risk of second lung cancer associated with NHL treatments was evaluated in multivariate models including both chemotherapy and radiotherapy. We used two approaches to assess risks related to infused chemotherapy. First (model A), we examined risks for patients who received any of the three main chemotherapy agents (cyclophosphamide, rituximab, fludarabine) or "other" infused chemotherapy, with separate indicator variables for each agent/group. Second (model B), we assessed risk according to the most frequently received *combinations* of these agents (see Table 2). For both analytic approaches, patients with no Medicare chemotherapy claims (i.e., no infused chemotherapy; includes patients who received oral agents exclusively) served as our referent group.

For investigation of lung cancer risks associated with autoimmune conditions and infections occurring before NHL diagnosis, we defined the follow-up period from age 65 or age at enrollment into Medicare to age of NHL diagnosis. Autoimmune conditions and infections diagnosed after NHL were evaluated as time-dependent covariates based on the timing of diagnoses of these conditions. Because treatment patterns differ by NHL subtype and because

second lung cancer risk has been shown to differ by NHL subtype, primary analyses were conducted separately for survivors of CLL/SLL, diffuse large B-cell lymphoma (DLBCL), FL, and other NHL subtypes. In secondary analyses of associated risk factors (Wald chi-square $P<0.05$ comparing models with and without the factor of interest), we restricted diagnoses to those occurring at least 2 years prior to lung cancer diagnosis in order to examine the possibility of reverse causality as an explanation for our findings. All analyses were conducted using SAS 9.3 (Cary, NC).

RESULTS

Study Population

We identified 44,870 one-year survivors of first primary NHL, including 13,950 individuals diagnosed with CLL/SLL, 10,311 with DLBCL, 7,437 with FL, 3,516 with marginal zone lymphoma, and 9,656 with other NHL subtypes (Table 1). The vast majority of survivors (91%) were white, and the median age at diagnosis was 74 years. Among the major NHL subtypes, more CLL/SLL survivors were male (54%), whereas more DLBCL and FL survivors were female (54% and 57% respectively). Approximately 24% of NHL survivors had claims for pre-NHL smoking status. A total of 700 second lung cancers were diagnosed during 247,883 total person-years of follow-up (mean person-years at risk=5.5; median interval from NHL to lung cancer=3.7 years). Lung cancer risks were higher among males, non-Hispanic Caucasians, and individuals with a history of smoking, and for survivors of CLL/SLL and FL compared with DLBCL (Supplementary Table 4). Lung cancers occurring after CLL/SLL were most frequently adenocarcinomas (34%), followed by squamous cell carcinomas (22%), and other non-small cell lung cancers (18%). A similar histologic distribution was observed for lung cancers occurring after FL, whereas after DLBCL, adenocarcinomas and squamous cell carcinomas were equally common (32% and 30%, respectively).

Non-Hodgkin Lymphoma Treatment

Of the 5,051 (36.3%) CLL/SLL survivors who received infused chemotherapy during follow-up, 2,712 (53.7%) initiated chemotherapy within the first 12 months after CLL/SLL diagnosis, and 2,339 (46.3%) initiated chemotherapy >12 months after CLL/SLL diagnosis. Rituximab (26.8%), fludarabine (21.2%), and cyclophosphamide (17.2%) were the most commonly received infused chemotherapy agents (Table 2). Lung cancer risk was non-significantly elevated among CLL/SLL survivors who received any fludarabine-containing chemotherapy (HR=1.41, 95% CI 0.98-2.02), whereas we observed an inverse relationship for cyclophosphamide-containing chemotherapy (HR=0.60, 95% CI 0.38-0.96). Further analyses accounting for combinations of infused chemotherapeutic agents showed significantly elevated lung cancer risks among CLL/SLL survivors who received fludarabine-containing chemotherapy without rituximab (N=29, HR=2.28, 95% CI 1.48-3.52). Lung cancer risk also was non-significantly elevated among the few (1,025, 7.3%) CLL/SLL survivors who received radiotherapy (HR=1.47, 95% CI 0.90-2.39).

A total of 8,842 (85.8%) DLBCL survivors received infused chemotherapy during follow-up, of whom the vast majority (8,669, 98.0%), began treatment within 12 months of diagnosis. Rituximab (63.5%) and cyclophosphamide (81.0%) were the most commonly received agents, whereas fewer patients received fludarabine (2.3%) or other agents (10.9%) (Table 2). Initial analyses did not show any increased risks of second lung cancer after treatment for DLBCL with any rituximab-, fludarabine-, or cyclophosphamide-containing chemotherapy. However, further analyses showed significantly increased lung cancer risks among DLBCL survivors who received cyclophosphamide-containing chemotherapy without rituximab (HR=2.13, 95% CI 1.01-4.47). Similar patterns of risk were observed among the 6,884 (52.3%) survivors of other NHL subtypes who received infused chemotherapy (cyclophosphamide-containing chemotherapy without rituximab: HR=1.47, 95% CI 0.98-2.21), whereas infused chemotherapy for FL was not

significantly associated with lung cancer risk in any analyses. Radiotherapy also was not related to lung cancer risk in survivors of DLBCL, FL, or other NHL subtypes.

Infections

Among CLL/SLL survivors, several different types of infections heightened lung cancer risk (Table 3). Lower airway infections occurred the most commonly and were associated with increased lung cancer risk (before CLL/SLL: HR=1.37, 95% CI 1.00-1.88; after CLL/SLL: HR=1.67, 95% CI 1.18-2.35). The association with lower airway infections was primarily driven by diagnoses of pneumonia and, to a lesser extent, acute bronchitis, whereas influenza was not associated with lung cancer risk. Cellulitis and cystitis/polynephritis urinary tract infections occurring after CLL/SLL also increased lung cancer risk (HR=2.05, 95% CI 1.43-2.94; HR=1.49, 95% CI 1.09-2.04, respectively). In contrast, prostatitis diagnosed before CLL/SLL was inversely related to lung cancer risk (HR=0.46, 95% CI 0.28-0.77).

Among DLBCL survivors, a different risk pattern between infections and lung cancer was observed. Lower respiratory infections were associated with increased risk, but the finding was limited to diagnoses occurring after DLBCL (HR=2.28, 95% CI 1.37-3.77). In contrast, inverse associations with lung cancer risk were observed for both upper respiratory infections (before DLBCL: HR=0.64, 95% CI 0.43-0.95; after DLBCL: HR=0.38, 95% CI 0.19-0.75) and cystitis/pyelonephritis urinary tract infections (before DLBCL: HR=0.62, 95% CI 0.40-0.96).

Infections did not play a major role in the development of lung cancer among survivors of FL or other NHLs. However, we did observe increased risks of second lung cancer associated with pneumonia diagnosed after FL (HR=1.98, 95% CI 1.31-3.00) and herpes zoster diagnosed after other NHL (HR=1.55, 95% CI 1.01-2.38). In contrast, an inverse relationship was observed between lung cancer risk and pharyngitis diagnosed before FL (HR=0.50, 95% CI 0.26-0.96).

Autoimmune Conditions

Autoimmune conditions were frequently diagnosed in our cohort of NHL survivors, but relatively few associations were observed between autoimmune condition diagnoses and lung cancer risk (Table 4). B-cell activating autoimmune conditions as a group occurring after DLBCL were associated with increased lung cancer risk (HR=1.63, 95% CI 1.00-2.66), but no significant associations were observed for any individual conditions. In contrast, T-cell activating autoimmune conditions as a group were significantly inversely associated after FL (HR=0.57, 95% CI 0.34-0.96), with the strongest association observed for skin autoimmune conditions (HR=0.35, 95% CI 0.14-0.87). Among patients with other NHL subtypes, T-cell activating autoimmune conditions occurring after NHL diagnosis were associated with increased risk of second lung cancer (HR=1.56, 95% CI 1.07-2.27), with the strongest association observed for asthma (HR=2.00, 95% CI 1.34-2.97), whereas gastrointestinal autoimmune conditions, particularly pernicious anemia, occurring before NHL were inversely associated with lung cancer risk (HR=0.53, 95% CI 0.28-1.00).

Risk estimates for the associations described above were materially unchanged in multivariate analyses that included all chemotherapeutic agents as well as autoimmune conditions and infections with $P<0.05$ in the same model. Additionally, the associations remained significant even when restricting diagnoses to those occurring 2+ years before lung cancer diagnoses.

DISCUSSION

In this large, population-based study of NHL survivors, we show for the first time that specific NHL treatments as well as immune-related medical conditions heighten risk of developing

second lung cancer. Increased treatment-related lung cancer risks were observed among CLL/SLL survivors who received fludarabine-containing chemotherapy, as well as among DLBCL and other NHL survivors treated with cyclophosphamide-containing chemotherapy. Lower airway infections, particularly pneumonia, also increased lung cancer risk after all NHL subtypes. Several other infections and autoimmune diseases also were associated with lung cancer risk. Together, these findings suggest that immune dysfunction contributes to the excess risk of lung cancer after NHL.

Our novel finding of chemotherapy-related lung cancer risks after NHL expand our understanding of the adverse pulmonary effects of systemic therapy. We observed more than two-fold increased risk of lung cancer among CLL/SLL survivors who received fludarabine, a purine analog. Previous studies have reported increased second cancer risks, particularly treatment-related acute myeloid leukemia (t-AML) and solid cancers, among patients treated with fludarabine,[45,167,170,188-193] but no previous study has compared lung risks in patients treated with and without fludarabine. We also observed two-fold increased risk of lung cancer among survivors of DLBCL and other NHL subtypes who received cyclophosphamide, an alkylating agent. These risks are consistent with previous studies among Hodgkin lymphoma survivors treated with alkylating agent-containing chemotherapy.[43,94,215-217] Although fludarabine and cyclophosphamide belong to different classes of systemic therapy, both are associated with direct DNA damaging effects as well as immunosuppression,[218,219] which both may plausibly contribute to lung carcinogenesis. Unlike other studies of cancer survivors,[52] we did not observe significantly increased risk of lung cancer after radiotherapy for NHL. However, our analysis was limited by lack of information on the radiotherapy field(s) and dose each patient received. Further research with more detailed data is needed to better understand the relationships and biologic mechanisms underlying treatment-related lung cancer.

We also observed associations between immune-related medical conditions and risk of subsequent lung cancer among NHL survivors. Most notably, lower airway respiratory infections, particularly pneumonia, were associated with increased lung cancer risk regardless of the type of first primary NHL, and risks remained elevated when we restricted analyses to diagnoses occurring at least 2 years prior to lung cancer. Previous studies have reported increased lung cancer risks following pneumonia,[220-228] with risks remaining for latencies of 1-10 years following infection.[222,225,228] The lungs also have been noted to be a site perturbed by chronic or repeated inflammation, which may be caused by infections such as pneumonia.[145,226] Serious respiratory infections can repeatedly initiate an immune response in which tissue repair is associated with cellular proliferation, leading to errors in chromosomal replication and production of further DNA damage.[145,226] Additionally, tissue repair involving angiogenesis can create an environment in the lungs where inflammation can initiate or promote lung cancer.[145,226] Our study findings for pneumonia and to a lesser extent acute bronchitis, support the importance of respiratory infections as a potential factor in developing second lung cancer after NHL.

In contrast, we observed inverse relationships for lung cancer and various upper respiratory infections, particularly sinusitis diagnosed before and after DLBCL, pharyngitis diagnosed before FL, and otitis media diagnosed before other NHLs. Antibiotic treatments for these conditions may eliminate potential infectious agents that have been previously observed to increase lung cancer risk.[226] Overall it is not clear why these respiratory infections show inverse associations with subsequent lung cancer risk, therefore, additional research is needed to identify possible mechanisms to explain these different patterns of risk.

The importance of localized inflammation in lung cancer risk after NHL is further supported by associations for certain autoimmune conditions, although the patterns of association were not consistent among NHL subtypes. We observed increased risk of second lung cancer among

patients diagnosed with B-cell activating conditions after DLBCL, with the highest risks observed for rheumatoid arthritis. Rheumatoid arthritis, a progressive autoimmune disease characterized by chronic inflammation, frequently affects the lungs and pleura and has been shown to increase lung cancer risk in previous studies.[229-233] We also observed that T-cell activating conditions were associated with increased risk of lung cancer after other NHLs, with the highest risks observed for asthma, which is characterized by chronic inflammation of the airways and also has been previously implicated to increase lung cancer risks.[234,235] Other associations between various autoimmune conditions and infections with subsequent lung cancer were also observed; however, these findings may be due to chance. We observed increased risk of lung cancer among survivors of other NHL diagnosed with herpes zoster, and skin and urinary tract infections diagnosed after CLL/SLL. Lung cancer risk associated with herpes zoster is plausible since T-cell immunity protects against the infection, and immunocompromised patients with T-cell dysfunction are at increased risk for herpes zoster and other severe disease, pointing to a possible indirect effect of the infection on lung cancer risk.[236] CLL/SLL patients in particular tend to have severe and chronic immune dysfunction which is characterized by poor T-cell function. The broad immunosuppressive effects of fludarabine coupled with the inherent predisposition to malignancy among CLL/SLL patients may increase susceptibility to increased numbers of infections.[143,186] The inverse relationships with lung cancer observed for prostatitis before CLL/SLL, cystitis/pyelonephritis urinary tract infections before DLBCL, skin autoimmune conditions diagnosed after FL and gastrointestinal autoimmune conditions diagnosed before other NHLs have not been reported previously, and the mechanisms underlying these potential associations are unknown.

The main limitation of our study was lack of dose data for NHL treatments and inability to capture information on oral chemotherapy agents during follow-up. In particular, we could not ascertain receipt of chlorambucil, one of the main treatments for CLL/SLL in the early years of our study period.[200] However, our fludarabine-related risk estimates are likely to be

conservative since patients who received chlorambucil were included in our referent group. Our study may have had misclassified exposures due to missing information on infections and autoimmune diseases diagnosed in patients prior to their entry into Medicare. Additionally, information on mild infections for which the patients did not receive medical care would not be captured in Medicare. We were only able to assess potential risk factors that generated medical billing claims; therefore, we could not assess key lung cancer risk factors such as smoking. However, we were able to use a proxy for smoking status since information was available on COPD and history of tobacco use before NHL diagnosis, and these variables combined have been shown to be a valid proxy for smoking status.[11,214] In general, second cancers may be underreported due to survivors leaving the SEER catchment areas, but this underreporting is unlikely to be related to the risk factors of interest in our study and thus should not affect the risk estimates.[36]

This study was one of the first analytic studies to investigate a range of risk factors to explain the excess occurrence of lung cancer among NHL survivors. Our study provides evidence that specific chemotherapeutic agents and immune-related medical conditions are related to second lung cancer risk after first primary NHL. Our findings also provide valuable information regarding risks that can be considered when evaluating risks and benefits of lung cancer screening. Further research is needed to better understand the biological mechanisms underlying these associations.

Table 1. Selected characteristics of 44,870 1-year survivors of first primary NHL, overall and by NHL subtype, diagnosed aged 66-84 years, 16 SEER registries, 1992-2009

	Total NHL		First primary NHL subtype									
			CLL/SLL		DLBCL		FL		MZL		Other	
	N	%	N	%	N	%	N	%	N	%	N	%
Total number of 1-year survivors	44,870		13,950		10,311		7,437		3,516		9,656	
Age at NHL diagnosis (years)												
65-69	9,673	21.6	2,901	20.8	2,169	21.0	1,828	24.6	767	21.8	2,008	20.8
70-74	13,120	29.2	3,982	28.5	3,038	29.5	2,243	30.2	988	28.1	2,869	29.7
75-79	12,754	28.4	4,030	28.9	2,934	28.5	1,985	26.7	958	27.3	2,847	29.5
80-84	9,323	20.8	3,037	21.8	2,170	21.1	1,381	18.6	803	22.8	1,932	20.0
Sex												
Male	22,097	49.3	7,590	54.4	4,725	45.8	3,229	43.4	1,439	40.9	5,114	53.0
Female	22,773	50.8	6,360	45.6	5,586	54.2	4,208	56.6	2,077	59.1	4,542	47.0
Race												
White	40,752	90.8	12,841	92.1	9,222	89.4	6,888	92.6	3,090	87.9	8,711	90.2
Other/unknown	4,118	9.2	1,109	7.9	1,089	10.6	549	7.4	426	12.1	945	9.8
Year of NHL diagnosis												
1992-1997 *	8,127	18.1	2,755	19.8	1,798	17.4	1,345	18.1	233	6.6	1,996	20.7
1998-2003	15,978	35.6	5,002	35.9	3,680	35.7	2,618	35.2	1,317	37.5	3,361	34.8
2004-2009	20,765	46.3	6,193	44.4	4,833	46.9	3,474	46.7	1,966	55.9	4,299	44.5
History of smoking												
No	34,220	76.3	10,652	76.4	7,996	77.6	5,749	77.3	2,553	72.6	7,270	75.3
Yes	10,650	23.7	3,298	23.6	2,315	22.5	1,688	22.7	963	27.4	2,386	24.7
Median age at NHL (years)	74.0		75.0		74.0		74.0		75.0		74.0	
Mean person-years at risk	5.5		5.6		5.4		5.8		5.6		5.3	
Total number of second lung cancers	700		259		116		127		61		137	
Median interval from NHL to lung cancer (years)	3.7		3.4		3.9		3.8		3.8		3.8	
Lung cancer histology												
Small cell	63	9.0	24	9.3	10	8.6	11	8.7	<10	~	10	7.3
Non-small cell	536		193		96		99		48		100	
Squamous and transitional cell	160	22.9	58	22.4	35	30.2	30	23.6	12	19.7	25	18.2
Adenocarcinoma	244	34.9	88	34.0	37	31.9	46	36.2	21	34.4	52	38.0
Other non-small cell	132	18.9	47	18.1	24	20.7	23	18.1	15	24.6	23	16.8
Carcinoma, not otherwise specified	101	14.4	42	16.2	10	8.6	17	13.4	<10	~	27	19.7

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); International Classification of Diseases for Oncology, 3rd edition (ICD-O-3); marginal zone lymphoma (MZL); non-Hodgkin lymphoma (NHL); Surveillance, Epidemiology and End Results (SEER).

~ Counts and percentages are not reported for less than 10 lung cancer cases to protect patient confidentiality.

* First primary NHL subtype defined by ICD-O-3 as DLBCL (9678-9680, 9684 [B-cell]), FL (9690-9691, 9695, 9698), CLL/SLL (9670, 9823), MZL (9689, 9699) and other NHL (9590-9596, 9671, 9673, 9675, 9684 [non B-cell], 9687, 9700-9702, 9705, 9708-9709, 9714-9719, 9727-9729, 9827 [primary site=(C.420-421, 424]).

† 1992-1997 includes 13 SEER registries, whereas 1998-2003 and 2004-2009 include 16 SEER registries.

§ Lung histology defined by ICD-O-3 as small cell (8002, 8041-8045), squamous and transitional cell (8051-8052, 8070-8076, 8078, 8083-8084, 8090, 8094, 8120, 8123), adenocarcinoma (8015, 8059, 8140-8141, 8143-8145, 8147, 8190, 8201, 8211, 8250-8255, 8260, 8290, 8310, 8320, 8323, 8333, 8401, 8440, 8470-8471, 8480-8481, 8490, 8503, 8507, 8550, 8570-8572, 8574, 8576), other non-small cell (8003-8004, 8012-8014, 8021-8022, 8030, 8031-8034, 8035, 8046, 8082, 8200, 8240-8241, 8243-8246, 8249, 8430, 8525, 8560, 8562, 8575), carcinoma, not otherwise specified (8000-8001, 8010-8011, 8020, 8230).

Table 2. Risk of lung cancer after first primary NHL, by subtype, in relation to NHL treatments

	Total NHL		Lung cancer cases			
NHL treatment *	**N**	**%**	**N**	**%**	**HR †**	**95% CI**
Patients diagnosed with first primary CLL/SLL						
Infused chemotherapy						
None recorded	8,899	63.8	171	66.0	1.00	Referent
Model A ‡						
Any rituximab	3,744	26.8	52	20.1	1.28	0.86-1.91
Any fludarabine	2,958	21.2	55	21.2	1.41	0.98-2.02
Any cyclophosphamide	2,402	17.2	29	11.2	0.60	0.38-0.96
Any other alkylating agents	398	2.9	<10	~	1.48	0.46-4.75
Model B						
Fludarabine without rituximab	917	6.6	29	11.2	2.28	1.48-3.52
Rituximab without fludarabine	1,703	12.2	26	10.0	1.27	0.81-1.98
Fludarabine + rituximab	2,041	14.6	26	10.0	0.91	0.60-1.39
Other alkylating agents	390	2.8	<10	~	1.22	0.53-2.77
Radiotherapy						
No	12,925	92.7	238	91.9	1.00	Referent
Yes	1,025	7.3	21	8.1	1.47	0.90-2.39
Patients diagnosed with first primary DLBCL						
Infused chemotherapy						
None recorded	1,469	14.3	<10	~	1.00	Referent
Model A ‡						
Any rituximab	6,552	63.5	63	54.3	1.43	0.79-2.58
Any fludarabine	234	2.3	<10	~	0	0
Any cyclophosphamide	8,350	81.0	104	90.0	1.57	0.84-2.97
Any other alkylating agents	1,128	10.9	10	8.6	1.00	0.48-2.07
Model B §						
Cyclophosphamide without rituximab	2,259	21.9	44	37.9	2.13	1.01-4.47
Rituximab without cyclophosphamide	461	4.5	<10	~	1.60	0.42-6.10
Cyclophosphamide + rituximab	6,091	59.1	60	51.7	1.82	0.87-3.80
Other alkylating agents	31	0.3	<10	~	0	0
Radiotherapy						
No	6,165	59.8	79	68.1	1.00	Referent
Yes	4,146	40.2	37	31.9	0.70	0.47-1.04
Patients diagnosed with first primary FL						
Infused chemotherapy						
None recorded	2,283	30.7	49	38.6	1.00	Referent
Model A ‡						
Any rituximab	4,206	56.6	56	44.1	0.90	0.56-1.44
Any fludarabine	945	12.7	13	10.2	1.23	0.66-2.27
Any cyclophosphamide	3,845	51.7	59	46.5	0.98	0.66-1.46
Any other alkylating agents	470	6.3	<10	~	0.33	0.05-2.39
Model B §						
Cyclophosphamide without rituximab	850	11.4	20	15.8	1.15	0.67-2.00
Rituximab without cyclophosphamide	1,211	16.3	17	13.4	0.96	0.54-1.74
Cyclophosphamide + rituximab	2,995	40.3	39	30.7	0.75	0.48-1.17
Other alkylating agents	98	1.3	<10	~	1.85	0.44-7.73
Radiotherapy						
No	5,125	68.9	84	66.1	1.00	Referent
Yes	2,312	31.1	43	33.9	1.19	0.82-1.74

Table 2 continued. Risk of lung cancer after first primary NHL, by subtype, in relation to NHL treatments

	Total NHL		Lung cancer cases			
NHL treatment *	**N**	**%**	**N**	**%**	**HR †**	**95% CI**
Patients diagnosed with other first primary NHL						
Infused chemotherapy						
None recorded	6,288	47.7	107	54.0	1.00	Referent
Model A ‡						
Any rituximab	4,968	37.7	51	25.8	0.88	0.59-1.31
Any fludarabine	1,324	10.1	20	10.1	1.46	0.89-2.41
Any cyclophosphamide	4,591	34.9	62	31.3	1.02	0.72-1.43
Any other alkylating agents	765	5.8	<10	~	0.73	0.27-2.01
Model B §						
Cyclophosphamide without rituximab	1,672	12.7	36	18.2	1.47	0.98-2.21
Rituximab without cyclophosphamide	2,049	15.6	25	12.6	1.19	0.76-1.87
Cyclophosphamide + rituximab	2,919	22.2	26	13.1	0.68	0.44-1.05
Other alkylating agents	244	1.9	<10	~	1.93	0.70-5.27
Radiotherapy						
No	9,761	74.1	148	74.8	1.00	Referent
Yes	3,411	25.9	50	25.2	1.03	0.74-1.42

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); confidence interval (CI); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); International Classification of Diseases for Oncology, 3rd edition (ICD-O-3); marginal zone lymphoma (MZL); hazard ratio (HR); non-Hodgkin lymphoma (NHL).

~ Counts and percentages are not reported for less than 10 lung cancer cases to protect patient confidentiality.

* Treatments received by fewer than 10 lung cancer cases are not reported here but are included in Supplementary Table 1 (e.g., other alkylating agents, epipodophyllotoxins, and hematopoietic stem cell transplantation).

† HR (95% CI) adjusted for sex, race, history of smoking, and follow-up time (time-dependent covariate) and stratified by calendar year. Age used as time scale. Time-dependent covariates used to indicate receipt of any radiotherapy or chemotherapy during follow-up based on timing of initiation of therapy. The HRs for chemotherapy in Models A and B were additionally adjusted for receipt of other alkylating agents. The HR for radiotherapy was additionally adjusted for chemotherapy using Model B.

‡ Percentages do not add up to 100% because groups are not mutually exclusive.

§ Percentages do not add up to 100% because a small number of patients received other agents.

Table 3. Risk of lung cancer after first primary NHL, by subtype, in relation to infections

	Prior to NHL diagnosis						After NHL diagnosis *					
	Total NHL		Lung cancer cases				Total NHL		Lung cancer cases			
Autoimmune conditions †	**N**	**%**	**N**	**%**	**HR ‡**	**95% CI**	**N**	**%**	**N**	**%**	**HR ‡**	**95% CI**
Patients diagnosed with first primary CLL/SLL												
Infections, by organ system												
Respiratory - upper airway	5,847	41.9	100	38.6	0.89	0.68-1.18	5,850	41.9	96	37.1	0.91	0.64-1.31
Otitis media	1,621	11.6	21	8.1	0.72	0.46-1.13	1,514	10.9	23	8.9	0.95	0.57-1.59
Pharyngitis	2,141	15.4	31	12.0	0.81	0.55-1.19	2,143	15.4	41	15.8	1.35	0.93-1.98
Sinusitis	4,074	29.2	76	29.3	1.05	0.79-1.39	4,238	30.4	71	27.4	0.93	0.64-1.36
Respiratory - lower airway	6,122	43.9	121	46.7	1.37	1.00-1.88	8,347	59.8	165	63.7	1.67	1.18-2.35
Acute bronchitis	4,526	32.4	87	33.6	1.15	0.86-1.54	5,081	36.4	102	39.4	1.42	1.02-1.98
Influenza	783	5.6	13	5.0	0.79	0.45-1.39	821	5.9	10	3.9	0.51	0.23-1.15
Pneumonia	2,872	20.6	63	24.3	1.53	1.10-2.12	6,414	46.0	125	48.3	2.21	1.65-2.96
Skin	2,125	15.2	46	17.8	1.43	1.02-2.00	3,490	25.0	66	25.5	1.55	1.12-2.15
Cellulitis	1,191	8.5	23	8.9	1.23	0.79-1.90	1,948	14.0	43	16.6	2.05	1.43-2.94
Herpes zoster	1,079	7.7	25	9.7	1.32	0.87-2.01	1,958	14	29	11.2	1.01	0.66-1.55
Urinary tract	6,227	44.6	91	35.1	0.81	0.61-1.09	7,942	56.9	126	48.7	1.38	1.00-1.90
Cystitis/pyelonephritis UTI	5,630	40.4	81	31.3	0.87	0.64-1.17	7,599	54.5	119	46.0	1.49	1.09-2.04
Prostatitis §	1,554	20.5	17	10.2	0.46	0.28-0.77	1,199	15.8	25	15.0	1.21	0.73-2.01
Gastrohepatic	2,084	14.9	33	12.7	0.84	0.58-1.22	2,594	18.6	40	15.4	1.07	0.72-1.58
Gastroenteritis	2,020	14.5	32	12.4	0.84	0.58-1.23	2,445	17.5	37	14.3	1.03	0.69-1.55
Patients diagnosed with first primary DLBCL												
Infections, by organ system												
Respiratory - upper airway	4,340	42.1	44	37.9	0.64	0.43-0.95	3,884	37.7	34	29.3	0.38	0.19-0.75
Otitis media	1,124	10.9	14	12.1	0.96	0.54-1.69	913	8.9	10	8.6	0.37	0.12-1.16
Pharyngitis	1,621	15.7	15	12.9	0.74	0.42-1.28	1,455	14.1	16	13.8	0.72	0.36-1.45
Sinusitis	3,005	29.1	35	30.2	0.87	0.58-1.32	2,576	25.0	17	14.7	0.41	0.18-0.89
Respiratory - lower airway	4,242	41.1	49	42.2	1.45	0.89-2.38	5,681	55.1	77	66.4	2.28	1.37-3.77
Acute bronchitis	3,212	31.2	39	33.6	1.18	0.76-1.82	2,975	28.9	48	41.4	1.66	1.00-2.73
Pneumonia	1,788	17.3	19	16.4	1.06	0.62-1.83	4,326	42.0	52	44.8	1.90	1.26-2.87
Skin	1,426	13.8	13	11.2	0.81	0.45-1.46	2,376	23.0	19	16.4	0.61	0.34-1.10
Cellulitis	785	7.6	<10	~	0.45	0.17-1.23	1,253	12.2	10	8.6	0.77	0.37-1.59
Herpes zoster	727	7.1	10	8.6	1.46	0.75-2.83	1,370	13.3	12	10.3	0.85	0.45-1.61
Urinary tract	4,648	45.1	39	33.6	0.57	0.37-0.88	5,902	57.2	50	43.1	0.82	0.51-1.33
Cystitis/pyelonephritis UTI	4,230	41.0	36	31.0	0.62	0.40-0.96	5,687	55.2	47	40.5	0.78	0.48-1.27
Prostatitis §	1,003	21.2	10	16.7	0.72	0.36-1.45	680	14.4	<10	~	0.76	0.30-1.97
Gastrohepatic	1,577	15.3	17	14.7	0.91	0.53-1.55	1,990	19.3	17	14.7	0.75	0.40-1.41
Gastroenteritis	1,512	14.7	17	14.7	0.95	0.55-1.61	1,855	18.0	17	14.7	0.80	0.42-1.51

Table 3 continued. Risk of lung cancer after first primary NHL, by subtype, in relation to infections

	Prior to NHL diagnosis						After NHL diagnosis *					
	Total NHL		Lung cancer cases				Total NHL		Lung cancer cases			
Autoimmune conditions †	**N**	**%**	**N**	**%**	**HR ‡**	**95% CI**	**N**	**%**	**N**	**%**	**HR ‡**	**95% CI**
Patients diagnosed with first primary FL												
Infections, by organ system												
Respiratory - upper airway	3,108	41.8	50	39.4	0.98	0.66-1.46	2,950	39.7	44	34.7	1.04	0.64-1.71
Otitis media	801	10.8	13	10.2	1.02	0.57-1.83	703	9.5	<10	~	0.60	0.22-1.63
Pharyngitis	1,128	15.2	10	7.9	0.50	0.26-0.96	1,070	14.4	14	11.0	0.82	0.46-1.49
Sinusitis	2,212	29.7	36	28.4	0.98	0.65-1.48	2,060	27.7	31	24.4	0.89	0.52-1.52
Respiratory - lower airway	2,992	40.2	49	38.6	1.00	0.65-1.55	3,919	52.7	70	55.1	1.25	0.78-1.99
Acute bronchitis	2,248	30.2	35	27.6	0.89	0.58-1.36	2,344	31.5	34	26.8	0.95	0.57-1.59
Pneumonia	1,245	16.7	23	18.1	1.21	0.73-2.01	2,771	37.3	54	42.5	1.98	1.31-3.00
Skin	996	13.4	20	15.8	1.38	0.84-2.28	1,609	21.6	23	18.1	0.97	0.57-1.65
Cellulitis	549	7.4	13	10.2	1.60	0.89-2.88	813	10.9	10	7.9	0.80	0.38-1.66
Herpes zoster	499	6.7	10	7.9	1.41	0.73-2.74	954	12.8	15	11.8	1.23	0.68-2.21
Urinary tract	3,347	45.0	45	35.4	0.77	0.50-1.16	4,213	56.7	56	44.1	1.04	0.65-1.65
Cystitis/pyelonephritis UTI	3,036	40.8	39	30.7	0.76	0.49-1.17	4,031	54.2	53	41.7	1.15	0.73-1.81
Prostatitis §	724	22.4	14	23.7	1.17	0.62-2.21	543	16.8	<10	~	0.52	0.16-1.74
Gastrohepatic	1,067	14.4	12	9.5	0.61	0.33-1.12	1,377	18.5	23	18.1	1.08	0.63-1.83
Gastroenteritis	1,038	14.0	11	8.7	0.58	0.31-1.09	1,312	17.6	23	18.1	1.19	0.71-1.99
Patients diagnosed with other first primary NHL												
Infections, by organ system												
Respiratory - upper airway	5,568	42.3	80	40.4	0.82	0.60-1.13	5,110	38.8	78	39.4	1.02	0.68-1.54
Laryngitis	629	4.8	<10	~	0.75	0.37-1.54	597	4.5	11	5.6	1.44	0.76-2.74
Otitis media	1,475	11.2	16	8.1	0.60	0.36-1.01	1,241	9.4	19	9.6	1.03	0.59-1.79
Pharyngitis	2,051	15.6	33	16.7	0.93	0.64-1.37	1,774	13.5	22	11.1	0.76	0.44-1.33
Sinusitis	3,892	29.6	59	29.8	0.95	0.68-1.31	3,484	26.5	55	27.8	1.12	0.73-1.71
Respiratory - lower airway	5,813	44.1	79	39.9	0.85	0.60-1.21	7,111	54.0	104	52.5	1.40	0.97-2.04
Acute bronchitis	4,359	33.1	59	29.8	0.81	0.58-1.13	4,039	30.7	64	32.3	1.16	0.78-1.71
Influenza	777	5.9	11	5.6	0.75	0.40-1.39	662	5.0	10	5.1	1.16	0.59-2.29
Pneumonia	2,634	20.0	33	16.7	0.74	0.49-1.11	5,286	40.1	69	34.9	1.35	0.96-1.89
Skin	2,079	15.8	26	13.1	0.90	0.59-1.38	3,040	23.1	44	22.2	1.30	0.89-1.90
Cellulitis	1,131	8.6	12	6.1	0.69	0.38-1.24	1,696	12.9	20	10.1	0.98	0.58-1.64
Herpes zoster	1,069	8.1	16	8.1	1.18	0.70-1.99	1,656	12.6	27	13.6	1.55	1.01-2.38
Urinary tract	6,167	46.8	72	36.4	0.77	0.55-1.07	7,347	55.8	95	48.0	1.10	0.76-1.60
Cystitis/pyelonephritis UTI	5,571	42.3	68	34.3	0.89	0.64-1.25	7,041	53.5	89	45.0	1.19	0.82-1.72
Prostatitis §	1,441	22.0	16	14.8	0.60	0.35-1.04	931	14.2	13	12.0	0.97	0.48-1.96
Gastrohepatic	2,236	17.0	32	16.2	0.86	0.58-1.28	2,559	19.4	34	17.2	0.88	0.56-1.39
Gastroenteritis	2,139	16.2	30	15.2	0.83	0.55-1.24	2,389	18.1	31	15.7	0.81	0.51-1.29

Table 3 continued. Risk of lung cancer after first primary NHL, by subtype, in relation to infections

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); confidence interval (CI); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); hazard ratio (HR); non-Hodgkin lymphoma (NHL); urinary tract infections (UTI).

~ Counts and percentages are not reported when less than 10 lung cancer cases to protect patient confidentiality.

* New claims occurring after NHL but prior to second cancer, death, end of study, or loss to follow-up, with no claims prior to NHL.

‡ Individuals with no history of the condition of interest comprise the referent group for each analysis. HR (95% CI) adjusted for sex, race, history of smoking, and follow-up time (time-dependent covariate) and stratified by calendar year. Age used as time scale.

§ Among males only.

Table 4. Risk of lung cancer after first primary NHL, by subtype, in relation to autoimmune conditions

	Prior to NHL diagnosis						After NHL diagnosis *					
	Total NHL		Lung cancer cases				Total NHL		Lung cancer cases			
Autoimmune conditions †	**N**	**%**	**N**	**%**	**HR ‡**	**95% CI**	**N**	**%**	**N**	**%**	**HR ‡**	**95% CI**
Patients diagnosed with first primary CLL/SLL												
B-cell activating conditions	2,263	16.2	37	14.3	0.99	0.69-1.42	3,637	26.1	53	20.5	1.20	0.82-1.74
T-cell activating conditions	5,488	39.3	96	37.1	0.93	0.69-1.24	6,749	48.4	111	42.9	1.02	0.73-1.44
Autoimmune conditions, by organ system												
Systemic/connective tissue	1,687	12.1	29	11.2	0.99	0.67-1.47	1,912	13.7	30	11.6	1.09	0.68-1.76
Rheumatoid arthritis	981	7.0	16	6.2	0.93	0.56-1.55	1,037	7.4	19	7.3	1.37	0.78-2.42
Cardiovascular	1,367	9.8	22	8.5	0.93	0.60-1.45	2,370	17.0	31	12.0	0.87	0.54-1.40
Chronic rheumatic heart disease	1,219	8.7	22	8.5	1.07	0.68-1.67	2,187	15.7	28	10.8	0.83	0.50-1.39
Endocrine	931	6.7	16	6.2	1.07	0.64-1.78	1,213	8.7	15	5.8	0.94	0.53-1.65
Graves disease	783	5.6	14	5.4	1.10	0.64-1.91	872	6.3	13	5.0	1.00	0.54-1.85
Skin	2,222	15.9	37	14.3	0.94	0.66-1.34	2,402	17.2	39	15.1	1.00	0.66-1.52
Localized scleroderma	1,809	13.0	31	12.0	0.99	0.68-1.45	1,924	13.8	27	10.4	0.85	0.53-1.37
Psoriasis	445	3.2	<10	~	0.78	0.36-1.65	431	3.1	12	4.6	1.83	0.90-3.73
Gastrointestinal	1,435	10.3	25	9.7	1.12	0.73-1.71	2,926	21.0	42	16.2	1.20	0.81-1.77
Pernicious anemia	1,119	8.0	19	7.3	1.18	0.73-1.90	2,548	18.3	38	14.7	1.27	0.85-1.90
Nervous system	110	0.8	<10	~	2.19	0.81-5.95	180	1.3	<10	~	0	0
Asthma	1,919	13.8	35	13.5	0.81	0.55-1.19	2,484	17.8	49	18.9	1.27	0.85-1.90
Patients diagnosed with first primary DLBCL												
B-cell activating conditions	2,003	19.4	16	13.8	0.80	0.46-1.39	2,612	25.3	31	26.7	1.63	1.00-2.66
T-cell activating conditions	4,328	42.0	43	37.1	0.74	0.48-1.13	4,943	47.9	52	44.8	0.74	0.44-1.25
Autoimmune conditions, by organ system												
Systemic/connective tissue	1,602	15.5	12	10.3	0.66	0.36-1.21	1,522	14.8	17	14.7	1.58	0.85-2.94
Rheumatoid arthritis	1,052	10.2	<10	~	0.49	0.21-1.13	871	8.5	10	8.6	1.89	0.91-3.95
Cardiovascular	1,076	10.4	11	9.5	0.92	0.49-1.75	1,951	18.9	16	13.8	0.86	0.47-1.58
Chronic rheumatic heart disease	932	9.0	11	9.5	1.08	0.57-2.04	1,831	17.8	16	13.8	0.92	0.50-1.69
Endocrine	810	7.9	<10	~	0.86	0.39-1.88	1,019	9.9	<10	~	0.87	0.40-1.90
Skin	1,836	17.8	23	19.8	1.23	0.77-1.97	1,549	15.0	18	15.5	0.83	0.41-1.68
Localized scleroderma	1,400	13.6	18	15.5	1.29	0.77-2.17	1,237	12.0	15	12.9	0.81	0.39-1.70
Gastrointestinal	1,115	10.8	<10	~	0.82	0.41-1.64	1,929	18.7	23	19.8	1.25	0.72-2.15
Pernicious anemia	840	8.2	<10	~	0.88	0.40-1.91	1,603	15.6	17	14.7	1.15	0.64-2.08
Nervous system	72	0.7	<10	~	0	0	122	1.2	<10	~	0.00	0
Asthma	1,404	13.6	16	13.8	0.77	0.44-1.34	1,620	15.7	16	13.8	0.58	0.27-1.28

Table 4 continued. Risk of lung cancer after first primary NHL, by subtype, in relation to autoimmune conditions

	Prior to NHL diagnosis						After NHL diagnosis *					
	Total NHL		Lung cancer cases				Total NHL		Lung cancer cases			
Autoimmune conditions †	**N**	**%**	**N**	**%**	**HR ‡**	**95% CI**	**N**	**%**	**N**	**%**	**HR ‡**	**95% CI**
Patients diagnosed with first primary FL												
B-cell activating conditions	1,193	16.0	12	9.5	0.57	0.31-1.06	1,699	22.9	15	11.8	0.63	0.33-1.23
T-cell activating conditions	2,969	39.9	45	35.4	0.74	0.49-1.12	3,604	48.5	40	31.5	0.57	0.34-0.96
Autoimmune conditions, by organ system												
Systemic/connective tissue	1,020	13.7	12	9.5	0.71	0.39-1.31	1,051	14.1	<10	~	0.39	0.14-1.06
Rheumatoid arthritis	639	8.6	10	7.9	0.97	0.50-1.89	586	7.9	<10	~	0.21	0.03-1.48
Cardiovascular	687	9.2	<10	~	0.70	0.34-1.45	1,276	17.2	13	10.2	0.72	0.36-1.43
Chronic rheumatic heart disease	615	8.3	<10	~	0.71	0.33-1.54	1,171	15.8	12	9.5	0.80	0.40-1.59
Endocrine	519	7.0	<10	~	0.69	0.30-1.58	665	8.9	<10	~	0.46	0.17-1.25
Skin	1,233	16.6	21	16.5	1.06	0.65-1.72	1,264	17.0	12	9.5	0.35	0.14-0.87
Localized scleroderma	995	13.4	15	11.8	0.91	0.53-1.58	1,022	13.7	<10	~	0.25	0.08-0.81
Gastrointestinal	640	8.6	<10	~	0.47	0.19-1.17	1,265	17.0	12	9.5	0.67	0.34-1.34
Nervous system	31	0.4	<10	~	0	0	84	1.1	<10	~	1.42	0.20-10.31
Asthma	1,002	13.5	17	13.4	0.88	0.51-1.51	1,283	17.3	15	11.8	0.87	0.45-1.68
Patients diagnosed with other first primary NHL												
B-cell activating conditions	2,817	21.4	36	18.2	0.85	0.59-1.25	3,767	28.6	38	19.2	0.80	0.50-1.28
T-cell activating conditions	5,845	44.4	79	39.9	0.97	0.68-1.37	6,654	50.5	104	52.5	1.56	1.07-2.27
Autoimmune conditions, by organ system												
Systemic/connective tissue	2,176	16.5	28	14.1	0.90	0.60-1.36	2,161	16.4	32	16.2	0.97	0.56-1.66
Rheumatoid arthritis	1,270	9.6	19	9.6	1.08	0.67-1.75	1,201	9.1	16	8.1	0.79	0.37-1.69
Cardiovascular	1,449	11.0	15	7.6	0.75	0.44-1.28	2,300	17.5	24	12.1	1.16	0.73-1.84
Chronic rheumatic heart disease	1,224	9.3	11	5.6	0.66	0.36-1.22	2,069	15.7	22	11.1	1.18	0.73-1.91
Endocrine	1,090	8.3	10	5.1	0.63	0.33-1.20	1,263	9.6	16	8.1	1.14	0.65-1.98
Graves disease	911	6.9	<10	~	0.51	0.24-1.10	888	6.7	11	5.6	1.07	0.56-2.05
Skin	2,579	19.6	39	19.7	0.99	0.69-1.42	2,581	19.6	37	18.7	0.91	0.57-1.45
Localized scleroderma	1,870	14.2	24	12.1	0.82	0.53-1.26	1,851	14.1	20	10.1	0.69	0.39-1.22
Psoriasis	783	5.9	16	8.1	1.37	0.82-2.29	790	6.0	17	8.6	1.14	0.58-2.24
Gastrointestinal	1,703	12.9	14	7.1	0.54	0.31-0.93	2,849	21.6	24	12.1	0.81	0.51-1.30
Pernicious anemia	1,325	10.1	10	5.1	0.53	0.28-1.00	2,421	18.4	20	10.1	0.85	0.52-1.39
Nervous system	91	0.7	<10	~	1.52	0.37-6.20	173	1.3	<10	~	1.77	0.56-5.62
Asthma	1,932	14.7	25	12.6	0.77	0.50-1.21	2,230	16.9	46	23.2	2.00	1.34-2.97

Table 4 continued. Risk of lung cancer after first primary NHL, by subtype, in relation to autoimmune conditions

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); confidence interval (CI); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); hazard ratio (HR); non-Hodgkin lymphoma (NHL).

~ Counts and percentages are not reported when less than 10 lung cancer cases to protect patient confidentiality.

* New claims occurring after NHL but prior to second cancer, death, end of study, or loss to follow-up, with no claims prior to NHL.

† B-cell activating conditions include rheumatoid arthritis, Sjogren's syndrome, discoid lupus erythematosus, reactive arthritis, Felty's syndrome, chronic thryoiditis, systemic/discoid lupus erythematosus, pernicious anemia, and myasthenia gravis. T-cell activating conditions include ankylosing spondylitis, dermatomyositis, polymyalgia rheumatica, sarcoidosis, systemic sclerosis, rheumatic fever, chronic rheumatic heart disease, giant cell arteritis, systemic vasculitis, Addison's disease, Graves' disease, primary biliary cirrhosis, alopecia areata, localized scleroderma, dermatitis herpetiformis, psoriasis, celiac disease, Crohn's disease, ulcerative colitis, amyotrophic sclerosis, multiple sclerosis, and asthma.

‡ Individuals with no history of the condition of interest comprise the referent group for each analysis. Hematologic autoimmune conditions (e.g., autoimmune hemolytic anemia, thrombocytopenia) were excluded from consideration because of difficulty distinguishing these diagnoses from manifestations of chemotherapy toxicity. HR (95% CI) adjusted for sex, race, history of smoking, and follow-up time (time-dependent covariate) and stratified by calendar year. Age used as time scale.

Risk factors for second acute myeloid leukemia/myelodysplastic syndrome among survivors of non-Hodgkin lymphoma

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ABSTRACT

Background

Increased risk of second acute myeloid leukemia/myelodysplastic syndrome (AML/MDS) has been established among non-Hodgkin lymphoma (NHL) survivors; however, previous studies focused on treatment effects, and data related to immune-related medical conditions are lacking.

Methods

We assessed second AML/MDS risk among 34,148 1-year survivors of first primary NHL diagnosed at ages 66-84 years during 2000-2009 from the Surveillance, Epidemiology, and End Results (SEER)-Medicare data linkage. Information on potential risk factors, including NHL treatments, autoimmune conditions, and selected infections, was derived from Medicare claims.

Results

A total of 155 second AML/MDS were diagnosed among NHL survivors. AML/MDS risk was significantly elevated among NHL survivors who received any cyclophosphamide-, fludarabine-, and rituximab-containing chemotherapy compared with those who did not receive any infused chemotherapy (HR=3.52, 95% 1.96-6.33). Risks were highest for survivors who received fludarabine- and rituximab-containing chemotherapy without cyclophosphamide (HR=4.72, 95% CI 2.53-8.84) as well as for those who received fludarabine -containing chemotherapy alone (HR=5.95, 95% CI 2.27-15.58). AML/MDS risks were increased 1.5- to 2.0-fold for autoimmune diseases occurring prior to NHL diagnosis for nearly all conditions we evaluated. Few associations were observed for diagnoses of autoimmune diseases occurring after NHL, with the exception of pernicious anemia (HR=2.24, 95% CI 1.46-3.42) and asthma (HR=1.98, 95% CI 1.22-3.19). Upper airway respiratory infections were associated with increased second AML/MDS risk (before NHL HR=1.47, 95% CI 1.01-2.12, after NHL HR=1.74, 95% CI 1.10-2.76), particularly sinusitis (after NHL HR=2.18, 95% CI 1.44-3.31). Additionally, subsequent AML/MDS was also

associated with pneumonia (after NHL HR=1.69, 95% CI 1.16-2.46). Other infections increased AML/MDS risks including skin infections likely driven by herpes zoster (HR=1.91, 95% CI 1.18-3.10), and urinary tract infections, particularly prostatitis (before NHL HR=1.71, 95% CI 1.05-2.76, after NHL HR=2.32, 95% CI 1.21-4.45) and cystitis/pyelonephritis (after NHL HR=1.68, 95% CI 1.07-2.62). Gastroenteritis was associated with AML/MDS diagnosed after NHL (HR=1.76, 95%CI=1.11-2.79).

Conclusion

Our findings highlight a potential role for immune-related medical conditions in the development of second AML/MDS after NHL. Further research is needed to better understand the immune-related biological mechanisms that contribute to AML/MDS.

INTRODUCTION

Due to improvements in diagnosis, treatment, and prognosis, approximately 14 million cancer survivors are alive in the US today.[1] However, these survivors are at risk of developing complications arising from their initial cancer diagnosis. Although rare, treatment-related acute myeloid leukemia/myelodysplastic syndrome (t-AML/MDS) can develop after cytotoxic chemotherapy and is highly fatal.[237-240] Evidence is accumulating that immune dysfunction also could play a role in the etiology of AML/MDS. Elevated risks of myeloid neoplasms associated with certain autoimmune diseases and infections have been reported in previous studies.[241-245] Additionally, a role for immune dysfunction in the development of AML/MDS is supported by increased risks observed in immunosuppressed populations such as solid organ transplant recipients and persons with HIV/AIDS.[142,154,163,246-249] However, immune-related medical conditions have not been evaluated as potential risk factors for AML/MDS among cancer survivors.

Non-Hodgkin lymphoma (NHL) survivors are a particularly important population in which to study AML/MDS etiology because of the known risks associated with cyclophosphamide and fludarabine,[21,22,24,30-32,34-37,40,41,45,88,89,98,167,170,189-193,211,250,251] which are commonly used to treated certain NHLs,[194,218,219] and because immune dysfunction also is associated with NHL.[6,7,9] Previous studies of AML/MDS after NHL have lacked the data necessary to consider immune-related medical conditions; therefore, we used the Surveillance, Epidemiology, and End Results-Medicare (SEER-Medicare) data linkage to assess second AML/MDS risks after NHL associated with NHL treatments, autoimmune disease, and selected infections among 34,148 first primary NHL survivors in the older adult population in the US.

METHODS

Study Population

We identified NHL survivors through SEER-Medicare, which has been previously described elsewhere.[174] Briefly, SEER-Medicare links two large population-based data sources to provide specific demographic, clinical, cause of death information, and cancer characteristics for persons diagnosed with cancer. The Surveillance, Epidemiology, and End Results (SEER) database, funded by the National Cancer Institute since 1973, provides cancer information on approximately 26% of the U.S. population.[177] Medicare provides federally funded health insurance for approximately 45 million persons aged 65 years and older. The linkage of SEER-Medicare matches 94% of SEER cancer cases over 65 years of age and includes all Medicare covered services for beneficiaries with fee-for-service coverage.

SEER was used to identify persons diagnosed with first primary NHL according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) (see Table 1 footnote).[4,176] Eligible patients included males and females diagnosed between 2000-2009 at ages 66-84 years who had continuous fee-for-service Medicare Parts A and B coverage at least 12 months before NHL diagnosis through the first 12 months following NHL diagnosis for ascertainment of treatment and medical condition exposures. NHL diagnoses and follow-up time at ages ≥85 years were excluded because of under-ascertainment of second malignancies at older ages.[39] Patients with less than one year of survival time after NHL diagnosis (N=1,157) or Medicare claims for HIV (N=171) or solid organ transplantation (N=107) were excluded from the analysis. Second primary acute myeloid leukemias/myelodysplastic syndromes that developed at least one year after first primary NHL were identified through SEER (ICD-O-3 morphology codes, AML: 9840, 9861, 9865-9867, 9869, 9871-9874, 9895-9898, 9910-9911, 9920, 9945-9946, and 9975; MDS: 9980, 9982-9987, and 9989; behavior code=3, sequence code=2).[177]

Ascertainment of NHL Treatments and Medical Conditions

Information on NHL treatments (infused chemotherapy and radiotherapy) and medical history (autoimmune diseases and infections) was derived from Medicare claims from hospital inpatient, physician, and outpatient services (see Supplementary Tables 1-3 for more details). For analyses of infused chemotherapy, we focused on combinations of the most commonly used specific chemotherapy agents (cyclophosphamide, rituximab, and fludarabine). We also evaluated the effects of granulocyte colony-stimulating factor (G-CSF),used to treat neutropenia in NHL patients,[252-254] and topoisomerase II inhibitors, used in conjunction with alkyating agents, because both of these classes of systemic therapy have been shown to increase risk for t-AML/MDS.[255-258] Information on bone marrow and hematopoietic stem cell transplants was used as a proxy for the intensity of treatment since these procedures were used in more aggressive treatment regimens.[259-262] We were unable to capture information regarding oral chemotherapy such as chlorambucil since data on prescription drugs was not available during the study period. Data on radiotherapy consisted of whether patients did or did not receive radiotherapy.

Occurrences of autoimmune diseases and infections were defined as having ≥1 Medicare claim at any time during follow-up, considering diagnoses occurring prior to NHL separately from those occurring after NHL diagnosis. Diagnoses of autoimmune conditions and infections occurring before the start of the study period in 2000 or prior to age 65 years (when individuals enrolled in Medicare) were not captured. Analyses considered individual conditions and infections with at least ten exposed AML/MDS cases, diagnosed either before or after NHL. We grouped diagnoses based on the tissue and organ systems involved due to the rarity of many diagnoses. We also grouped autoimmune conditions according to whether they activate B- or T-cells (see Table 3 footnotes).[178-182] Hematologic autoimmune conditions (e.g., autoimmune hemolytic anemia, thrombocytopenia) were excluded from consideration because of difficulty distinguishing these diagnoses from manifestations of chemotherapy toxicity.

Statistical Analysis

Follow-up began one year after first primary NHL diagnosis and continued until second AML/MDS diagnosis, age 85 years, death, loss to follow-up, or end of study (December 31, 2009), whichever came first. Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) to assess the association between specific risk factors and risk of second AML/MDS after NHL. Analyses used age as the time scale and were adjusted by sex, race (white, other), intensity of treatment (bone marrow/hematopoietic stem cell transplants), and follow-up time (modeled as a time-dependent covariate: 1-1.9, 2-2.9, 3-3.9, 4-4.9, 5-6.9, and ≥7 years). Additionally, the analyses were stratified by calendar year of NHL diagnosis to account for differing exposure periods as well as NHL subtype to account for differing AML/MDS risks among the subtypes since we were unable to evaluate risks separately due to small numbers.

Time-dependent covariates were used to indicate receipt of infused chemotherapy or radiotherapy during follow-up based on the timing of initiation of therapy. Risk of second AML/MDS associated with NHL treatments was evaluated in multivariate models including both chemotherapy and radiotherapy. We assessed risk according to the most frequently received combinations of cyclophosphamide, rituximab, and fludarabine (see Table 2). Patients with no Medicare chemotherapy claims (i.e., no infused chemotherapy; includes patients who received oral agents exclusively) served as our referent group.

For investigation of AML/MDS risks associated with autoimmune conditions and infections occurring before NHL diagnosis, we defined the follow-up period from age 65 or age at enrollment into Medicare to age of NHL diagnosis. Autoimmune conditions and infections diagnosed after NHL were evaluated as time-dependent covariates based on the timing of diagnoses of these conditions. Because of the established risk of treatment-related AML/MDS after NHL[98,146] analyses of autoimmune conditions and infections were adjusted for NHL

treatment (chemotherapy and radiotherapy) and intensity of treatment. All analyses were conducted using SAS 9.3 (Cary, NC).

RESULTS

We identified 34,148 one-year first primary NHL survivors (Table 1). The vast majority of survivors were white (90.7%), and median age at diagnosis was 75 years. A total of 155 second AML/MDS (71 AML, 84 MDS) were diagnosed during 172,994 total person-years of follow-up (mean person-years at risk=5.1; median interval from NHL to AML/MDS=3.2 years). AML/MDS risks were higher among males, whites, and survivors of diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and other NHL compared with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Non-Hodgkin Lymphoma Treatment

Of the 19,854 (58.1%) NHL survivors who received infused chemotherapy during follow-up, 16,991 (85.6%) initiated chemotherapy within the first 12 months after NHL diagnosis, and 2,863 (14.4%) initiated chemotherapy >12 months after NHL diagnosis. Cyclophosphamide- and rituximab-containing chemotherapy without fludarabine was the most commonly received infused chemotherapy combination (31.4%) followed by rituximab-containing chemotherapy without cyclophosphamide or fludarabine (11.2%) (Table 2). AML/MDS risk was significantly elevated among NHL survivors who received any cyclophosphamide-, fludarabine-, and rituximab-containing chemotherapy compared with those who did not receive any infused chemotherapy (HR=3.52, 95% 1.96-6.33). Risks were highest for survivors who received fludarabine- and rituximab-containing chemotherapy without cyclophosphamide (HR=4.72, 95% CI 2.53-8.84) as well as for those who received fludarabine -containing chemotherapy alone (HR=5.95, 95% CI 2.27-15.58). AML/MDS risk was non-significantly elevated among NHL survivors

who received rituximab-containing chemotherapy without cyclophosphamide or fludarabine (HR=1.69, 95% CI 0.90-3.16). Radiotherapy was not related to AML/MDS risk in NHL survivors.

Autoimmune Conditions and Infections

In multivariate models adjusting for NHL treatment, we also observed increased risk of AML/MDS among NHL survivors with diagnoses of a range of autoimmune conditions and infections (Table 3). Specifically, risks were increased 1.5- to 2.0-fold for autoimmune diseases occurring prior to NHL diagnosis for nearly all conditions we evaluated. In contrast, few associations were observed for diagnoses of autoimmune diseases occurring after NHL, with the exception of pernicious anemia (HR=2.24, 95% CI 1.46-3.42) and asthma (HR=1.98, 95% CI 1.22-3.19).

Infections also were broadly associated with risks for subsequent AML/MDS, with significantly elevated risks observed for diagnoses occurring both before and after NHL (Table 3). Upper airway respiratory infections were associated with increased second AML/MDS risk (before NHL HR=1.47, 95% CI 1.01-2.12, after NHL HR=1.74, 95% CI 1.10-2.76), with the highest associations for sinusitis (after NHL HR=2.18, 95% CI 1.44-3.31). Additionally, elevated risks of subsequent AML/MDS were also associated with pneumonia diagnosed after NHL (HR=1.69, 95% CI 1.16-2.46). Increased AML/MDS risks were observed with other various infections including skin infections likely driven by herpes zoster (HR=1.91, 95% CI 1.18-3.10), and urinary tract infections due to prostatitis (before NHL HR=1.71, 95% CI 1.05-2.76, after NHL HR=2.32, 95% CI 1.21-4.45) and cystitis/pyelonephritis (after NHL HR=1.68, 95% CI 1.07-2.62). Gastroenteritis showed non-significantly elevated AML/MDS risks before NHL (HR=1.43, 95% CI 0.93-2.20) but significantly increased risks when diagnosed after NHL (HR=1.72, 95% CI 1.08-2.73).

DISCUSSION

In this large, population-based study of NHL survivors, we show for the first time that AML/MDS risk is related to diagnoses of immune-related medical conditions in addition to NHL treatments. Increased treatment-related AML/MDS risks were observed among NHL survivors who received various combinations of cyclophosphamide-, fludarabine-, and rituximab-containing chemotherapy, particularly those involving fludarabine. After accounting for treatment effects, we showed that numerous autoimmune conditions and infections also were associated with subsequent AML/MDS risk. These findings support the importance of immune dysfunction in addition to direct DNA damage as potential mechanisms explaining increased risks of AML/MDS after NHL.

The associations we observed between NHL treatments and risk of subsequent AML/MDS are consistent with previous studies.[21,22,24,30-32,34-37,40,41,45,88,89,98,167,170,189-193,211,250,251] In our study, the highest risks were found for fludarabine-containing regimens, with risks for other combinations of cyclophosphamide and rituximab non-significantly elevated. Fludarabine, a purine analog most frequently used to treat CLL/SLL,has been reported to increase AML/MDS risks in previous studies.[21,45,167,170,189-193] Cyclophosphamide , an alkylating agent used to treat a number of NHLs as part of the multi-drug regimen CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), also has been associated with AML/MDS in previous studies.[94,116,217,263-267] Both chemotherapeutic agents are associated with immunosuppression, thus the loss of immunosurveillance may also play a role in the development of second AML/MDS after NHL.[45,218,219] Elevated AML/MDS risks after bone marrow/hematopoietic stem cell transplants and G-CSF may be markers of individuals who received the highest or most intensive chemotherapeutic regimens.[252-254,259-262] A previous registry-based study showed that AML/MDS risk among NHL survivors has tripled in the last several decades which may be due to the increasing use of fludarabine and stem cell transplant, both of which are associated with higher risks than cyclophosphamide alone.[250] Although radiotherapy has been shown to develop

AML/MDS in previous studies;[268-270] we did not observe increased risk of AML/MDS after radiotherapy for NHL. However, we were limited in our analyses due to the lack of information on the radiotherapy field(s) and dose.

Our observation that various autoimmune conditions and infections increase risk of subsequent AML/MDS among NHL survivors extends previous research on these risk factors conducted in the general population.[241-245] In our study, increased AML/MDS risks were observed for several autoimmune conditions with similar risks reported in previous studies evaluating the same conditions, particularly rheumatoid arthritis and chronic rheumatic heart disease.[241-244] However, our 2.0 to 2.2-fold increased AML/MDS risk for pernicious anemia diagnosed before and after NHL was notably higher than in other studies,[243,244] but similar to the risks found in one previous study.[241] Similarly, the risks for localized scleroderma were higher in our study.[241] Although we found increased AML/MDS risks associated with Graves' disease, our finding is not consistent with the inverse relationships reported in previous studies.[242,243] In a new finding, asthma diagnosed after NHL increased AML/MDS risks. Asthma initiates similar chronic inflammatory pathways of cytokine activity found in other autoimmune conditions and may manifest the immune disruption that precedes the development of AML/MDS.[234] Although the exact mechanism by which autoimmune conditions may influence AML/MDS risk is unknown, the most likely explanation involves immunosuppression resulting from treatments given to patients for these conditions.[241-244] Alternatively, it is possible that these conditions could share common genetic predispositions with AML and MDS,[241-244,271,272] or that autoimmune diseases may have a more direct effect by damaging myeloid precursor cells in the bone marrow.[241]

The importance of immune dysfunction in the etiology of AML/MDS is further supported by observed associations for various infections. In general, our infection-related AML/MDS risks were similar to those reported in previous studies;[243,245] however, several of our risks were

higher, particularly for those infections diagnosed after NHL. In our study, NHL survivors had 1.7 to 2.2-fold increased risk of AML/MDS when diagnosed with various respiratory infections, specifically sinusitis and pneumonia, higher than the 1.2 to 1.5-fold risks observed in other studies.[243,245] Increased AML/MDS risks with skin infections (cellutis and herpes zoster), urinary tract infections (prostatitis and cystitis/pyelonephritis), and gastroenteritis were also higher than risks reported previously.[243,245] It is not clear how infections can increase the risk for AML/MDS, but the biological mechanism may involve an underlying immune dysfunction that could predispose NHL survivors to AML/MDS.[243,245] Additionally, infectious agents can use a variety of virulent mechanisms to initiate production of pathogenic viral factors including M proteins, fever inducing cytokines, and super antigens in already immunocompromised individuals leaving them with inhibited or impaired immune function through genetic adaptation and evolution.[242,273-276] Although antigenic stimulation could be the driving mechanism for developing AML/MDS, our findings could indicate additional immunosuppression combined with the early stage of an immunocompromised state in the process of malignant transformation.[243,277-279]

The main limitation of this analysis was the lack of dose data for NHL treatments along with the inability to collect information on oral chemotherapy agents during follow-up. We could not ascertain whether patients received chlorambucil, which is one of the main treatments for one of the main NHL subtypes, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).[45] However, our risk estimates, especially related to fludarabine, are likely to be conservative since patients who received chlorambucil were included in our referent group. Patients may also have had misclassified exposures because we could not capture information on infections and autoimmune diseases diagnosed prior to entry into Medicare. Information on mild infections for which patients did not seek medical care would also not be captured in Medicare. Due to the nature of the Medicare claims data, we were only able to assess potential risk factors that generated medical billing claims; therefore, we could not assess any

other possible risk factors for AML/MDS such as genetics. However, we were able to assess currently established risk factors for AML/MDS including age, sex, and previous cancer treatment. Second cancers can be underreported due to survivors leaving the SEER registry areas; however, our risk estimates should not be affected since this underreporting is unlikely to be related to the risk factors we assessed in our study.

This study is one of the first analytic studies to investigate immune-related risk factors for second AML/MDS in cancer survivors after accounting for receipt of previous cancer treatments. We were able to utilize a large population-based cohort to identify these risk factors and provide long-term follow-up for the exposure assessment and second AML/MDS ascertainment. Furthermore, this study design eliminated selection bias since all subjects in the cohort developed first primary NHL. Additionally, our study results are generalizable to the elderly population in the US since we used a cohort that represents this population. Our findings highlight a potential role for immune-related medical conditions in the development of second AML/MDS after NHL. Further research is needed to better understand the immune-related biological mechanisms that contribute to AML/MDS.

Table 1. Selected characteristics and risk of AML/MDS among 34,148 1-year survivors of first primary NHL diagnosed at ages 66-84 years, 16 SEER registries, 2000-2009

	Total NHL*		AML		MDS		AML/MDS cases	
	N	%	N	%	N	%	HR†	95% CI
Age at NHL diagnosis (years)								
65-69	7,255	21.3	18	25.4	22	26.2		
70-74	9,712	28.4	24	33.8	33	39.3		
75-79	9,777	28.6	22	31.0	26	31.0		
80-84	7,404	21.7	<10	~	<10	~		
Year of NHL diagnosis								
2000-2004	17,146	50.2	51	71.8	61	72.6		
2005-2009	17,002	49.8	20	28.2	23	27.4		
Sex								
Male	16,873	49.4	48	67.6	41	48.8	1.00	Referent
Female	17,275	50.6	23	32.4	43	51.2	0.67	0.49-0.92
Race								
White	30,959	90.7	65	91.6	77	91.7	1.00	Referent
Other/unknown	3,189	9.3	<10	~	<10	~	0.92	0.52-1.62
NHL subtype								
CLL/SLL	10,445	30.6	13	18.3	22	26.2	1.00	Referent
DLBCL	7,909	23.2	17	23.9	24	28.6	1.70	1.08-2.67
FL	5,663	16.6	16	22.5	15	17.9	1.66	1.02-2.70
MZ	3,074	9.0	<10	~	<10	~	1.39	0.73-2.63
Other	7,057	20.7	18	25.4	17	20.2	1.66	1.04-2.65

Abbreviations: acute myeloid leukemias/myelodysplastic syndromes (AML/MDS); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); International Classification of Diseases for Oncology, 3rd edition (ICD-O-3); marginal zone lymphoma (MZ); non-Hodgkin lymphoma (NHL); Surveillance, Epidemiology and End Results (SEER).

* First primary NHL subtype defined by ICD-O-3 as DLBCL (9678-9680, 9684 [B-cell]), FL (9690-9691, 9695, 9698), CLL/SLL (9670, 9823), MZL (9689, 9699) and other NHL (9590-9596, 9671, 9673, 9675, 9684 [non B-cell], 9687, 9700-9702, 9705, 9708-9709, 9714-9719, 9727-9729, 9827 [primary site=(C.420-421, 424]).

~ Counts and percentages are not reported for less than 10 AML/MDS cases to protect patient confidentiality.

† HR (95% CI) derived from a multivariate model including sex, race, NHL subtype, and follow-up time (time-dependent covariate) and stratified by calendar year. Age was used as the time scale.

Table 2. Risk of AML/MDS after first primary NHL in relation to NHL treatments

	Total NHL		AML/MDS cases			
NHL treatment *	**N**	**%**	**N**	**%**	**HR †**	**95% CI**
Infused chemotherapy						
None recorded	14,294	41.9	36	23.2	1.00	Referent
Cyclophosphamide without fludarabine or rituximab	1,495	4.4	10	6.5	1.55	0.66-3.67
Fludarabine without cyclophosphamide or rituximab	401	1.2	<10	~	5.95	2.27-15.58
Rituximab without cyclophosphamide or fludarabine	3,823	11.2	14	9.0	1.69	0.90-3.16
Cyclophosphamide + rituximab without fludarabine	10,732	31.4	51	32.9	1.24	0.67-2.30
Fludarabine + rituximab without cyclophosphamide	1,314	3.9	16	10.3	4.72	2.53-8.84
Cyclophosphamide + fludarabine + rituximab	1,998	5.9	23	14.8	3.52	1.96-6.33
Radiotherapy						
No	28,438	83.3	134	86.5	1.00	Referent
Yes	5,710	16.7	21	13.6	0.80	0.52-1.24
Bone marrow/hematopoietic stem cell transplant						
No	33,922	99.3	150	96.8	1.00	Referent
Yes	226	0.7	<10	~	3.63	1.36-9.61
Granulocyte colony-stimulating factor						
No	27,985	82.0	95	61.3	1.00	Referent
Yes	6,163	18.0	60	38.7	1.75	1.20-2.57
Topoisomerase II inhibitors						
No	23,398	68.5	89	57.4	1.00	Referent
Yes	10,750	31.5	66	42.6	0.99	0.59-1.65

Abbreviations: acute myeloid leukemia/myelodysplastic syndrome (AML/MDS); confidence interval (CI); hazard ratio (HR); non-Hodgkin lymphoma (NHL).

~ Counts and percentages are not reported for less than 10 AML/MDS cases to protect patient confidentiality.

* Treatments received by fewer than 10 AML/MDS cases are not reported here but are included in Supplementary Table 1 (e.g., other alkylating agents).

† HR (95% CI) adjusted for sex, race, and follow-up time (time-dependent covariate), and stratified by calendar year and NHL subtype. Age was used as the time scale. Time-dependent covariates were used to indicate receipt of specific NHL treatments during follow-up based on timing of initiation of therapy.

Table 3. Risk of AML/MDS after first primary NHL in relation to autoimmune conditions and infections

	Prior to NHL diagnosis						After NHL diagnosis *					
	Total NHL		AML/MDS cases				Total NHL		AML/MDS cases			
Autoimmune conditions †	**N**	**%**	**N**	**%**	**HR ‡**	**95% CI**	**N**	**%**	**N**	**%**	**HR ‡**	**95% CI**
B-cell activating conditions	6,848	20.1	36	23.2	1.63	1.10-2.43	8,586	25.1	57	36.8	1.96	1.28-3.01
T-cell activating conditions	15,108	44.3	73	47.1	1.54	1.06-2.23	16,057	47.0	77	49.7	1.52	0.96-2.40
Autoimmune conditions, by organ system												
Systemic/connective tissue	5,348	15.7	29	18.7	1.52	1.00-2.31	4,776	14.0	29	18.7	1.26	0.67-2.37
Rheumatoid arthritis	3,278	9.6	16	10.3	1.27	0.75-2.15	2,684	7.9	17	11.0	1.39	0.64-2.99
Cardiovascular	3,814	11.2	21	13.6	1.56	0.97-2.50	5,679	16.6	22	14.2	1.00	0.58-1.73
Chronic rheumatic heart disease	3,354	9.8	18	11.6	1.52	0.92-2.51	5,247	15.4	19	12.3	0.92	0.51-1.65
Endocrine	2,802	8.2	17	11.0	1.55	0.92-2.60	2,887	8.5	10	6.5	0.84	0.39-1.82
Graves' disease	2,353	6.9	17	11.0	1.84	1.09-3.08	2,000	5.9	<10	~	0.56	0.18-1.78
Skin	6,361	18.6	36	23.2	1.47	0.99-2.16	5,458	16.0	26	16.8	1.23	0.70-2.18
Localized scleroderma	4,936	14.5	30	19.4	1.57	1.04-2.38	4,204	12.3	22	14.2	1.31	0.73-2.36
Gastrointestinal	4,096	12.0	23	14.8	1.72	1.08-2.73	6,561	19.2	45	29.0	2.28	1.52-3.43
Pernicious anemia	3,172	9.3	20	12.9	2.00	1.23-3.26	5,561	16.3	40	25.8	2.24	1.46-3.42
Nervous system	241	0.7	<10	~	1.82	0.45-7.47	392	1.2	<10	~	1.15	0.16-8.37
Asthma	5,246	15.4	18	11.6	0.92	0.56-1.52	5,618	16.5	31	20.0	1.98	1.22-3.19
Infections, by organ system												
Respiratory - upper airway	15,120	44.3	74	47.7	1.47	1.01-2.12	12,858	37.7	80	51.6	1.74	1.10-2.76
Otitis media	3,982	11.7	22	14.2	1.31	0.83-2.08	2,956	8.7	14	9.0	1.18	0.59-2.35
Pharyngitis	5,540	16.2	29	18.7	1.30	0.86-1.97	4,480	13.1	27	17.4	1.36	0.81-2.31
Sinusitis	10,808	31.7	46	29.7	1.16	0.79-1.68	9,050	26.5	63	40.7	2.18	1.44-3.31
Respiratory - lower airway	15,140	44.3	73	47.1	1.44	0.98-2.11	17,554	51.4	86	55.5	1.38	0.88-2.16
Acute bronchitis	11,609	34.0	56	36.1	1.23	0.86-1.74	10,108	29.6	50	32.3	1.07	0.66-1.73
Influenza	1,852	5.4	11	7.1	1.35	0.72-2.52	1,289	3.8	<10	~	1.34	0.58-3.09
Pneumonia	6,697	19.6	29	18.7	1.22	0.79-1.88	12,763	37.4	62	40.0	1.69	1.16-2.46
Skin	5,372	15.7	32	20.7	1.63	1.08-2.44	7,326	21.5	33	21.3	1.04	0.65-1.65
Cellulitis	2,958	8.7	14	9.0	1.26	0.72-2.19	3,972	11.6	18	11.6	1.45	0.85-2.46
Herpes zoster	2,762	8.1	20	12.9	1.91	1.18-3.10	4,066	11.9	19	12.3	1.05	0.62-1.80
Urinary tract	16,532	48.4	73	47.1	1.31	0.89-1.92	18,574	54.4	93	60.0	1.68	1.07-2.62
Cystitis/pyelonephritis, UTI	15,040	44.0	61	39.4	1.19	0.81-1.74	17,768	52	83	53.6	1.69	1.11-2.58
Prostatitis §	3,841	22.8	27	30.3	1.71	1.05-2.76	2,454	14.5	25	28.1	2.32	1.21-4.45
Gastrohepatic	5,430	15.9	29	18.7	1.41	0.93-2.15	5,693	16.7	33	21.3	1.63	1.02-2.58
Gastroenteritis	5,197	15.2	28	18.1	1.43	0.93-2.20	5,268	15.4	33	21.3	1.72	1.08-2.73

Table 3 continued. Risk of AML/MDS after first primary NHL in relation to autoimmune conditions and infections

Abbreviations: acute myeloid leukemia/myelodysplastic syndrome (AML/MDS); confidence interval (CI); hazard ratio (HR); non-Hodgkin lymphoma (NHL); urinary tract infections (UTI).

~ Counts and percentages are not reported for less than 10 AML/MDS cases to protect patient confidentiality.

* New claims occurring after NHL but prior to second cancer, death, end of study, or loss to follow-up, with no claims prior to NHL.

† B-cell activating conditions include rheumatoid arthritis, Sjogren's syndrome, discoid lupus erythematosus, reactive arthritis, Felty's syndrome, chronic thryoiditis, systemic/discoid lupus erythematosus, pernicious anemia, and myasthenia gravis. T-cell activating conditions include ankylosing spondylitis, dermatomyositis, polymyalgia rheumatica, sarcoidosis, systemic sclerosis, rheumatic fever, chronic rheumatic heart disease, giant cell arteritis, systemic vasculitis, Addison's disease, Graves' disease, primary biliary cirrhosis, alopecia areata, localized scleroderma, dermatitis herpetiformis, psoriasis, celiac disease, Crohn's disease, ulcerative colitis, amyotrophic sclerosis, multiple sclerosis, and asthma.

‡ Individuals with no history of the condition of interest comprise the referent group for each analysis. Hematologic autoimmune conditions (e.g., autoimmune hemolytic anemia, thrombocytopenia) were excluded from consideration because of difficulty distinguishing these diagnoses from manifestations of chemotherapy toxicity. HR (95% CI) adjusted for sex, race, NHL treatment (including chemotherapy, radiotherapy, and hematopoietic stem cell transplant, as listed in Table 2), and follow-up time (time-dependent covariate) and stratified by calendar year and NHL subtype. Age was used as the time scale.

§ Among males only.

Chapter 5: Conclusion

The number of cancer survivors in the United States is increasing every year as modern advances in early stage detection and treatment have contributed to increased survival rates following a cancer diagnosis in the recent decades.[1] However, approximately 19% of newly diagnosed cancers now occur in individuals who have a previous cancer diagnosis,[2] and second cancers risks have become a leading cause of morbidity and mortality and have taken on greater importance.[280] Studies of second cancers are needed to identify various risk factors that may increase subsequent cancer risks, particularly among survivors of first primary cancers with better prognoses.

NHL is the 6th most common cancer diagnosed in the US today, and represents an estimated 4.3% of all new cancers.[3] With substantial advances in treatment, the 5-year relative survival rate for overall NHL has improved to approximately 67%, though survival rates differ dramatically for specific subtypes.[3] I conducted three analytic studies of second cancer risk factors after first primary NHL. Numerous previous studies have shown that NHL survivors are at higher risk of developing second cancers compared to the general population,[19-27,29-41,89,98] and I chose to investigate second melanoma, lung cancer, and AML/MDS because these cancers are common and have been shown to be in excess after NHL. NHL treatments[98,146] and immune dysfunction related to the development of NHL[9,10] have been hypothesized to play a role in these increased second cancer risks. However, previous studies have lacked the data necessary to investigate NHL treatments and immune-related medical conditions as major risk factors for second melanoma, lung cancer, and AML/MDS after NHL.

By utilizing a large scale population based linkage of cancer registry and medical claims data, I show for the first time that lung cancer, melanoma, and AML/MDS have complex multifactorial etiologies with contributions from both NHL treatment and immune dysfunction. I have shown

that specific chemotherapeutic agents, namely fludarabine and to a lesser extent cyclophosphamide, are associated with increased risk of second melanoma, lung cancer, and AML/MDS. I also identified numerous autoimmune conditions and infections that were associated with increased risk of second malignancies after NHL, particularly T-cell mediated diseases and melanoma, respiratory conditions and lung cancer, and B-cell and T-cell mediated autoimmune conditions and various infections and AML/MDS.

I confirm and extend our understanding of treatment effects on second cancers after NHL, particularly for fludarabine which appeared to be the primary agent responsible for treatment-related increased risks. I found increased melanoma risks after CLL/SLL among patients who received infused fludarabine-containing chemotherapy with or without rituximab. Similarly, in my second study, I also found increased 2-fold subsequent lung cancer risks among CLL/SLL survivors who received fludarabine-containing chemotherapy without rituximab. Furthermore, fludarabine- and rituximab-containing chemotherapy without cyclophosphamide also showed higher increased risks of subsequent AML/MDS. Although the exact mechanism of action of fludarabine in the induction of second malignancies is unknown, the increased second cancer risks may be due to the broad immunosuppressive and DNA-damaging effects of fludarabine combined with the inherent predisposition to malignancy among CLL/SLL patients.[143,186,194,218] I also saw elevated risks of second malignancies among NHL survivors who were treated with cyclophosphamide-containing chemotherapy, particularly for second lung cancers among DLBCL survivors. Although fludarabine and cyclophosphamide belong to different classes of chemotherapeutic agents, both are associated with direct DNA damaging effects as well as immunosuppression, both of which may plausibly contribute to increased risks of second malignancies.[194,218,219] With particular regards to subsequent AML/MDS risks, fludarabine combined with cyclophosphamide has been hypothesized to have a synergistic effect that is

likely related to the DNA damage induced by the alkylating agent and the inhibition of subsequent DNA repair by fludarabine.[45]

In contrast to the numerous associations I observed between different chemotherapy agents and second cancer risks, I did not observe any increased risks of second malignancies after radiotherapy for NHL; however, the lack of detailed information on radiotherapy including dose and field limited my analyses.

My findings provided the first evidence showing that various autoimmune conditions and infections are related to second malignancy risks among NHL survivors; however the patterns of association differed for the three outcomes I considered. I found significantly elevated risks associated with T-cell activating autoimmune diseases diagnosed before and after CLL/SLL including Graves' disease, psoriasis, chronic rheumatic heart disease, localized scleroderma, and asthma. CLL/SLL patients especially tend to have severe and chronic immune dysfunction that is characterized by poor T-cell function,[143,186] and my findings support the importance of T-cell dysfunction as a contributor to melanoma risk after CLL/SLL, especially since melanoma is an immune-dependent tumor.[9,10,48,138,148,197-199] In contrast, among patients with other NHLs not including CLL/SLL, melanoma risk was not associated with specific treatments or with T-cell/B-cell activating autoimmune diseases, findings which may further support the role of T-cell function in CLL/SLL patients. Similar to second melanoma, pernicious anemia, Graves' disease, and localized scleroderma were associated with subsequent risks of AML/MDS. These conditions could share common genetic predispositions with AML and MDS;[145,226,245,271-273] however it is more likely that treatments given to these patients for these conditions play a role in AML/MDS development.[145,226,271,272] Among second lung cancers, the role of autoimmune conditions was not as clear. I observed increased risks for B-cell activating autoimmune conditions occurring after DLBCL, particularly rheumatoid arthritis, as well as for T-cell

activating conditions diagnosed after other NHL subtypes, particularly asthma. In contrast, T-cell activating autoimmune conditions were significantly inversely associated after FL, likely driven by skin autoimmune conditions, particularly localized scleroderma. However the biological mechanisms behind these inverse associations are not clear; therefore additional research is needed to identify any immune-related mechanisms, particularly as potential risk factors for second lung cancer.

Infections appeared to have direct effects on immune function with regards to second lung cancer and AML/MDS, but did not play a major role in second melanoma. Previous studies have implicated respiratory infections as risk factors for lung cancer,[274,275] and I expand on this with my findings of increased risks of second lung cancer associated with lower airway respiratory infections, particularly pneumonia, diagnosed before and after all NHL subtypes. Additionally, the risks remained elevated after restrictions to diagnoses that occurred at least 2 years prior to the lung cancer ruling out reverse causality as an explanation for my findings. Serious respiratory infections such as pneumonia can repeatedly initiate an immune response in which cellular proliferation associated with tissue repair can lead to errors in chromosomal replication and can produce further DNA damage.[274,275] Furthermore, tissue repair including angiogenesis can induce inflammation in the lungs which can initiate or promote lung cancer development.[274,275] Previous studies also have suggested that various infections including respiratory infections, particularly sinusitis and pneumonia, increased the risk of developing AML/MDS,[145,271,277] and generally my findings for second AML/MDS were consistent with those associations although I had more elevated risks. Other associations between infections and AML/MDS have been identified, particularly skin conditions (herpes zoster), urinary tract infections (prostatitis and cystitis/pyelonephritis), and gastroenteritis,[145,271,277] which match the associations I found in my study; however, the magnitude of our risks were much higher compared to previous studies. It remains unclear how infections can increase the risk of

AML/MDS, but underlying immune dysfunction could predispose NHL survivors to AML/MDS,[145,277] antigenic stimulation could be the driving mechanism behind AML/MDS development,[187,272,278,279] or my findings could indicate additional immunosuppression combined with an early stage of an immunocompromised state in the process of malignant transformation.[145] Overall, I provide the first evidence that infections can contribute to the development of second malignancies after NHL, and my findings highlight the importance of localized inflammation initiated by immune-related medical conditions in lung carcinogenesis after NHL, as well as suggest immune disruption in the development of second AML/MDS.

In some of my analyses, the pattern of second cancer risk factors differed for survivors of different subtypes of NHL. CLL/SLL survivors had higher risks for developing second melanoma and lung cancer compared to survivors with other NHL subtypes. CLL/SLL is an indolent lymphoma and not all of these patients are treated at time of diagnosis. Currently the treatment recommendation for early stage CLL/SLL is observation whereas later stage CLL/SLL is often treated with fludarabine-containing regimens, particularly during the years included in our study period.[194] Other NHL subtypes, particularly DLBCL and FL, are treated with different standard regimens such as R-CHOP with or with radiotherapy. It appears the inherent immunosuppression characteristic of CLL/SLL survivors, which is different from the natural histories of other NHL subtypes, combined with fludarabine treatment increases the risk of second cancers. I also found differences between the NHL subtypes with regards to autoimmune conditions and infections. CLL/SLL survivors experience profound and prolonged immune dysfunction which is characterized by defective B- and T-cell function, which contributes to increased risk of infections and autoimmune diseases.[143,186] I saw a clear relationship between these immune-related medical conditions and second melanoma since deficient T-cell function appeared to play a major role in the various increased risk associations with various T-cell activating conditions. In contrast, the relationships between

other NHL subtypes and second cancers are not as clear. I found a two-fold increased risk of lung cancer among survivors of DLBCL and other NHL subtypes who received cyclophosphamide as part of their treatment; however I found no significant associations between melanoma risk and treatment for other NHL subtypes aside from one non-significant elevation in risk among these survivors who received cyclophosphamide. I found little evidence that T- or B-cell activating autoimmune conditions and infections were related to subsequent melanoma after other NHL subtypes, raising the possibility that these conditions may only contribute to second melanoma after NHL in an environment of extreme immunosuppression found among CLL/SLL survivors. Additionally, while I observed various associations between immune-related medical conditions and subsequent lung cancer after all other NHL subtypes, particularly for respiratory infections, no other clear patterns of immune dysfunction observed among the different NHL subtypes.

Various limitations impacted all three analyses including lack of detailed treatment data, lack of genetic and lifestyle risk factors, inability to generalize to younger populations, potential misclassification of infections and autoimmune conditions, and underreporting of second malignancies. My main limitation was the lack of information on oral chemotherapy agents, particularly chlorambucil, which was one of the main treatments given to CLL/SLL patients in the early years of our study period.[45] Specifically, the lack of detailed chlorambucil data is a confounder and can bias the observed fludarabine results toward the null, making the true strength of the association between fludarabine treatment for primary CLL/SLL land second melanoma development. However, as a result, my treatment-related risk estimates, especially those regarding fludarabine, are likely to be conservative since patients who received chlorambucil were included in the referent group. I could only obtain information on risk factors that generated a medical billing claim; therefore I was unable to ascertain information on risk factors pertaining to genetics or lifestyle (e.g. smoking, sun exposure). These

limitations could also act as confounders which would alter the associations; however, I was able to adjust for residence as a proxy for sun exposure in my melanoma analyses because it has been previously shown to be a valid.[183] Similarly, I combined the prevalence of chronic obstructive pulmonary disorder with the history of tobacco use in my study population to create a proxy for smoking in my lung analyses as done in previous studies.[11,214] However, there is likely residual confounding, particularly due to the lack of specific data on smoking status, duration and intensity, all of which are important predictors of lung cancer risk. Patients may also have had misclassified exposures because we could not capture information on infections and autoimmune diseases if diagnosed prior to their entry into Medicare. It is possible that patients who had developed the specific infections and autoimmune diseases before their entered Medicare would be misclassified if they did not have additional Medicare claims regarding those conditions, leading to nondifferential misclassification of the exposures that would minimize the associations I observed. Information on mild infections for which patients did not seek medical care would also not be captured in Medicare, also leading to nondifferential misclassification that would bias my results towards the null. SEER-Medicare primarily collections information patients 65 years and older; therefore, this dataset cannot be used to evaluate risk factors that arise earlier in life or among younger NHL survivors, thus limiting the generalizability of our findings to younger populations. Lastly, second cancers can be underreported due to survivors leaving the SEER registry catchment areas; however, my risk estimates should not be affected since this underreporting is unlikely to be related to any of the risk factors I assessed in our studies.

The primary strength of these studies was analyses of a large population-based cohort to identify specific risk factors for second malignancy after first primary NHL. Furthermore, I present the first analytic studies to consider non-treatment risk factors, and I had the ability to explore whether the second malignancy risks differed by NHL subtype. The cohort study design

also provided long-term follow-up for exposure assessment and second malignancy ascertainment, as well as eliminated selection bias since all subjects in the cohort developed a first primary NHL and there was no opportunity to decline to participate since it was a records-based study.

Future Directions

My studies were the first to provide evidence that specific chemotherapy agents and immune-related conditions increased second melanoma, lung cancer, and AML/MDS, and have furthered the understanding of second malignancies after NHL. My findings warrant replication in additional studies, particularly by expanding on my findings by involving younger populations, improved exposure assessment, and better understanding of biological mechanisms underlying the effects of treatment and various medical conditions. It would be informative to reexamine our results in a younger population to see if the associations I saw in my studies would be different in a younger population compared to the older adults. I focused on analyses involving the elderly due to the availability of Medicare claims data to assess information regarding our risk factors of interest. As of today a comparable national database for younger populations in the US is not readily available, but data derived from private health insurance plans could potentially be utilized for this research. The use of this data might provide more detailed and complete information especially regarding autoimmune conditions and infections that arise earlier in life before NHL diagnosis.

Future studies can incorporate more information on lifestyle risk factors such as smoking and sun exposure, detailed treatment data including dose and irradiated fields, and genetic data such as family history of specific cancers[33] to help provide a clearer picture of the associations I

found in my study. As of today I have not identified a potential dataset where I could address these concerns; however, I provided proxies to measure for specific lifestyle risk factors associated with the second malignances I evaluated in my studies. Additional data on smoking exposure (e.g. duration in pack-years, age when smoking initiated, number of packs per day, etc.) would help determine how smoking status affects the risk of developing second lung cancer. Similarly, additional information on sun exposure (e.g. occupation, sunscreen use, time spent outdoors, etc.) would also help clarify subsequent melanoma risks due to immunosuppression via the risk factors of interest versus risks due to UV radiation.

SEER currently does not collect information cancer treatment other than the first course of treatment, but even this information lacks specific drugs used, dosages of the drugs, and duration of use. Medicare was used to ascertain initial and subsequent treatments, but due to the nature of the billing claims database, specific dose information for chemotherapy and radiotherapy as well as specific irradiated field information is lacking. Future research can expand on my associations by potentially establishing a dose-response relationship for the chemotherapy regimens I highlighted to be associated with increased risks of second malignancies, namely fludarabine and potentially cyclophosphamide.

Additional future analyses can also consider accounting for multiple infections and autoimmune conditions. Although I was able to account for reverse causality in my study by assessing infections diagnosed one to two years before second malignancy, I was limited in my analyses to determine the duration of the infections I included in my studies. Therefore I was not able to classify repeated infections of the same type. The creation of a score index that accounted for various infections could provide a more accurate reflection of an individual's immune dysfunction than consideration of single infections separately. This is particularly important

for second malignancies such as second lung cancer, where it is suggested that their medical condition status has a direct effect on their immune function.

More research is needed on the mechanisms of immune dysfunction in relation to autoimmune conditions and infections, and studies that could include identify and measure additional biomarkers may help elucidate those biological mechanisms underlying the immunosuppression in NHL survivors. While I have an established understanding of B- and T-cell immune function among the various autoimmune conditions and infections,[178-182] it is will unknown how all of these conditions directly or indirectly disrupt the immune process. Better understanding of the biological mechanisms underlying these various medical conditions either separately or in conjunction with treatment-related immune dysfunction can help determine the level of risks of developing a second malignancy.

Public Health Implications

Advances in diagnoses and treatments have provided NHL survivors with improved prognoses; however, these survivors experience numerous complications of their disease and treatment. As evidenced in numerous previous studies and concurrent with my study, NHL survivors have high risks of developing second cancers. With the increasing number of NHL survivors, it was important to better understand the associations between NHL treatments and specific medical conditions and the risk of developing second melanoma, lung cancer, and AML/MDS in my studies. My studies have provided valuable information regarding risks that can be considered when evaluating the risks and benefits of screening, particularly for melanoma and lung cancer. It is clear that more studies are needed to examine other second malignancy risks in this high risk population. Furthermore, my findings highlight the importance of better understanding how these different risk factors fit together to elevate second malignancy risks

among other high risk population of primary cancer survivors so that we can expand our current knowledge of the etiology of second malignancies. The findings from these studies can be used to better inform clinicians and their patients about treatment options and follow-up monitoring for their first cancers to improve long term health outcomes for these patients.

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Appendices

Appendix 1 – Additional Tables for Risk Factors for Melanoma Among Survivors of Non-Hodgkin Lymphoma

Supplementary Table 1. Frequency of receipt and medical claim codes for specific chemotherapeutic agents

		Total NHL		Melanoma cases*	
Chemotherapy	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**
Patients diagnosed with first primary CLL/SLL					
Most common agents					
Cyclophosphamide	J8530, J9070, J9080, J9090-J9097	2,402	17.2	19	20.9
Fludarabine	J9185	2,958	21.2	28	30.8
Rituximab	J9310	3,744	26.8	27	29.7
Plant Alkaloids					
Vincristine	J9370, J9375, J9380	1,590	11.4	13	14.3
Patients diagnosed with first primary NHL other than CLL/SLL					
Most common agents					
Cyclophosphamide	J8530, J9070, J9080, J9090-J9097	16,786	54.3	68	61.3
Rituximab	J9310	15,726	50.9	53	47.8
Antimetabolites					
Topoisomerases II inhibitors					
Doxorubicin	J9000-J9001	12,115	39.2	56	50.5
Plant Alkaloids					
Vincristine	J9370, J9375, J9380	16,365	52.9	63	56.8
Colony Stimulating Factors					
G-CSF	J1440-J1441	7,027	22.7	26	23.4

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); granulocyte colony-stimulating factor (G-CSF); granulocyte colony-stimulating factor (GM-CSF); Healthcare Common Procedure Coding System (HCPCS); Current Procedural Technology (CPT); non-Hodgkin lymphoma (NHL).

* Counts and percentages are not reported when less than 10 melanoma cases to protect patient confidentiality. Chemotherapy agents with less than 10 melanoma cases include aldesleukin, alemtuzumab, idarubicin, ixabepilone, asparaginase, azacitidine, bendamustine, bevacizumab, bleomycin, bortezomib, busulfan, carboplatin, carmustine, cetuximab, cisplatin, cladribine, clofarabine, cytarabine, dacarbazine, dactinomycin, daunorubicin, decitabine, denileukin, diftitox, docetaxel, epirubicin, etoposide, floxuridine, fluorouracil, gefitinib, gemcitabine, gemtuzumab, GM-CSF, ibritumomab, ifosfamide, interferons (1B, 2A, 2B, A1, N3), irinotecan, leucovorin, lomustine, mechlorethamine, melphalan, methotrexate, mitomycin, mitoxantrone, nelarabine, oxaliplatin, paclitaxel, panitumumab, pegaspargase, pemetrexed, pentostatin, plicamycin, streptozocin, temsirolimus, teniposide, thiotepa, topotecan, tositumomab, trastuzumab, valrubicin, vinblastine, and vinorelbine.

~ Information on oral chemotherapy agents not captured in study include capecitabine, chlorambucil, cyclophosphamide, levamisole, procarbazine, and temozolomide.

Supplementary Table 2. Frequency of diagnosis and medical claim codes for autoimmune conditions

		Total NHL				Melanoma cases			
		Prior to NHL		After NHL*		Prior to NHL		After NHL*	
Autoimmune conditions	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients diagnosed with first primary CLL/SLL									
B-cell activating conditions †	conditions below	2,263	16.2	3,637	26.1	<10	~	13	14.3
T-cell activating conditions †	conditions below	5,488	39.3	6,749	48.4	36	39.6	49	53.9
By organ system involved									
Systemic/connective tissue		1,687	12.1	1,912	13.7	<10	~	<10	~
Ankylosing spondylitis	720	321	2.3	377	2.7	<10	~	<10	~
Dermatomyositis/polymyositis	710.3, 710.4	37	0.3	39	0.3	<10	~	<10	~
Felty's syndrome	714.1	15	0.1	15	0.1	<10	~	<10	~
Systemic lupus erythematosus	710	348	2.5	424	3.0	<10	~	<10	~
Polymyalgia rheumatica	725	256	1.8	295	2.1	<10	~	<10	~
Reactive arthritis	99.3	<10	~	<10	~	<10	~	<10	~
Rheumatic fever	390-392	46	0.3	52	0.4	<10	~	<10	~
Rheumatoid arthritis	714	981	7.0	1,037	7.4	<10	~	<10	~
Sarcoidosis	135	35	0.3	43	0.3	<10	~	<10	~
Sjogren's syndrome	710.2	123	0.9	128	0.9	<10	~	<10	~
Systemic sclerosis/scleroderma	710.1	17	0.1	24	0.2	<10	~	<10	~
Cardiovascular		1,367	9.8	2,370	17.0	<10	~	15	16.5
Chronic rheumatic heart disease	393-398	1,219	8.7	2,187	15.7	<10	~	15	16.5
Giant cell arteritis	446.5	127	0.9	134	1.0	<10	~	<10	~
Systemic vasculitis	446,447.60	174	1.3	239	1.7	<10	~	<10	~
Endocrine		931	6.7	1,213	8.7	<10	~	<10	~
Addison's disease	255.4	71	0.5	242	1.7	<10	~	<10	~
Chronic thyroiditis/Hashimoto	245.2	103	0.7	134	1.0	<10	~	<10	~
Graves' disease	242	783	5.6	872	6.3	<10	~	<10	~
Primary biliary cirrhosis	571.6	12	0.1	23	0.2	<10	~	<10	~
Skin		2,222	15.9	2,402	17.2	18	19.8	21	23.1
Alopecia areata	704.1	25	0.2	55	0.4	<10	~	<10	~
Dermatitis herpetiformis	694	56	0.4	114	0.8	<10	~	<10	~
Discoid lupus erythematosus	695.4	34	0.2	38	0.3	<10	~	<10	~
Localized scleroderma	701	1,809	13.0	1,924	13.8	12	13.2	13	14.3
Psoriasis	696	445	3.2	431	3.1	<10	~	<10	~
Gastrointestinal		1,435	10.3	2,926	21.0	<10	~	<10	~
Celiac disease	579	149	1.1	203	1.5	<10	~	<10	~
Crohn's disease	555	105	0.8	142	1.0	<10	~	<10	~
Pernicious anemia	281	1,119	8.0	2,548	18.3	<10	~	<10	~
Ulcerative colitis	556	187	1.3	255	1.8	<10	~	<10	~
Nervous system		110	0.8	180	1.3	<10	~	<10	~
Amyotrophic sclerosis	335.2	10	0.1	48	0.3	<10	~	<10	~
Multiple sclerosis	340	54	0.4	69	0.5	<10	~	<10	~
Myasthenia gravis	358	50	0.4	69	0.5	<10	~	<10	~
Respiratory (Asthma)	493	1,919	13.8	2,484	17.8	13	14.3	18	19.8
Autoimmune disease, NOS	279.4	32	0.23	64	0.5	<10	~	<10	~

Supplementary Table 2 continued. Frequency of diagnosis and medical claim codes for autoimmune conditions

		Total NHL				Melanoma cases			
		Prior to NHL		After NHL*		Prior to NHL		After NHL*	
Autoimmune conditions	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients diagnosed with first primary NHL other than CLL/SLL									
B-cell activating conditions †	conditions below	6,013	19.5	8,078	26.1	16	14.4	24	21.6
T-cell activating conditions †	conditions below	13,142	42.5	15,201	49.2	36	32.4	35	31.5
By organ system involved									
Systemic/connective tissue		4,798	15.5	4,734	15.3	<10	~	<10	~
Ankylosing spondylitis	720	790	2.6	853	2.8	<10	~	<10	~
Dermatomyositis/polymyositis	710.3, 710.4	126	0.4	113	0.4	<10	~	<10	~
Felty's syndrome	714.1	32	0.1	31	0.1	<10	~	<10	~
Systemic lupus erythematosus	710	1,146	3.7	1,189	3.9	<10	~	<10	~
Polymyalgia rheumatica	725	727	2.4	671	2.2	<10	~	<10	~
Reactive arthritis	99.3	12	0.0	<10	~	<10	~	<10	~
Rheumatic fever	390-392	78	0.3	99	0.3	<10	~	<10	~
Rheumatoid arthritis	714	2,961	9.6	2,658	8.6	<10	~	<10	~
Sarcoidosis	135	144	0.5	180	0.6	<10	~	<10	~
Sjogren's syndrome	710.2	446	1.4	495	1.6	<10	~	<10	~
Systemic sclerosis/scleroderma	710.1	99	0.3	106	0.3	<10	~	<10	~
Cardiovascular		3,212	10.4	5,527	17.9	<10	~	<10	~
Chronic rheumatic heart disease	393-398	2,771	9.0	5,071	16.4	<10	~	<10	~
Giant cell arteritis	446.5	368	1.2	355	1.2	<10	~	<10	~
Systemic vasculitis	446,447.60	521	1.7	585	1.9	<10	~	<10	~
Endocrine		2,419	7.8	2,947	9.5	<10	~	<10	~
Addison's disease	255.4	146	0.5	586	1.9	<10	~	<10	~
Chronic thyroiditis/Hashimoto	245.2	307	1.0	441	1.4	<10	~	<10	~
Graves' disease	242	2,042	6.6	2,067	6.7	<10	~	<10	~
Primary biliary cirrhosis	571.6	34	0.1	56	0.2	<10	~	<10	~
Skin		5,648	18.3	5,394	17.5	23	20.7	18	16.2
Alopecia areata	704.1	47	0.2	50	0.2	<10	~	<10	~
Dermatitis herpetiformis	694	173	0.6	214	0.7	<10	~	<10	~
Discoid lupus erythematosus	695.4	151	0.5	135	0.4	<10	~	<10	~
Localized scleroderma	701	4,265	13.8	4,110	13.3	22	19.8	17	15.3
Psoriasis	696	1,465	4.7	1,357	4.4	<10	~	<10	~
Gastrointestinal		3,458	11.2	6,043	19.5	10	9.0	15	13.5
Celiac disease	579	364	1.2	507	1.6	<10	~	<10	~
Crohn's disease	555	291	0.9	372	1.2	<10	~	<10	~
Pernicious anemia	281	2,635	8.5	5,068	16.4	<10	~	<10	~
Ulcerative colitis	556	469	1.5	612	2.0	<10	~	<10	~
Nervous system		194	0.6	379	1.2	<10	~	<10	~
Amyotrophic sclerosis	335.2	30	0.1	77	0.3	<10	~	<10	~
Multiple sclerosis	340	69	0.2	145	0.5	<10	~	<10	~
Myasthenia gravis	358	102	0.3	163	0.5	<10	~	<10	~
Respiratory (Asthma)	493	4,338	14.0	5,133	16.6	<10	~	<10	~
Autoimmune disease, NOS	279.4	120	0.4	161	0.5	<10	~	<10	~

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); Current Procedural Technology (CPT); Healthcare Common Procedure Coding System (HCPCS); not otherwise specified (NOS).

~ Counts and percentages are not reported for less than 10 melanoma cases to protect patient confidentiality.

* New claims occurring after NHL but prior to second cancer, death, end of study, or loss to follow-up, with no claims prior to NHL.

† B-cell activating conditions include rheumatoid arthritis, Sjogren's syndrome, discoid lupus erythematosus, reactive arthritis, Felty's syndrome, chronic thryoiditis, systemic/discoid lupus erythematosus, pernicious anemia, and myasthenia gravis. T-cell activating conditions include ankylosing spondylitis, dermatomyositis, polymyalgia rheumatica, sarcoidosis, systemic sclerosis, rheumatic fever, chronic rheumatic heart disease, giant cell arteritis, systemic vasculitis, Addison's disease, Graves' disease, primary biliary cirrhosis, alopecia areata, localized scleroderma, dermatitis herpetiformis, psoriasis, celiac disease, Crohn's disease, ulcerative colitis, amyotrophic sclerosis, multiple sclerosis, and asthma. Hematologic autoimmune conditions (e.g., autoimmune hemolytic anemia, thrombocytopenia) were excluded from consideration because of difficulty distinguishing these diagnoses from manifestations of chemotherapy toxicity.

Supplementary Table 3. Frequency of diagnosis and medical claim codes for infections

		Total NHL				Melanoma cases			
		Prior to NHL		After NHL *		Prior to NHL		After NHL *	
Infections	HCPCS/CPT codes	N	%	N	%	N	%	N	%
Patients diagnosed with first primary CLL/SLL									
Respiratory - upper airway		5,847	41.9	5,850	41.9	35	38.5	35	38.5
Laryngitis	464-464.4, 476-476.1	593	4.3	614	4.4	<10	~	<10	~
Otitis media	017.4, 055.2, 381.0-381.4, 382, 383.0-383.1	1,621	11.6	1,514	10.9	<10	~	<10	~
Pharyngitis	462,472.1	2,141	15.4	2,143	15.4	10	11.0	11	12.1
Sinusitis	461,473	4,074	29.2	4,238	30.4	24	26.4	29	31.9
Respiratory - lower airway		6,122	43.9	8,347	59.8	37	40.7	41	45.1
Acute bronchitis	466	4,526	32.4	5,081	36.4	27	29.7	34	37.4
Influenza	487	783	5.6	821	5.9	<10	~	<10	~
Pneumonia	480-486, 770	2,872	20.6	6,414	46.0	16	17.6	21	23.1
Tuberculosis	010-018	122	0.9	150	1.1	<10	~	<10	~
Skin		2,125	15.2	3,490	25.0	17	18.7	21	23.1
Cellulitis	682.9	1,191	8.5	1,948	14.0	11	12.1	11	12.1
Herpes zoster	53	1,079	7.7	1,958	14	<10	~	13	14.3
Urinary tract		6,227	44.6	7,942	56.9	39	42.9	46	50.6
Cystitis/pyelonephritis, UTI	599	5,630	40.4	7,599	54.5	34	37.4	40	44.0
Prostatitis †	601	1,554	20.5	1,199	15.8	17	23.0	14	18.9
Gastrohepatic		2,084	14.9	2,594	18.6	11	12.1	12	13.2
Gastroenteritis	558.9	2,020	14.5	2,445	17.5	11	12.1	11	12.1
HBV	070.2-070.3	36	0.3	96	0.7	<10	~	<10	~
HCV	070.4, 070.5, 070.7	51	0.4	133	1.0	<10	~	<10	~
Patients diagnosed with first primary NHL other than CLL/SLL									
Respiratory - upper airway		13,016	42.1	11,944	38.6	41	36.9	40	36.0
Laryngitis	464-464.4, 476-476.1	1,467	4.7	1,390	4.5	<10	~	<10	~
Otitis media	017.4, 055.2, 381.0-381.4, 382, 383.0-383.1	3,400	11.0	2,857	9.2	11	9.9	<10	~
Pharyngitis	462,472.1	4,800	15.5	4,299	13	18	16.2	12	10.8
Sinusitis	461,473	9,109	29.5	8,120	26.3	30	27.0	26	23.4
Respiratory - lower airway		13,047	42.2	16,711	54.1	41	36.9	46	41.4
Acute bronchitis	466	9,819	31.8	9,358	30.3	30	27.0	27	24.3
Influenza	487	1,707	5.5	1,531	5.0	<10	~	<10	~
Pneumonia	480-486, 770	5,667	18.3	12,383	40.1	27	24.3	25	22.5
Tuberculosis	010-018	315	1.0	454	1.5	<10	~	<10	~
Skin		4,501	14.6	7,025	22.7	13	11.7	15	13.5
Cellulitis	682.9	2,465	8.0	3,762	12.2	<10	~	11	9.9
Herpes zoster	53	2,295	7.4	3,980	12.9	<10	~	<10	~
Urinary tract		14,162	45.8	17,462	56.5	53	47.8	54	48.7
Cystitis/pyelonephritis, UTI	599	12,837	41.5	16,759	54.2	39	35.1	51	46.0
Prostatitis †	601	3,168	21.8	2,154	14.9	19	25.0	<10	~
Gastrohepatic		4,880	15.8	5,926	19.2	14	12.6	21	18.9
Gastroenteritis	558.9	4,689	15.2	5,556	18.0	13	11.7	19	17.1
HBV	070.2-070.3	95	0.3	198	0.6	<10	~	<10	~
HCV	070.4, 070.5, 070.7	196	0.6	336	1.1	<10	~	<10	~

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); Current Procedural Technology (CPT); Healthcare Common Procedure Coding System (HCPCS); hepatitis B virus (HBV); hepatitis C virus (HCV); International Classification of Diseases (ICD); urinary tract infection (UTI).

~ Counts and percentages are not reported for less than 10 melanoma cases to protect patient confidentiality.

* New claims occurring after NHL but prior to second cancer, death, end of study, or loss to follow-up, with no claims prior to NHL.

† Among males only.

Supplementary Table 4. Risk of melanoma after first primary NHL, by subtype

	Total NHL				CLL/SLL				Other NHL subtypes			
	N	%	HR*	95% CI	N	%	HR*	95% CI	N	%	HR*	95% CI
Sex												
Male	22,097	49.3	1.00	Referent	7,590	54.4	1.00	Referent	14,507	46.9	1.00	Referent
Female	22,773	50.8	0.32	0.23-0.44	6,360	45.6	0.25	0.15-0.42	16,413	53.1	0.38	0.25-0.57
Race												
White	40,752	90.8	1.00	Referent	12,841	92.1	1.00	Referent	27,911	90.3	1.00	Referent
Other/unknown	4,118	9.2	0.31	0.14-0.70	1,109	7.9	0.13	0.02-0.96	3,009	9.7	0.42	0.17-1.03
Residence at time of NHL diagnosis †												
North	20,348	45.4	1.00	Referent	6,691	48.0	1.00	Referent	13,657	44.2	1.00	Referent
Central	12,778	28.5	1.02	0.72-1.46	3,727	26.7	1.18	0.70-1.99	9,051	29.3	0.94	0.58-1.52
South	11,744	26.2	1.41	1.02-1.95	3,532	25.3	1.46	0.90-2.39	8,212	26.6	1.36	0.88-2.11
NHL subtype												
DLBCL	10,311	23.0	1.00	Referent								
CLL/SLL	13,950	31.1	1.67	1.12-2.48								
FL	7,437	16.6	1.28	0.80-2.06								
MZ	3,516	7.8	0.90	0.44-1.83								
Other	9,656	21.5	0.98	0.60-1.58								

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); confidence interval (CI); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); hazard ratio (HR); marginal zone lymphoma (MZL); non-Hodgkin lymphoma (NHL).

* HR (95% CI) adjusted for sex, race, residence, and follow-up time (time-dependent covariate) and stratified by calendar year. Age was used as the time scale.

† Residence defined by SEER registry areas, including north (Connecticut, Detroit, Iowa, Seattle, and New Jersey), central (San Francisco, Utah, San Jose, Greater California, and Kentucky), and south (Hawaii, New Mexico, Atlanta, Los Angeles, Rural Georgia, Greater Georgia, and Louisiana).

Appendix 2 – Additional Tables for Risk Factors for Second Lung Cancers Among Survivors of Non-Hodgkin Lymphoma

Supplementary Table 1. Frequency of receipt and medical claim codes for specific infused chemotherapeutic agents

		Total NHL		Lung cancer cases*	
Infused chemotherapy	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**
Patients diagnosed with first primary CLL/SLL					
Most common agents					
Cyclophosphamide	J8530, J9070, J9080, J9090-J9097	2,402	17.2	29	11.2
Fludarabine	J9185	2,958	21.2	55	21.2
Rituximab	J9310	3,744	26.8	52	20.1
Plant Alkaloids					
Vincristine	J9370, J9375, J9380	1,590	11.4	20	7.7
Colony Stimulating Factors					
G-CSF	J1440-J1441	1,421	10.2	17	6.6
Patients diagnosed with first primary DLBCL					
Most common agents					
Cyclophosphamide	J8530, J9070, J9080, J9090-J9097	8,350	81.0	104	89.7
Rituximab	J9310	6,552	63.5	63	54.3
Topoisomerases II inhibitors					
Doxorubicin	J9000-J9001	7,077	68.6	90	77.6
Mitoxantrone	J9293	883	8.6	10	8.6
Plant Alkaloids					
Vincristine	J9370, J9375, J9380	8,185	79.4	105	90.5
Colony Stimulating Factors					
G-CSF	J1440-J1441	3,225	31.3	39	33.6
Patients diagnosed with first primary FL					
Most common agents					
Cyclophosphamide	J8530, J9070, J9080, J9090-J9097	3,845	51.7	59	46.5
Fludarabine	J9185	945	12.7	13	10.2
Rituximab	J9310	4,206	56.6	56	44.1
Topoisomerases II inhibitors					
Doxorubicin	J9000-J9001	2,237	30.1	33	26.0
Plant Alkaloids					
Vincristine	J9370, J9375, J9380	3,736	50.2	58	45.7
Colony Stimulating Factors					
G-CSF	J1440-J1441	1,489	20.0	17	13.4

Supplementary Table 1 continued. Frequency of receipt and medical claim codes for specific infused chemotherapeutic agents

		Total NHL		Lung cancer cases*	
Infused chemotherapy	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**
Patients diagnosed with other first primary NHL					
Most common agents					
Cyclophosphamide	J8530, J9070, J9080, J9090-J9097	4,591	34.9	62	31.3
Fludarabine	J9185	1,324	10.1	20	10.1
Rituximab	J9310	4,968	37.7	51	25.8
Topoisomerases II inhibitors					
Doxorubicin	J9000-J9001	2,801	21.3	40	20.2
Mitoxantrone	J9293	680	5.2	11	5.6
Plant Alkaloids					
Vincristine	J9370, J9375, J9380	4,444	33.7	60	30.3
Colony Stimulating Factors					
G-CSF	J1440-J1441	2,313	17.6	27	13.6

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); granulocyte colony-stimulating factor (G-CSF); granulocyte macrophage colony-stimulating factor (GM-CSF); Healthcare Common Procedure Coding System (HCPCS); Current Procedural Technology (CPT); non-Hodgkin lymphoma (NHL).

* Counts and percentages are not reported when less than 10 lung cases to protect patient confidentiality. Chemotherapy agents with less than 10 lung cases include aldesleukin, alemtuzumab, idarubicin, ixabepilone, asparaginase, azacitidine, bendamustine, bevacizumab, bleomycin, bortezomib, busulfan, carboplatin, carmustine, cetuximab, cisplatin, cladribine, clofarabine, cytarabine, dacarbazine, dactinomycin, daunorubicin, decitabine, denileukin, diftitox, docetaxel, epirubicin, etoposide, floxuridine, fluorouracil, gefitinib, gemcitabine, gemtuzumab, GM-CSF, ibritumomab, ifosfamide, interferons (1B, 2A, 2B, A1, N3), irinotecan, leucovorin, lomustine, mechlorethamine, melphalan, mesna, methotrexate, mitomycin, nelarabine, oxaliplatin, paclitaxel, panitumumab, pegaspargase, pemetrexed, pentostatin, plicamycin, streptozocin, temsirolimus, teniposide, thiotepa, topotecan, tositumomab, trastuzumab, valrubicin, vinblastine, and vinorelbine.

~ Information on oral chemotherapy agents not captured in study include capecitabine, chlorambucil, cyclophosphamide, levamisole, procarbazine, and temozolomide.

Supplementary Table 2. Frequency of diagnosis and medical claim codes for infections

		Total NHL				Lung cancer cases			
		Prior to NHL		After NHL *		Prior to NHL		After NHL *	
Infections	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients diagnosed with first primary CLL/SLL									
Respiratory - upper airway		5,847	41.9	5,850	41.9	100	38.6	96	37.1
Laryngitis	464-464.4, 476-476.1	593	4.3	614	4.4	<10	~	<10	~
Otitis media	017.4, 055.2, 381.0-381.4, 382, 383.0-383.1	1,621	11.6	1,514	10.9	21	8.1	23	8.9
Pharyngitis	462,472.1	2,141	15.4	2,143	15.4	31	12.0	41	15.8
Sinusitis	461,473	4,074	29.2	4,238	30.4	76	29.3	71	27.4
Respiratory - lower airway		6,122	43.9	8,347	59.8	121	46.7	165	63.7
Acute bronchitis	466	4,526	32.4	5,081	36.4	87	33.6	102	39.4
Influenza	487	783	5.6	821	5.9	13	5.0	10	3.9
Pneumonia	480-486, 770	2,872	20.6	6,414	46.0	63	24.3	125	48.3
Tuberculosis	010-018	122	0.9	150	1.1	<10	~	<10	~
Skin		2,125	15.2	3,490	25.0	46	17.8	66	25.5
Cellulitis	682.9	1,191	8.5	1,948	14.0	23	8.9	43	16.6
Herpes zoster	53	1,079	7.7	1,958	14	25	9.7	29	11.2
Urinary tract		6,227	44.6	7,942	56.9	91	35.1	126	48.7
Cystitis/pyelonephritis UTI	599	5,630	40.4	7,599	54.5	81	31.3	119	46.0
Prostatitis †	601	1,554	20.5	1,199	15.8	17	10.2	25	15.0
Gastrohepatic		2,084	14.9	2,594	18.6	33	12.7	40	15.4
Gastroenteritis	558.9	2,020	14.5	2,445	17.5	32	12.4	37	14.3
HBV	070.2-070.3	36	0.3	96	0.7	<10	~	<10	~
HCV	070.4, 070.5, 070.7	51	0.4	133	1.0	<10	~	<10	~

Supplementary Table 2 continued. Frequency of diagnosis and medical claim codes for infections

		Total NHL				Lung cancer cases			
		Prior to NHL		After NHL *		Prior to NHL		After NHL *	
Infections	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients diagnosed with first primary DLBCL									
Respiratory - upper airway		4,340	42.1	3,884	37.7	44	37.9	34	29.3
Laryngitis	464-464.4, 476-476.1	479	4.7	435	4.2	<10	~	<10	~
Otitis media	017.4, 055.2, 381.0-381.4, 382, 383.0-383.1	1,124	10.9	913	8.9	14	12.1	10	8.6
Pharyngitis	462,472.1	1,621	15.7	1,455	14.1	15	12.9	16	13.8
Sinusitis	461,473	3,005	29.1	2,576	25.0	35	30.2	17	14.7
Respiratory - lower airway		4,242	41.1	5,681	55.1	49	42.2	77	66.4
Acute bronchitis	466	3,212	31.2	2,975	28.9	39	33.6	48	41.4
Influenza	487	565	5.5	512	5.0	<10	~	<10	~
Pneumonia	480-486, 770	1,788	17.3	4,326	42.0	19	16.4	52	44.8
Tuberculosis	010-018	105	1.0	175	1.7	<10	~	<10	~
Skin		1,426	13.8	2,376	23.0	13	11.2	19	16.4
Cellulitis	682.9	785	7.6	1,253	12.2	<10	~	10	8.6
Herpes zoster	53	727	7.1	1,370	13.3	10	8.6	12	10.3
Urinary tract		4,648	45.1	5,902	57.2	39	33.6	50	43.1
Cystitis/pyelonephritis UTI	599	4,230	41.0	5,687	55.2	36	31.0	47	40.5
Prostatitis †	601	1,003	21.2	680	14.4	10	16.7	<10	~
Gastrohepatic		1,577	15.3	1,990	19.3	17	14.7	17	14.7
Gastroenteritis	558.9	1,512	14.7	1,855	18.0	17	14.7	17	14.7
HBV	070.2-070.3	39	0.4	75	0.7	<10	~	<10	~
HCV	070.4, 070.5, 070.7	60	0.6	120	1.2	<10	~	<10	~

Supplementary Table 2 continued. Frequency of diagnosis and medical claim codes for infections

		Total NHL				Lung cancer cases			
		Prior to NHL		After NHL *		Prior to NHL		After NHL *	
Infections	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients diagnosed with first primary FL									
Respiratory - upper airway		3,108	41.8	2,950	39.7	50	39.4	44	34.7
Laryngitis	464-464.4, 476-476.1	359	4.8	358	4.8	<10	~	<10	~
Otitis media	017.4, 055.2, 381.0-381.4, 382, 383.0-383.1	801	10.8	703	9.5	13	10.2	8	6.3
Pharyngitis	462,472.1	1,128	15.2	1,070	14.4	10	7.9	14	11.0
Sinusitis	461,473	2,212	29.7	2,060	27.7	36	28.4	31	24.4
Respiratory - lower airway		2,992	40.2	3,919	52.7	49	38.6	70	55.1
Acute bronchitis	466	2,248	30.2	2,344	31.5	35	27.6	34	26.8
Influenza	487	365	4.9	357	4.8	<10	~	<10	~
Pneumonia	480-486, 770	1,245	16.7	2,771	37.3	23	18.1	54	42.5
Tuberculosis	010-018	56	0.8	94	1.3	<10	~	<10	~
Skin		996	13.4	1,609	21.6	20	15.8	23	18.1
Cellulitis	682.9	549	7.4	813	10.9	13	10.2	10	7.9
Herpes zoster	53	499	6.7	954	12.8	10	7.9	15	11.8
Urinary tract		3,347	45.0	4,213	56.7	45	35.4	56	44.1
Cystitis/pyelonephritis UTI	599	3,036	40.8	4,031	54.2	39	30.7	53	41.7
Prostatitis †	601	724	22.4	543	16.8	14	23.7	<10	~
Gastrohepatic		1,067	14.4	1,377	18.5	12	9.5	23	18.1
Gastroenteritis	558.9	1,038	14.0	1,312	17.6	11	8.7	23	18.1
HBV	070.2-070.3	19	0.3	44	0.6	<10	~	<10	~
HCV	070.4, 070.5, 070.7	29	0.4	52	0.7	<10	~	<10	~

Supplementary Table 2 continued. Frequency of diagnosis and medical claim codes for infections

		Total NHL				Lung cancer cases			
		Prior to NHL		After NHL *		Prior to NHL		After NHL *	
Infections	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients diagnosed with other first primary NHL									
Respiratory - upper airway		5,568	42.3	5,110	38.8	80	40.4	78	39.4
Laryngitis	464-464.4, 476-476.1	629	4.8	597	4.5	<10	~	11	5.6
Otitis media	017.4, 055.2, 381.0-381.4, 382, 383.0-383.1	1,475	11.2	1,241	9.4	16	8.1	19	9.6
Pharyngitis	462,472.1	2,051	15.6	1,774	13.5	33	16.7	22	11.1
Sinusitis	461,473	3,892	29.6	3,484	26.5	59	29.8	55	27.8
Respiratory - lower airway		5,813	44.1	7,111	54.0	79	39.9	104	52.5
Acute bronchitis	466	4,359	33.1	4,039	30.7	59	29.8	64	32.3
Influenza	487	777	5.9	662	5.0	11	5.6	10	5.1
Pneumonia	480-486, 770	2,634	20.0	5,286	40.1	33	16.7	69	34.9
Tuberculosis	010-018	154	1.2	185	1.4	<10	~	<10	~
Skin		2,079	15.8	3,040	23.1	26	13.1	44	22.2
Cellulitis	682.9	1,131	8.6	1,696	12.9	12	6.1	20	10.1
Herpes zoster	53	1,069	8.1	1,656	12.6	16	8.1	27	13.6
Urinary tract		6,167	46.8	7,347	55.8	72	36.4	95	48.0
Cystitis/pyelonephritis UTI	599	5,571	42.3	7,041	53.5	68	34.3	89	45.0
Prostatitis †	601	1,441	22.0	931	14.2	16	14.8	13	12.0
Gastrohepatic		2,236	17.0	2,559	19.4	32	16.2	34	17.2
Gastroenteritis	558.9	2,139	16.2	2,389	18.1	30	15.2	31	15.7
HBV	070.2-070.3	37	0.3	79	0.6	<10	~	<10	~
HCV	070.4, 070.5, 070.7	107	0.8	164	1.3	<10	~	<10	~

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); Current Procedural Technology (CPT); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); Healthcare Common Procedure Coding System (HCPCS); hepatitis B virus (HBV); hepatitis C virus (HCV); International Classification of Diseases (ICD); urinary tract infection (UTI).

~ Counts and percentages are not reported when less than 10 lung cancer cases to protect patient confidentiality.

* New claims occurring after NHL but prior to second cancer, death, end of study, or loss to follow-up, with no claims prior to NHL.

† Among males only.

Supplementary Table 3. Frequency of diagnosis and medical claim codes for autoimmune conditions

		Total NHL				Lung cancer cases			
		Prior to NHL		After NHL*		Prior to NHL		After NHL*	
Autoimmune conditions	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients diagnosed with first primary CLL/SLL									
B-cell activating conditions †	conditions below	2,263	16.2	3,637	26.1	37	14.3	53	20.5
T-cell activating conditions †	conditions below	5,488	39.3	6,749	48.4	96	37.1	111	42.9
By organ system involved									
Systemic/connective tissue		1,687	12.1	1,912	13.7	29	11.2	30	11.6
Ankylosing spondylitis	720	321	2.3	377	2.7	<10	~	<10	~
Dermatomyositis/polymyositis	710.3, 710.4	37	0.3	39	0.3	<10	~	<10	~
Felty's syndrome	714.1	15	0.1	15	0.1	<10	~	<10	~
Systemic lupus erythematosus	710	348	2.5	424	3.0	<10	~	<10	~
Polymyalgia rheumatica	725	256	1.8	295	2.1	<10	~	<10	~
Reactive arthritis	99.3	<10	~	<10	~	<10	~	<10	~
Rheumatic fever	390-392	46	0.3	52	0.4	<10	~	<10	~
Rheumatoid arthritis	714	981	7.0	1,037	7.4	16	6.2	19	7.3
Sarcoidosis	135	35	0.3	43	0.3	<10	~	<10	~
Sjogren's syndrome	710.2	123	0.9	128	0.9	<10	~	<10	~
Systemic sclerosis/scleroderma	710.1	17	0.1	24	0.2	<10	~	<10	~
Cardiovascular		1,367	9.8	2,370	17.0	22	8.5	31	12.0
Chronic rheumatic heart disease	393-398	1,219	8.7	2,187	15.7	22	8.5	28	10.8
Giant cell arteritis	446.5	127	0.9	134	1.0	<10	~	<10	~
Systemic vasculitis	446,447.60	174	1.3	239	1.7	<10	~	<10	~
Endocrine		931	6.7	1,213	8.7	16	6.2	15	5.8
Addison's disease	255.4	71	0.5	242	1.7	<10	~	<10	~
Chronic thyroiditis/Hashimoto	245.2	103	0.7	134	1.0	<10	~	<10	~
Graves' disease	242	783	5.6	872	6.3	14	5.4	13	5.0
Primary biliary cirrhosis	571.6	12	0.1	23	0.2	<10	~	<10	~
Skin		2,222	15.9	2,402	17.2	37	14.3	39	15.1
Alopecia areata	704.1	25	0.2	55	0.4	<10	~	<10	~
Dermatitis herpetiformis	694	56	0.4	114	0.8	<10	~	<10	~
Discoid lupus erythematosus	695.4	34	0.2	38	0.3	<10	~	<10	~
Localized scleroderma	701	1,809	13.0	1,924	13.8	31	12.0	27	10.4
Psoriasis	696	445	3.2	431	3.1	<10	~	<10	~
Gastrointestinal		1,435	10.3	2,926	21.0	25	9.7	42	16.2
Celiac disease	579	149	1.1	203	1.5	<10	~	<10	~
Crohn's disease	555	105	0.8	142	1.0	<10	~	<10	~
Pernicious anemia	281	1,119	8.0	2,548	18.3	19	7.3	38	14.7
Ulcerative colitis	556	187	1.3	255	1.8	<10	~	<10	~
Nervous system		110	0.8	180	1.3	<10	~	<10	~
Amyotrophic sclerosis	335.2	10	0.1	48	0.3	<10	~	<10	~
Multiple sclerosis	340	54	0.4	69	0.5	<10	~	<10	~
Myasthenia gravis	358	50	0.4	69	0.5	<10	~	<10	~
Respiratory (Asthma)	493	1,919	13.8	2,484	17.8	35	13.5	49	18.9
Autoimmune disease, NOS	279.4	32	0.23	64	0.5	<10	~	<10	~

Supplementary Table 3 continued. Frequency of diagnosis and medical claim codes for autoimmune conditions

		Total NHL				Lung cancer cases			
		Prior to NHL		After NHL*		Prior to NHL		After NHL*	
Autoimmune conditions	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients diagnosed with first primary DLBCL									
B-cell activating conditions †	conditions below	2,003	19.4	2,612	25.3	16	13.8	31	26.7
T-cell activating conditions †	conditions below	4,328	42.0	4,943	47.9	43	37.1	52	44.8
By organ system involved									
Systemic/connective tissue		1,602	15.5	1,522	14.8	12	10.3	17	14.7
Ankylosing spondylitis	720	239	2.3	270	2.6	<10	~	<10	~
Dermatomyositis/polymyositis	710.3, 710.4	43	0.4	40	0.4	<10	~	<10	~
Felty's syndrome	714.1	10	0.1	<10	~	<10	~	<10	~
Systemic lupus erythematosus	710	361	3.5	354	3.4	<10	~	<10	~
Polymyalgia rheumatica	725	214	2.1	196	1.9	<10	~	<10	~
Reactive arthritis	99.3	<10	~	<10	~	<10	~	<10	~
Rheumatic fever	390-392	23	0.2	32	0.3	<10	~	<10	~
Rheumatoid arthritis	714	1,052	10.2	871	8.5	<10	~	10	8.6
Sarcoidosis	135	55	0.5	69	0.7	<10	~	<10	~
Sjogren's syndrome	710.2	134	1.3	146	1.4	<10	~	<10	~
Systemic sclerosis/scleroderma	710.1	33	0.3	33	0.3	<10	~	<10	~
Cardiovascular		1,076	10.4	1,951	18.9	11	9.5	16	13.8
Chronic rheumatic heart disease	393-398	932	9.0	1,831	17.8	11	9.5	16	13.8
Giant cell arteritis	446.5	115	1.1	89	0.9	<10	~	<10	~
Systemic vasculitis	446,447.60	161	1.6	159	1.5	<10	~	<10	~
Endocrine		810	7.9	1,019	9.9	<10	~	<10	~
Addison's disease	255.4	44	0.4	220	2.1	<10	~	<10	~
Chronic thyroiditis/Hashimoto	245.2	121	1.2	183	1.8	<10	~	<10	~
Graves' disease	242	681	6.6	679	6.6	<10	~	<10	~
Primary biliary cirrhosis	571.6	12	0.1	19	0.2	<10	~	<10	~
Skin		1,836	17.8	1,549	15.0	23	19.8	18	15.5
Alopecia areata	704.1	17	0.2	15	0.2	<10	~	<10	~
Dermatitis herpetiformis	694	50	0.5	53	0.5	<10	~	<10	~
Discoid lupus erythematosus	695.4	46	0.5	36	0.4	<10	~	<10	~
Localized scleroderma	701	1,400	13.6	1,237	12.0	18	15.5	15	12.9
Psoriasis	696	443	4.3	330	3.2	<10	~	<10	~
Gastrointestinal		1,115	10.8	1,929	18.7	<10	~	23	19.8
Celiac disease	579	112	1.1	165	1.6	<10	~	<10	~
Crohn's disease	555	95	0.9	126	1.2	<10	~	<10	~
Pernicious anemia	281	840	8.2	1,603	15.6	<10	~	17	14.7
Ulcerative colitis	556	161	1.6	190	1.8	<10	~	<10	~
Nervous system		72	0.7	122	1.2	<10	~	<10	~
Amyotrophic sclerosis	335.2	13	0.1	27	0.3	<10	~	<10	~
Multiple sclerosis	340	24	0.2	48	0.5	<10	~	<10	~
Myasthenia gravis	358	37	0.4	50	0.5	<10	~	<10	~
Respiratory (Asthma)	493	1,404	13.6	1,620	15.7	16	13.8	16	13.8
Autoimmune disease, NOS	279.4	44	0.4	50	0.5	<10	~	<10	~

Supplementary Table 3 continued. Frequency of diagnosis and medical claim codes for autoimmune conditions

		Total NHL				Lung cancer cases			
		Prior to NHL		After NHL*		Prior to NHL		After NHL*	
Autoimmune conditions	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients diagnosed with first primary FL									
B-cell activating conditions †	conditions below	1,193	16.0	1,699	22.9	12	9.5	15	11.8
T-cell activating conditions †	conditions below	2,969	39.9	3,604	48.5	45	35.4	40	31.5
By organ system involved									
Systemic/connective tissue		1,020	13.7	1,051	14.1	12	9.5	<10	~
Ankylosing spondylitis	720	182	2.5	210	2.8	<10	~	<10	~
Dermatomyositis/polymyositis	710.3, 710.4	20	0.3	20	0.3	<10	~	<10	~
Felty's syndrome	714.1	<10	~	<10	~	<10	~	<10	~
Systemic lupus erythematosus	710	200	2.7	251	3.4	<10	~	<10	~
Polymyalgia rheumatica	725	144	1.9	154	2.1	<10	~	<10	~
Reactive arthritis	99.3	<10	~	<10	~	<10	~	<10	~
Rheumatic fever	390-392	18	0.2	18	0.2	<10	~	<10	~
Rheumatoid arthritis	714	639	8.6	586	7.9	10	7.9	<10	~
Sarcoidosis	135	15	0.2	30	0.4	<10	~	<10	~
Sjogren's syndrome	710.2	72	1.0	89	1.2	<10	~	<10	~
Systemic sclerosis/scleroderma	710.1	15	0.2	23	0.3	<10	~	<10	~
Cardiovascular		687	9.2	1,276	17.2	<10	~	13	10.2
Chronic rheumatic heart disease	393-398	615	8.3	1,171	15.8	<10	~	12	9.5
Giant cell arteritis	446.5	71	1.0	90	1.2	<10	~	<10	~
Systemic vasculitis	446,447.60	93	1.3	134	1.8	<10	~	<10	~
Endocrine		519	7.0	665	8.9	<10	~	<10	~
Addison's disease	255.4	32	0.4	116	1.6	<10	~	<10	~
Chronic thyroiditis/Hashimoto	245.2	58	0.8	78	1.1	<10	~	<10	~
Graves' disease	242	450	6.1	500	6.7	<10	~	<10	~
Primary biliary cirrhosis	571.6	<10	~	<10	~	<10	~	<10	~
Skin		1,233	16.6	1,264	17.0	21	16.5	12	9.5
Alopecia areata	704.1	<10	~	14	0.2	<10	~	<10	~
Dermatitis herpetiformis	694	32	0.4	49	0.7	<10	~	<10	~
Discoid lupus erythematosus	695.4	31	0.4	19	0.3	<10	~	<10	~
Localized scleroderma	701	995	13.4	1,022	13.7	15	11.8	<10	~
Psoriasis	696	239	3.2	237	3.2	<10	~	<10	~
Gastrointestinal		640	8.6	1,265	17.0	<10	~	12	9.5
Celiac disease	579	83	1.1	121	1.6	<10	~	<10	~
Crohn's disease	555	64	0.9	74	1.0	<10	~	<10	~
Pernicious anemia	281	470	6.3	1,044	14.0	<10	~	<10	~
Ulcerative colitis	556	89	1.2	129	1.7	<10	~	<10	~
Nervous system		31	0.4	84	1.1	<10	~	<10	~
Amyotrophic sclerosis	335.2	<10	~	19	0.3	<10	~	<10	~
Multiple sclerosis	340	<10	~	33	0.4	<10	~	<10	~
Myasthenia gravis	358	18	0.2	34	0.5	<10	~	<10	~
Respiratory (Asthma)	493	1,002	13.5	1,283	17.3	17	13.4	15	11.8
Autoimmune disease, NOS	279.4	16	0.2	24	0.3	<10	~	<10	~

Supplementary Table 3 continued. Frequency of diagnosis and medical claim codes for autoimmune conditions

		Total NHL				Lung cancer cases			
		Prior to NHL		After NHL*		Prior to NHL		After NHL*	
Autoimmune conditions	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients diagnosed with other first primary NHL									
B-cell activating conditions †	conditions below	2,817	21.4	3,767	28.6	36	18.2	38	19.2
T-cell activating conditions †	conditions below	5,845	44.4	6,654	50.5	79	39.9	104	52.5
By organ system involved									
Systemic/connective tissue		2,176	16.5	2,161	16.4	28	14.1	32	16.2
Ankylosing spondylitis	720	369	2.8	373	2.8	<10	~	<10	~
Dermatomyositis/polymyositis	710.3, 710.4	63	0.5	53	0.4	<10	~	<10	~
Felty's syndrome	714.1	17	0.1	22	0.2	<10	~	<10	~
Systemic lupus erythematosus	710	585	4.4	584	4.4	<10	~	<10	~
Polymyalgia rheumatica	725	369	2.8	321	2.4	<10	~	<10	~
Reactive arthritis	99.3	<10	~	<10	~	<10	~	<10	~
Rheumatic fever	390-392	37	0.3	49	0.4	<10	~	<10	~
Rheumatoid arthritis	714	1,270	9.6	1,201	9.1	19	9.6	16	8.1
Sarcoidosis	135	74	0.6	81	0.6	<10	~	<10	~
Sjogren's syndrome	710.2	240	1.8	260	2.0	<10	~	<10	~
Systemic sclerosis/scleroderma	710.1	51	0.4	50	0.4	<10	~	<10	~
Cardiovascular		1,449	11.0	2,300	17.5	15	7.6	24	12.1
Chronic rheumatic heart disease	393-398	1,224	9.3	2,069	15.7	11	5.6	22	11.1
Giant cell arteritis	446.5	182	1.4	176	1.3	<10	~	<10	~
Systemic vasculitis	446,447.60	267	2.0	292	2.2	<10	~	<10	~
Endocrine		1,090	8.3	1,263	9.6	10	5.1	16	8.1
Addison's disease	255.4	70	0.5	250	1.9	<10	~	<10	~
Chronic thyroiditis/Hashimoto	245.2	128	1.0	180	1.4	<10	~	<10	~
Graves' disease	242	911	6.9	888	6.7	<10	~	11	5.6
Primary biliary cirrhosis	571.6	19	0.1	29	0.2	<10	~	<10	~
Skin		2,579	19.6	2,581	19.6	39	19.7	37	18.7
Alopecia areata	704.1	21	0.2	21	0.2	<10	~	<10	~
Dermatitis herpetiformis	694	91	0.7	112	0.9	<10	~	<10	~
Discoid lupus erythematosus	695.4	74	0.6	80	0.6	<10	~	<10	~
Localized scleroderma	701	1,870	14.2	1,851	14.1	24	12.1	20	10.1
Psoriasis	696	783	5.9	790	6.0	16	8.1	17	8.6
Gastrointestinal		1,703	12.9	2,849	21.6	14	7.1	24	12.1
Celiac disease	579	169	1.3	221	1.7	<10	~	<10	~
Crohn's disease	555	132	1.0	172	1.3	<10	~	<10	~
Pernicious anemia	281	1,325	10.1	2,421	18.4	10	5.1	20	10.1
Ulcerative colitis	556	219	1.7	293	2.2	<10	~	<10	~
Nervous system		91	0.7	173	1.3	<10	~	<10	~
Amyotrophic sclerosis	335.2	11	0.1	31	0.2	<10	~	<10	~
Multiple sclerosis	340	36	0.3	64	0.5	<10	~	<10	~
Myasthenia gravis	358	47	0.4	79	0.6	<10	~	<10	~
Respiratory (Asthma)	493	1,932	14.7	2,230	16.9	25	12.6	46	23.2
Autoimmune disease, NOS	279.4	60	0.5	87	0.7	<10	~	<10	~

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); Current Procedural Technology (CPT); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); Healthcare Common Procedure Coding System (HCPCS); not otherwise specified (NOS).

~ Counts and percentages are not reported when less than 10 lung cancer cases to protect patient confidentiality.

* New claims occurring after NHL but prior to second cancer, death, end of study, or loss to follow-up, with no claims prior to NHL.

† B-cell activating conditions include rheumatoid arthritis, Sjogren's syndrome, discoid lupus erythematosus, reactive arthritis, Felty's syndrome, chronic thyroiditis, systemic/discoid lupus erythematosus, pernicious anemia, and myasthenia gravis. T-cell activating conditions include ankylosing spondylitis, dermatomyositis, polymyalgia rheumatica, sarcoidosis, systemic sclerosis, rheumatic fever, chronic rheumatic heart disease, giant cell arteritis, systemic vasculitis, Addison's disease, Graves' disease, primary biliary cirrhosis, alopecia areata, localized scleroderma, dermatitis herpetiformis, psoriasis, celiac disease, Crohn's disease, ulcerative colitis, amyotrophic sclerosis, multiple sclerosis, and asthma.

Supplementary Table 4. Risk of lung cancer after first primary NHL, by subtype

	Total NHL				CLL/SLL				DLBCL				FL				Other NHL			
	N	%	HR*	95% CI	N	%	HR*	95% CI	N	%	HR*	95% CI	N	%	HR*	95% CI	N	%	HR*	95% CI
Sex																				
Male	22,097	49.3	1.00	Referent	7,590	54.4	1.00	Referent	4,725	45.8	1.00	Referent	3,229	43.4	1.00	Referent	6,553	49.7	1.00	Referent
Female	22,773	50.8	0.72	0.62-0.84	6,360	45.6	0.62	0.48-0.80	5,586	54.2	0.78	0.54-1.13	4,208	56.6	0.82	0.57-1.16	6,619	50.3	0.80	0.60-1.06
Race																				
White	40,752	90.8	1.00	Referent	12,841	92.1	1.00	Referent	9,222	89.4	1.00	Referent	6,888	92.6	1.00	Referent	11,801	89.6	1.00	Referent
Other/unknown	4,118	9.2	0.79	0.59-1.05	1,109	7.9	1.06	0.68-1.66	1,089	10.6	0.95	0.51-1.78	549	7.4	0.52	0.21-1.27	1,371	10.4	0.54	0.30-0.97
History of smoking																				
No	34,220	76.3	1.00	Referent	10,652	76.4	1.00	Referent	7,996	77.6	1.00	Referent	5,749	77.3	1.00	Referent	9,823	74.6	1.00	Referent
Yes	10,650	23.7	3.17	2.72-3.70	3,298	23.6	3.06	2.37-3.95	2,315	22.5	3.89	2.66-5.70	1,688	22.7	2.84	1.96-4.12	3,349	25.4	3.16	2.36-4.23
NHL subtype																				
DLBCL	10,311	23.0	1.00	Referent																
CLL/SLL	13,950	31.1	1.46	1.17-1.81																
FL	7,437	16.6	1.34	1.04-1.72																
MZ	3,516	7.8	1.48	1.08-2.02																
Other	9,656	21.5	1.21	0.94-1.55																

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); confidence interval (CI); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); hazard ratio (HR); marginal zone lymphoma (MZL); non-Hodgkin lymphoma (NHL).

* HR (95% CI) adjusted for sex, race, residence, and follow-up time (time-dependent covariate) and stratified by calendar year. Age was used as the time scale.

Appendix 3 – Additional Tables for Risk Factors for Second Acute Myeloid Leukemia/Myelodysplastic Syndromes Among Survivors of Non-Hodgkin Lymphoma

Supplementary Table 1. Frequency of receipt and medical claim codes for specific chemotherapeutic agents

		Total NHL		AML/MDS cases*	
Chemotherapy	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**
Most common agents					
Cyclophosphamide	J8530, J9070, J9080, J9090-J9097	14,225	41.7	84	54.2
Fludarabine	J9185	3,703	10.8	44	28.4
Rituximab	J9310	17,732	51.9	104	67.1
Topoisomerases II inhibitors					
Doxorubicin	J9000-J9001	9,677	28.3	55	35.5
Mitoxantrone	J9293	1,370	4.0	13	8.4
Plant Alkaloids					
Vincristine	J9370, J9375, J9380	13,131	38.5	63	40.6
Colony Stimulating Factors					
G-CSF	J1440-J1441	6,163	18.0	60	38.7

Abbreviations: acute myeloid leukemia/myelodysplastic syndrome (AML/MDS); granulocyte colony-stimulating factor (G-CSF); granulocyte colony-stimulating factor (GM-CSF); Healthcare Common Procedure Coding System (HCPCS); Current Procedural Technology (CPT); non-Hodgkin lymphoma (NHL).

* Counts and percentages are not reported when less than 10 AML/MDS cases to protect patient confidentiality. Chemotherapy agents with less than 10 AML/MDS cases include aldesleukin, alemtuzumab, idarubicin, ixabepilone, asparaginase, azacitidine, bendamustine, bevacizumab, bleomycin, bortezomib, busulfan, carboplatin, carmustine, cetuximab, cisplatin, cladribine, clofarabine, cytarabine, dacarbazine, dactinomycin, daunorubicin, decitabine, denileukin, diftitox, docetaxel, epirubicin, etoposide, floxuridine, fluorouracil, gefitinib, gemcitabine, gemtuzumab, GM-CSF, ibritumomab, ifosfamide, interferons (1B, 2A, 2B, A1, N3), irinotecan, leucovorin, lomustine, mechlorethamine, melphalan, methotrexate, mitomycin, nelarabine, oxaliplatin, paclitaxel, panitumumab, pegaspargase, pemetrexed, pentostatin, plicamycin, streptozocin, temsirolimus, teniposide, thiotepa, topotecan, tositumomab, trastuzumab, valrubicin, vinblastine, and vinorelbine.

~ Information on oral chemotherapy agents not captured in study include capecitabine, chlorambucil, cyclophosphamide, levamisole, procarbazine, and temozolomide.

Supplementary Table 2. Frequency of diagnosis and medical claim codes for autoimmune conditions

		Total NHL				AML/MDS cases			
		Prior to NHL		After NHL*		Prior to NHL		After NHL*	
Autoimmune conditions	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
B-cell activating conditions †	conditions below	6,848	20.1	8,586	25.1	36	23.2	57	36.8
T-cell activating conditions †	conditions below	15,108	44.3	16,057	47.0	73	47.1	77	49.7
By organ system involved									
Systemic/connective tissue		5,348	15.7	4,776	14.0	29	18.7	29	18.7
Ankylosing spondylitis	720	947	2.8	908	2.7	<10	~	<10	~
Dermatomyositis/polymyositis	710.3, 710.4	135	0.4	107	0.3	<10	~	<10	~
Felty's syndrome	714.1	39	0.1	32	0.1	<10	~	<10	~
Systemic lupus erythematosus	710	1,222	3.6	1,142	3.3	<10	~	<10	~
Polymyalgia rheumatica	725	786	2.3	658	1.9	<10	~	<10	~
Reactive arthritis	99.3	10	0.0	<10	~	<10	~	<10	~
Rheumatic fever	390-392	93	0.3	85	0.3	<10	~	<10	~
Rheumatoid arthritis	714	3,278	9.6	2,684	7.9	16	10.3	17	11.0
Sarcoidosis	135	154	0.5	169	0.5	<10	~	<10	~
Sjogren's syndrome	710.2	461	1.4	459	1.3	<10	~	<10	~
Systemic sclerosis/scleroderma	710.1	96	0.3	99	0.3	<10	~	<10	~
Cardiovascular		3,814	11.2	5,679	16.6	21	13.6	22	14.2
Chronic rheumatic heart disease	393-398	3,354	9.8	5,247	15.4	18	11.6	19	12.3
Giant cell arteritis	446.5	390	1.1	334	1.0	<10	~	<10	~
Systemic vasculitis	446,447.60	552	1.6	549	1.6	<10	~	<10	~
Endocrine		2,802	8.2	2,887	8.5	17	11.0	10	6.5
Addison's disease	255.4	189	0.6	592	1.7	<10	~	<10	~
Chronic thyroiditis/Hashimoto thyroiditi	245.2	346	1.0	413	1.2	<10	~	<10	~
Graves' disease	242	2,353	6.9	2,000	5.9	17	11.0	<10	~
Primary biliary cirrhosis	571.6	39	0.1	61	0.2	<10	~	<10	~
Skin		6,361	18.6	5,458	16.0	36	23.2	26	16.8
Alopecia areata	704.1	59	0.2	75	0.2	<10	~	<10	~
Dermatitis herpetiformis	694	177	0.5	211	0.6	<10	~	<10	~
Discoid lupus erythematosus	695.4	145	0.4	129	0.4	<10	~	<10	~
Localized scleroderma	701	4,936	14.5	4,204	12.3	30	19.4	22	14.2
Psoriasis	696	1,542	4.5	1,239	3.6	<10	~	<10	~
Gastrointestinal		4,096	12.0	6,561	19.2	23	14.8	45	29.0
Celiac disease	579	438	1.3	511	1.5	<10	~	<10	~
Crohn's disease	555	299	0.9	373	1.1	<10	~		
Pernicious anemia	281	3,172	9.3	5,561	16.3	20	12.9	40	25.8
Ulcerative colitis	556	562	1.7	646	1.9	<10	~	<10	~
Nervous system		241	0.7	392	1.2	<10	~	<10	~
Amyotrophic sclerosis	335.2	27	0.1	84	0.3	<10	~	<10	~
Multiple sclerosis	340	100	0.3	154	0.5	<10	~	<10	~
Myasthenia gravis	358	121	0.4	162	0.5	<10	~	<10	~
Respiratory (Asthma)	493	5,246	15.4	5,618	16.5	18	11.6	31	20.0
Autoimmune disease, NOS	279.4	139	0.4	173	0.5	<10	~	<10	~

Abbreviations: acute myeloid leukemia/myelodysplastic syndrome (AML/MDS); Current Procedural Technology (CPT); Healthcare Common Procedure Coding System (HCPCS); non-Hodgkin lymphoma (NHL); not otherwise specified (NOS).

~ Counts and percentages are not reported for less than 10 AML/MDS cases to protect patient confidentiality.

* New claims occurring after NHL but prior to second cancer, death, end of study, or loss to follow-up, with no claims prior to NHL.

† B-cell activating conditions include rheumatoid arthritis, Sjogren's syndrome, discoid lupus erythematosus, reactive arthritis, Felty's syndrome, chronic thryoiditis, systemic/discoid lupus erythematosus, pernicious anemia, and myasthenia gravis. T-cell activating conditions include ankylosing spondylitis, dermatomyositis, polymyalgia rheumatica, sarcoidosis, systemic sclerosis, rheumatic fever, chronic rheumatic heart disease, giant cell arteritis, systemic vasculitis, Addison's disease, Graves' disease, primary biliary cirrhosis, alopecia areata, localized scleroderma, dermatitis herpetiformis, psoriasis, celiac disease, Crohn's disease, ulcerative colitis, amyotrophic sclerosis, multiple sclerosis, and asthma. Hematologic autoimmune conditions (e.g., autoimmune hemolytic anemia, thrombocytopenia) were excluded from consideration because of difficulty distinguishing these diagnoses from manifestations of chemotherapy toxicity.

Supplementary Table 3. Frequency of diagnosis and medical claim codes for infections

		Total NHL				AML/MDS cases			
		Prior to NHL		After NHL *		Prior to NHL		After NHL *	
Infections	**HCPCS/CPT codes**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Respiratory - upper airway		15,120	44.3	12,858	37.7	74	47.7	80	51.6
Laryngitis	464-464.4, 476-476.1	1,706	5.0	1,380	4.0	<10	~	<10	~
Otitis media	017.4, 055.2, 381.0-381.4, 382, 383.0-383.1	3,982	11.7	2,956	8.7	22	14.2	14	9.0
Pharyngitis	462,472.1	5,540	16.2	4,480	13.1	29	18.7	27	17.4
Sinusitis	461,473	10,808	31.7	9,050	26.5	46	29.7	63	40.7
Respiratory - lower airway		15,140	44.3	17,554	51.4	73	47.1	86	55.5
Acute bronchitis	466	11,609	34.0	10,108	29.6	56	36.1	50	32.3
Influenza	487	1,852	5.4	1,289	3.8	11	7.1	<10	~
Pneumonia	480-486, 770	6,697	19.6	12,763	37.4	29	18.7	62	40.0
Tuberculosis	010-018	304	0.9	322	0.9	<10	~	<10	~
Skin		5,372	15.7	7,326	21.5	32	20.7	33	21.3
Cellulitis	682.9	2,958	8.7	3,972	11.6	14	9.0	18	11.6
Herpes zoster	53	2,762	8.1	4,066	11.9	20	12.9	19	12.3
Urinary tract		16,532	48.4	18,574	54.4	73	47.1	93	60.0
Cystitis/pyelonephritis, UTI	599	15,040	44.0	17,768	52	61	39.4	83	53.6
Prostatitis †	601	3,841	22.8	2,454	14.5	27	30.3	25	28.1
Gastrohepatic		5,430	15.9	5,693	16.7	29	18.7	33	21.3
Gastroenteritis	558.9	5,197	15.2	5,268	15.4	28	18.1	33	21.3
HBV	070.2-070.3	117	0.3	228	0.7	<10	~	<10	~
HCV	070.4, 070.5, 070.7	231	0.7	371	1.1	<10	~	<10	~

Abbreviations: acute myeloid leukemia/myelodysplastic syndrome (AML/MDS); Current Procedural Technology (CPT); Healthcare Common Procedure Coding System (HCPCS); hepatitis B virus (HBV); hepatitis C virus (HCV); International Classification of Diseases (ICD); non-Hodgkin lymphoma (NHL); urinary tract infection (UTI).

~ Counts and percentages are not reported for less than 10 AML/MDS cases to protect patient confidentiality.

* New claims occurring after NHL but prior to second cancer, death, end of study, or loss to follow-up, with no claims prior to NHL.

† Among males only.

Appendix 4 – Exclusion Criteria for Study Populations

Figure 1. Exclusions for total study population of 44,870 non-Hodgkin lymphoma 1-year survivors for second melanoma and lung cancer analyses

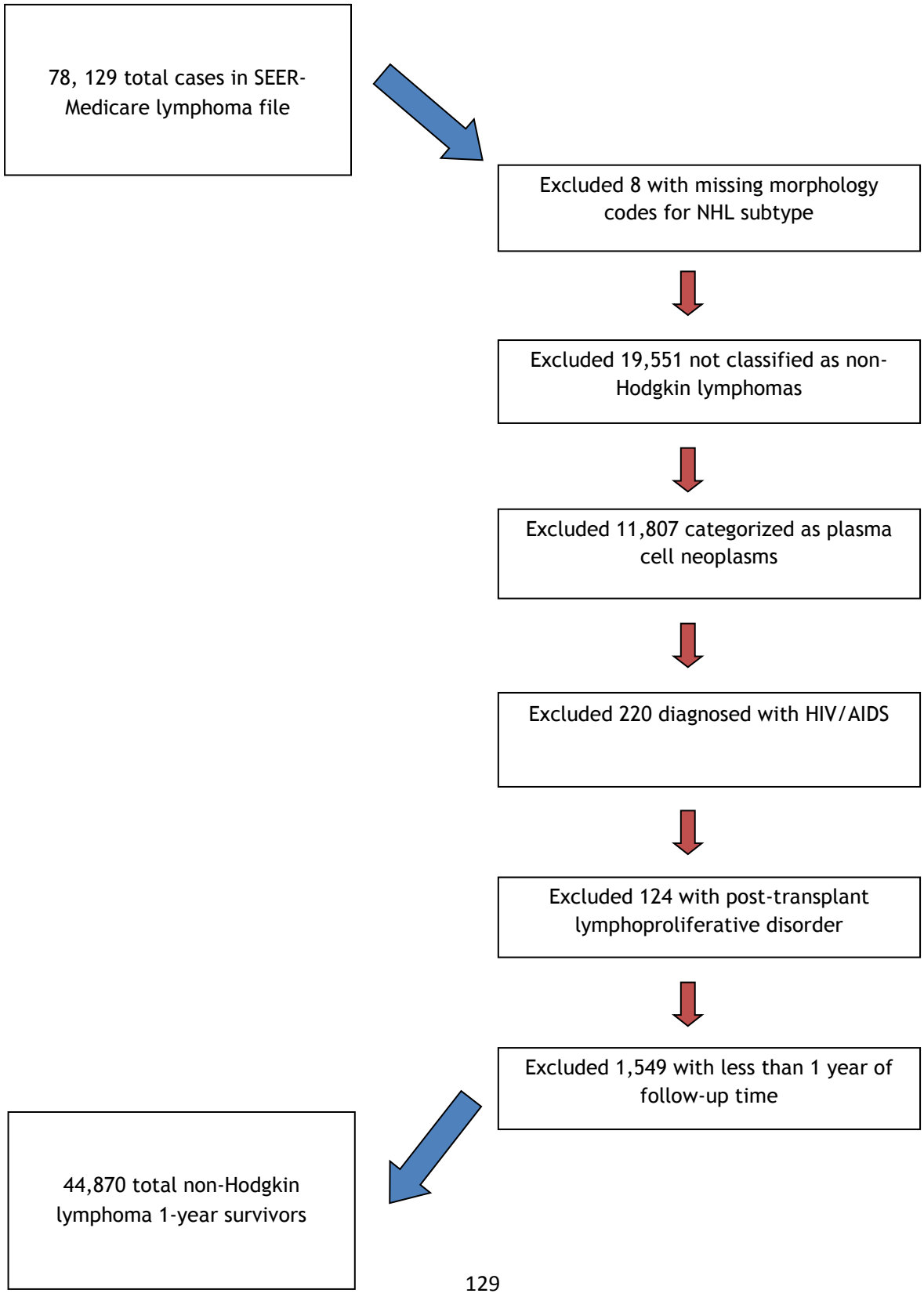
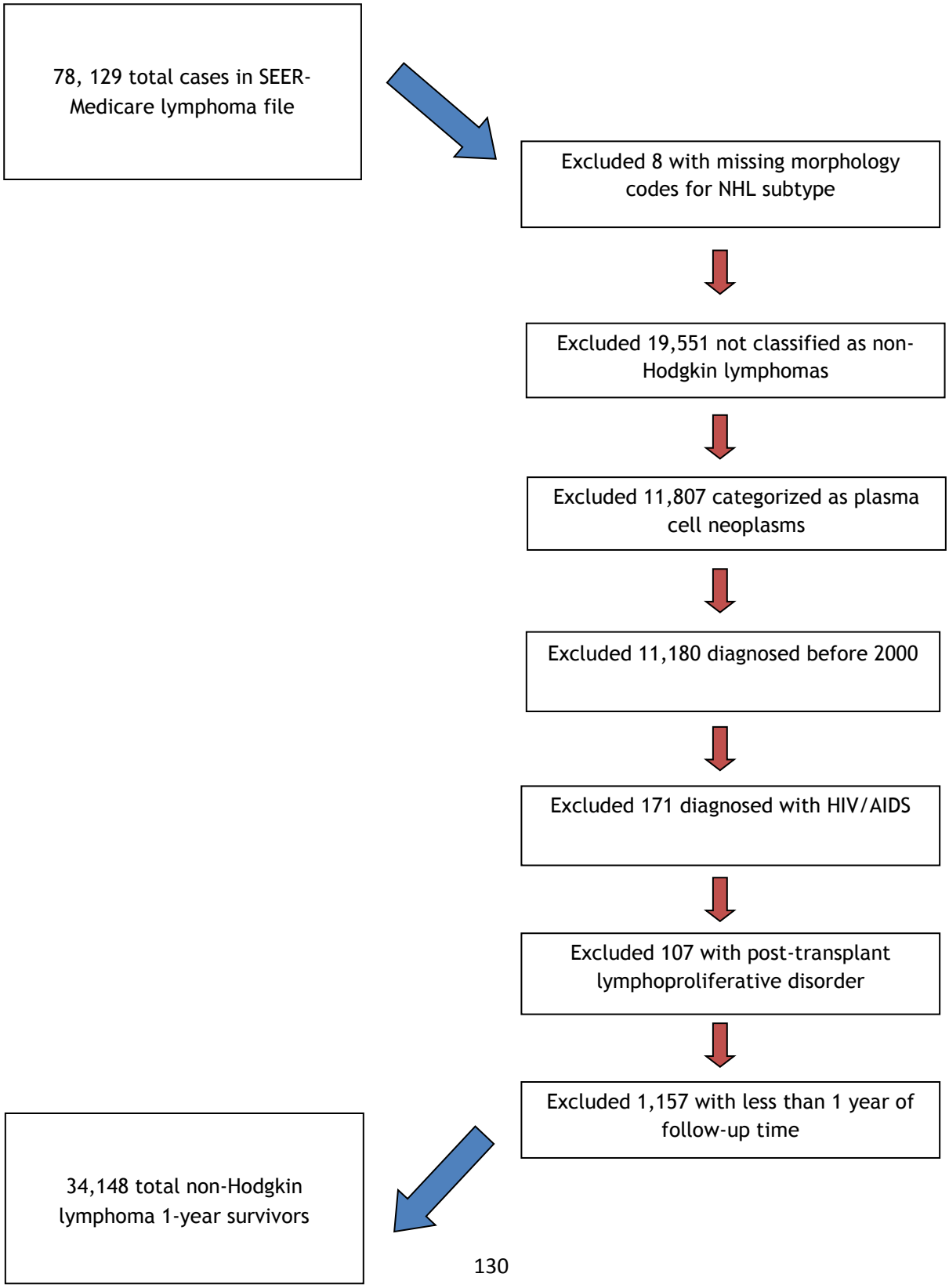
Figure 2. Exclusions for total study population of 34,148 non-Hodgkin lymphoma 1-year survivors for second acute myeloid leukemia/myelodysplastic syndromes analyses