Cohort Study

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Risk of second primary cancers in nodal non-Hodgkin lymphoma patients by primary lymph node location: a retrospective cohort population-based study

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Background: Non-Hodgkin lymphoma (NHL) is a diverse group of blood cancers with increasing incidence and survival rates due to advancements in treatment and early detection. However, NHL survivors are at significant risk of developing second primary cancers, which can adversely impact their long-term survival.

Methods: This retrospective population-based cohort study utilized data from the Surveillance, Epidemiology, and End Results database, covering 17 geographic areas in the United States from 2000 to 2021. The authors included patients diagnosed with nodal NHL as a first primary cancer and excluded those diagnosed at autopsy or via death certificate only. Standardized Incidence Ratios, Absolute Excess Risks, and Person-Years at Risk were calculated to evaluate the risk of developing SPCs according to the primary lymph node site and stratified by latency periods following the initial NHL diagnosis.

Results: The cohort included 54 012 NHL patients. The authors' results showed that for most SPCs, the risk of development was different for different primary NHL lymph node locations. The highest risks were observed for thyroid cancer, acute myeloid leukemia, and Hodgkin lymphoma. Notably, the risk for thyroid cancer was highest in the first year post-diagnosis, while hematological malignancies such as acute myeloid leukemia and Hodgkin lymphoma showed elevated risks in the intermediate and late latency periods.

Conclusion: NHL survivors are at an increased risk of developing SPCs, influenced by the primary lymph node site and latency period. These findings highlight the need for tailored surveillance strategies and preventive measures to mitigate the long-term risks of SPCs in NHL survivors. Further research is necessary to elucidate the underlying mechanisms and to develop targeted interventions for this high-risk population.

Keywords: non-Hodgkin lymphoma, primary lymph node site, second primary cancer

Introduction

Non-Hodgkin lymphoma (NHL) is a diverse group of blood cancers that develop in the lymphatic system. NHL can start in various lymph nodes throughout the body and encompasses a wide variety of subtypes, each with distinct pathological and clinical features. The incidence of NHL has been rising globally, with an estimated 77 240 new cases diagnosed in the United States in 2020 alone[1]. Due to advancements in treatment and early detection, the number of NHL survivors has also increased significantly[2], with over 700 000 survivors currently living in the United States[1]. Despite these improvements, the causes of death within 5 years of an NHL diagnosis remain concerning. Studies have shown that about 20–30% of patients with aggressive NHL subtypes succumb to the disease within five years, with higher mortality rates observed in older adults and those with advanced-stage disease at diagnosis[3]. The primary causes of death for NHL patients include progression of the lymphoma itself and treatmen t-related complications[4]. Infections and cardiovascular diseases also contribute significantly to mortality due to the immunosup pressive effects of both the disease and its treatment[5–7]. Second

HIGHLIGHTS

- Non-Hodgkin lymphoma survivors face a markedly higher risk of developing second primary cancers.
- The study identifies for the first time that the primary lymph node location significantly influences the risk of specific SPCs, such as thyroid cancer, acute myeloid leukemia, and Hodgkin lymphoma.
- There is a necessity for personalized surveillance and monitoring strategies tailored to the primary lymph node site to improve early detection and management of SPCs in NHL survivors.

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primary cancers (SPCs) in particular significantly contribute to higher mortality rates among these patients. An SPC is defined as a new, distinct cancer that develops in an individual who has previously been diagnosed with a primary cancer. SPCs are not recurrences, metastases, or extensions of the original cancer; rather, they are new cancers that occur in a different tissue or organ[8]. SPCs are an important concern in oncology, as cancer survivors are at an elevated risk due to treatments like chemother apy and radiation. SPCs significantly impact long-term health, increasing mortality and morbidity in survivors, particularly those of NHL. Their occurrence necessitates long-term surveil lance and personalized follow-up care to improve outcomes. Additionally, SPCs pose challenges for clinical management and quality of life, requiring further research and psychosocial support to mitigate these effects[9]. Chattopadhyay *et al.*[4] noted that second primary cancers significantly decreased survival probabilities in NHL patients, with a hazard ratio of 1.59.

The risk of SPCs in NHL patients has been well-documented in numerous studies that have consistently shown higher incidence rates compared to the general population[10–15]. Factors such as younger age at NHL diagnosis and male gender have been implicated in increasing the risk for SPCs in NHL patients[16]. Furthermore, patients with NHL are at an increased risk of developing second primary cancers due to several factors, including the underlying biology of NHL[9,17,18], the immuno suppressive effects of the disease[19], and the long-term side effects of treatments such as chemotherapy and radiation therapy[20]. Morton *et al.* identified a locus on chromosome 6q21 that is associated with SPC risk in lymphoma patients who received radiotherapy[15]. The latency period for developing second pri mary cancers can also vary. Studies have shown that the risk is particularly high within the first few years following NHL diag nosis and treatment, but it can persist for many years[17,21]. For example, a study found that the risk of developing second pri mary cancers remains elevated even 10 years after the initial NHL diagnosis[22].

The effects of SPCs on mortality in NHL warrants a need to assess the factors associated with SPC development. While the literature provides evidence for a multitude of factors that govern SPC development in NHL patients, the role of primary lymph node location has never been studied. In the present research study, we aim to assess the role of primary lymph node location in SPC development in NHL patients and provide a comprehensive analysis of the risk of developing certain SPCs according to pri mary nodal NHL location across a 10-year latency period. Our goal is to provide a comprehensive analysis that can inform clinical practice, improve patient monitoring, and guide targeted preventive strategies to reduce the incidence and impact of SPCs in NHL patients.

Methods

Study population

This retrospective cohort study was conducted using data collected from the Surveillance, Epidemiology, and End Results (SEER) database supported by the National Cancer Institute. We utilized data from the SEER 17, which includes registries from 17 geographic areas of the United States (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco–Oakland, Seattle–Puget Sound, Utah, Los Angeles, San Jose–Monterey, Rural Georgia, Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia) covering around 34.6% of the US population providing a comprehensive and representative sample of the US population. The dataset utilized for this study was the November 2023 submission, covering the period from 2000 to 2021.

We included patients diagnosed with nodal NHL as a first primary cancer. Specific primary lymph node sites included C77.0–C77.5, C77.8, and C77.9 codes as classified by the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). We included only patients with primary nodal NHL originating in lymph nodes of the following regions only: C77.0—head, face, and neck, C77.1—intrathor acic, C77.2—intra-abdominal, C77.3—axilla or arm, C77.4—inguinal region or leg, C77.5—P LNs. Patients with first primary nodal NHL originating in regions classified at C77.8—multiple regions and C77.9—not otherwise classified were not included in our study. Patients diagnosed with primary nodal NHL at autopsy or reported through death certificate only were not included. We chose the latency exclusion period to be 2 months; that is all patients who were diagnosed with a second primary cancer within less than two months of diagnosis with primary NHL lymphoma were excluded. This is in compliance with the ICD's international rules for multiple primary cancers[23]. In addition, we extracted data pertinent to each patient's age, sex, race, subtype of primary nodal non-Hodgkin lymphoma, and location of second primary cancer if applicable.

The SEER database minimizes selection bias by covering a large, diverse population and including all eligible cancer cases based on strict coding and inclusion criteria. It controls for attrition bias by continuously updating cancer outcomes from medical records and vital statistics, reducing the risk of partici pants dropping out. However, some underrepresentation of cer tain populations and occasional missing data remain as limitations that should be acknowledged when using SEER data. Our reporting is compliant with the STROCCS-2021 statement[24].

Statistical analysis

Statistical analyses were performed using SEERStat software (version 8.4.3, National Cancer Institute). We employed a mul tiple primary-standardized incidence ratio (MP-SIR) session to calculate the standardized incidence ratios (SIRs), absolute excess risks (AERs), and person-years at risk (PYRs), stratified by pri mary NHL lymph node region, assuming a Poisson distribution for the observed number of SPC. The MP-SIR session in SEERStat compares the observed number of second primary cancers in the present cohort to the expected number based on general popu lation cancer incidence rates, adjusted for age, sex, and calendar period. The SIR is the ratio of observed to expected cases. It is calculated by dividing the observed number of second primary cancers by the expected number, which is based on the incidence rates in the general population. The AER represents the excess number of cancer cases per 10 000 person-year at risk (PYR). It is calculated by subtracting the expected number of cases from the observed number and then dividing by the PYR. PYR is the total amount of time that the cohort is at risk of developing second primary cancers, calculated from the time of initial NHL diag nosis to either the diagnosis of a second primary cancer, death, or end of the study period[25]. The SIR, AER, and PYR were

calculated for each primary lymph node site and stratified by three latency periods. The latency periods of 2–11 months, 12–59 months, and 60–119 months were chosen to capture the varying risk patterns of SPCs at different times following the initial NHL diagnosis, allowing for a comprehensive analysis of the temporal risk of SPCs. The statistical significance of the SIRs was determined using Poisson regression models to calculate 95% CIs. An SIR was considered statistically significant if the 95% CI did not include 1.0 and the *P* value was less than 0.05[26].

Ethical considerations

As the study involves retrospective analysis of deidentified data and does not require direct patient contact or intervention, an Institutional Review Board (IRB) approval was not required. All data handling and analysis was conducted in compliance with relevant ethical guidelines and regulations to ensure patient privacy and data security.

Results

The cohort of this study included a total of 54 012 patients diagnosed with non-Hodgkin lymphoma (NHL) from SEER 17, covering the period from 2000 to 2021. Table 1 provides a comprehensive overview of this study's cohort. Table 2 shows the SIR and AER for developing a specific second primary cancer in NHL lymphoma patients according to site of the primary lymph node and stratified according to the latency period. Figure 1, 2 and 3 represent a visualization of the SIR of a given SPC according to primary NHL lymph node location stratified by the three latency periods.

For patients with nodal NHL originating in the Head, Face, and Neck lymph node group, the highest risks of developing SPCs were observed early, within 2–11 months post-diagnosis. Nasopharyngeal cancer showed the most elevated risk, followed by thyroid cancer, Hodgkin lymphoma, and non-Hodgkin lymphoma. In the 12–59 months period, Hodgkin lymphoma remained the leading SPC, with acute myeloid leukemia and acute non-lymphocytic leukemia also posing significant risks.

In the Intrathoracic lymph node group, thyroid cancer was the most prominent SPC in the early 2–11 months post-diagnosis, followed by acute monocytic leukemia. Other significant risks included acute non-lymphocytic leukemia, non-Hodgkin lymphoma, and kidney cancer, as well as myeloma and lung cancer.

For the intra-abdominal lymph node group, early SPC risks were highest for acute monocytic leukemia, followed by thyroid cancer and non-Hodgkin lymphoma. As time progressed to 12–59 months, acute non-lymphocytic leukemia led the risks, with acute myeloid leukemia and anus cancer also demonstrating substantial risks.

For patients with nodal NHL in the Axilla or Arm lymph node group, Hodgkin lymphoma was the most frequent SPC within the first 2–11 months, followed by kidney cancer, non-Hodgkin lymphoma, and thyroid cancer. Myeloma and lung cancer also presented significant risks during this time.

In the Inguinal lymph node group, Hodgkin lymphoma showed the highest risk of SPCs within the first 2–11 months, followed by non-Hodgkin lymphoma and thyroid cancer. Kidney cancer and lung cancer also demonstrated substantial risks. Over the 12–59 months latency period, non-Hodgkin lymphoma continued to lead the risks, with lung cancer remaining a concern.

Table 1

Cohort characteristics.

Patient characteristics	Frequency (*n*)	Percentage (%)
Total number of patients included in our cohort	54 012	
Sex		
Male	28 963	53.6
Female	25 049	46.4
Race		
White	46 082	85.3
Black	3705	6.9
Other	3601	6.7
Unknown	624	1.2
Mean age at primary non-Hodgkin lymphoma diagnosis (in years)	62.15 years	
Mean age at secondary primary cancer diagnosis (in years)	70.86 years	
Primary lymph node site		
Head, face, and neck	18 819	34.8
Intrathoracic	5082	9.4
Intra-abdominal	14 385	26.6
Axilla or arm	6332	11.7
Inguinal region or leg	7908	14.6
Pelvic	1479	2.7
Lymphoma subtype		
Lymphoblastic	854	1.6
Burkitt	1187	2.2
Diffuse large B-cell	21 208	39.3
Primary mediastinal large B-cell excluded from DLBCL	32	.1
Anaplastic T- and null-cell excluding NK/T-cell	1814	3.4
Follicular	16 471	30.5
NK/T-cell (excluded from anaplastic T-cell)	20	.0
Mucosa-associated lymphoid tissue	2380	4.4
Other non-Hodgkin lymphomas (Not otherwise specified)	7823	14.5
Other B- and T-cell lymphomas	685	1.2
Patients that developed a second primary cancer	8083	14.96

DLBCL, diffuse large B-cell lymphoma.

At 60–119 months, Hodgkin lymphoma again posed the highest risk, followed by non-Hodgkin lymphoma and lung cancer.

For the Pelvic lymph node group, thyroid cancer was the most significant SPC in the first 2–11 months post-diagnosis. In the 12–59 months period, lung cancer became more prominent, alongside non-Hodgkin lymphoma. At 60–119 months, non-Hodgkin lymphoma remained a leading concern, with continued risk for lung cancer.

Discussion

The rationale for our study stems from the increasing recognition of the elevated risk of SPCs in patients with NHL. Advances in NHL treatment have significantly improved survival rates, resulting in a growing population of long-term survivors who are at risk for developing SPCs. The influence of primary lymph node site on SPC risk has never been studied. Our study aims to fill this gap by evaluating the risk of SPCs in NHL patients based on primary lymph node site and identifying critical latency periods during which this risk is heightened, contributing to this increased risk is crucial for developing targeted surveillance and preventive strategies Our data showed that the risk for overall SPC at any site was increased ~1.5 fold, which is similar to another

Table 2

The risk of nodal non-Hodgkin lymphoma patients to develop a second primary cancer across three latency periods stratified by location of primary lymph node.

Primary lymph node site	Head, face, and neck						Intrathoracic						Intra-abdominal						Axilla or arm						Inguinal region or leg						Pelvic			
	2–11		12–59		60–119		2–11		12–59		60–119		2–11		12–59		60–119		2–11		12–59		60–119		2–11		12–59		60–119		2–11		12–59	
Latency (months)	14 484.88		53 917.48		42 763.83		3790.77		13 419.77		11 096.13		10 516.61		36 257.98		27 283.87		4827.35		17 177.13		12 681.79		6096.43		22 846.46		18 056.24		1079.75		3607.44	
Person-years at risk	SIR	AER	SIR	AER	SIR	AER	SIR	AER	SIR	AER	SIR	AER	SIR	AER	SIR	AER	SIR	AER	SIR	AER	SIR	AER	SIR	AER	SIR	AER	SIR	AER	SIR	AER	SIR	AER	SIR	AER
All sites	1.61[a]	83.03	1.26[a]	35.31	1.32[a]	45.66	1.92[a]	93.58	1.57[a]	56.23	1.27[a]	25.09	1.41[a]	61.81	1.28[a]	43.22	1.24[a]	38.46	1.69[a]	96.18	1.31[a]	44.03	1.37[a]	54.76	1.56[a]	78.92	1.44[a]	64.10	1.35[a]	52.86	1.31	46.53	1.32[a]	48.56
Lip	0.00	−0.25	3.03	0.50	0.00	−0.25	0.00	−0.19	8.35[a]	1.31	5.57	0.74	3.46	0.68	0.00	−0.28	0.00	−0.29	0.00	−0.23	2.51	0.35	0.00	54.76	6.08	1.37	1.62	0.17	2.00	0.28	0.00	−0.27	0.00	−0.28
Salivary gland	3.80	1.02	1.47	0.18	3.41[a]	0.99	0.00	−0.29	0.00	−.29	0.00	−0.27	0.00	−0.41	2.60	0.68	1.56	0.26	0.00	−0.36	4.67	1.37	0.00	−0.24	0.00	−0.39	3.25	0.91	1.26	0.11	0.00	−0.41	0.00	−0.43
Nasopharynx	11.03[a]	1.26	1.50	0.06	0.00	−0.12	0.00	−0.09	8.84	0.66	0.00	−0.08	0.00	−0.13	0.00	−0.12	0.00	−0.12	0.00	−0.11	0.00	−0.11	7.27	−0.40	0.00	−0.12	0.00	−0.12	0.00	−0.12	0.00	−0.12	0.00	−0.12
Esophagus	2.82[a]	2.67	1.11	0.17	0.45	−0.87	4.71	4.16	1.41	0.43	1.86	0.84	0.57	-0.73	0.80	−0.34	0.20	−1.46	3.02	2.77	0.83	−0.24	3.25[a]	0.68	2.05	1.68	1.06	0.11	1.28	0.49	0.00	−1.66	0.00	−1.71
Stomach	1.85	1.91	0.74	-0.58	0.99	−0.01	1.58	0.96	2.36	2.15	1.25	0.36	2.74[a]	4.23	1.46	1.13	1.27	0.70	2.81	4.00	1.56	1.25	1.36	3.27	2.83	4.24	1.68	1.60	1.60	1.45	0.00	−2.45	1.12	0.29
Small intestine	3.32	1.45	1.13	0.09	0.97	−0.02	5.59	2.17	6.37[a]	2.51	0.00	−0.46	0.00	−0.70	1.87	0.64	0.90	−0.08	3.10	1.40	0.00	−0.70	2.08	0.84	2.54	0.99	1.28	0.19	0.00	−0.76	0.00	−0.70	3.78	2.04
Colon	1.50	4.84	1.03	0.30	0.98	−0.15	1.88	6.18	1.46	3.07	1.07	0.42	1.30	3.10	1.08	0.86	0.95	−0.52	−1.64	6.47	1.04	0.39	1.34	0.82	0.00[a]	−9.99	0.98	−0.20	1.02	0.24	1.80	8.22	0.27	−7.46
Anus	1.48	0.22	2.28	0.62	1.32	0.17	0.00	-0.34	0.00	−0.35	0.00	0.36	3.74	1.39	3.07[a]	1.12	0.00	−0.59	3.86	1.53	1.03	0.02	2.65	3.41	0.00	−0.48	0.87	−0.06	2.98	1.10	0.00	−0.50	0.00	−0.52
Liver	1.62	1.32	0.99	−0.02	1.22	0.56	0.00	−1.55	0.99	−0.01	0.62	−0.56	1.19	0.47	1.76[a]	1.90	1.87[a]	2.38	3.12	4.22	1.94	1.98	0.00	0.98	0.74	−0.57	0.74	−0.60	0.64	−0.95	8.05	16.22	3.44	5.90
Lung and bronchus	1.18	3.49	1.17	3.26	1.32[a]	6.48	2.77[a]	25.27	1.61[a]	8.20	1.21	2.48	1.20	4.30	1.08	1.67	1.01	0.13	1.85[a]	17.09	1.11	2.21	1.17	−2.32	1.73[a]	14.54	1.45[a]	9.11	1.44[a]	9.07	0.87	−2.66	2.06[a]	22.80
Trachea	0.00	-0.02	0.00	−0.02	0.00	−0.02	0.00	-0.01	70.11[a]	0.73	0.00	−0.01	0.00	−0.02	0.00	−0.02	0.00	−0.02	0.00	−0.02	0.00	−0.01	0.00	3.59	0.00	−0.02	0.00	−0.02	0.00	−0.02	0.00	−0.02	0.00	−0.02
Bones and joints	0.00	-0.14	1.29	0.04	0.00	−0.15	0.00	−0.13	0.00	−0.12	0.00	−0.12	0.00	−0.15	1.81	0.12	0.00	−0.16	0.00	−0.14	4.09	0.44	0.00	−0.01	0.00	-0.14	2.98	0.29	3.54	0.40	0.00	−0.15	0.00	−0.15
Melanoma	1.21	1.30	1.08	0.55	1.16	1.22	0.00	−5.10	1.59	3.04	1.74	3.82	2.09[a]	7.94	1.36	2.76	1.26	2.28	0.67	−2.05	1.86[a]	5.65	1.32	−0.15	1.20	1.38	1.20	1.46	0.47[a]	−4.30	0.00	−7.18	2.16	8.92
Female breast	0.8	-6.57	0.81	−6.32	0.80	−7.00	0.49	−11.62	0.88	−2.67	0.87	−5.02	0.42[a]	−20.52	0.82	−6.52	0.9	−3.90	0.31[a]	−24.75	1.01	0.38	0.98	−0.63	1.04	1.30	0.88	−4.16	0.96	−1.31	0.60	−13.49	0.88	−4.08
Bladder	1.50	3.68	0.88	−0.90	1.27	2.19	0.45	−3.16	0.54	−2.53	1.27	1.33	1.46	3.90	1.40[a]	3.44	0.96	-0.35	1.81	5.55	0.98	-0.12	0.95	1.06	1.02	0.16	1.47	3.94	1.25	2.24	3.26	19.27	0.62	−3.36
Kidney	4.40[a]	13.87	1.39	1.68	0.87	−0.58	4.28[a]	10.11	0.49	−1.54	0.61	−1.16	2.67[a]	7.73	1.60[a]	2.91	1.06	0.33	5.07[a]	16.63	1.10	0.41	1.40	−0.39	3.79[a]	12.07	1.54	2.45	0.68	−1.58	0.00	−4.52	0.59	−1.93
Thyroid	9.21[a]	14.77	2.16[a]	2.19	1.52	1.04	14.82[a]	22.14	2.59	2.74	2.78[a]	3.46	5.93[a]	9.49	2.19[a]	2.40	1.74	1.56	4.15[a]	6.29	0.84	−0.32	0.74	1.82	8.07[a]	12.93	1.81	1.57	1.33	0.69	14.67[a]	25.89	2.81	3.57
Hodgkin lymphoma	6.21[a]	1.74	6.60[a]	1.89	6.22[a]	1.77	7.71	2.30	26.43[a]	8.60	2.79	0.58	5.50	1.56	3.97[a]	1.03	13.59[a]	4.41	12.50[a]	3.81	5.25[a]	1.41	11.91[a]	−0.56	14.24[a]	4.58	3.78	0.97	16.04[a]	5.19	26.72	8.91	7.95	2.42
Non-Hodgkin lymphoma	4.92[a]	22.55	4.06[a]	18.18	4.88[a]	24.54	4.82[a]	16.73	3.50[a]	10.65	3.80[a]	11.29	5.55[a]	28.84	4.15[a]	20.72	3.74[a]	19.60	4.20[a]	18.94	5.24[a]	25.91	5.27[a]	3.61	8.78[a]	46.51	5.53[a]	27.97	5.71[a]	31.06	2.94	12.23	2.97[a]	12.87
Myeloma	3.08[a]	4.19	1.06	0.12	0.61	−0.91	5.19[a]	6.39	2.00	1.49	1.90	1.28	0.42	-1.31	0.82	−0.44	0.56	−1.17	3.85[a]	6.13	0.78	−0.50	0.33	27.48	1.57	1.19	0.80	−0.44	0.46	−1.30	0.00	−2.29	0.00	−2.40
Acute lymphocytic leukemia	5.02	0.55	1.34	0.05	4.91[a]	0.56	0.00	−0.13	0.00	−0.13	0.00	−0.12	0.00	−0.14	1.92	0.13	7.27[a]	0.95	15.73	1.94	4.32	0.45	0.00	−1.63	12.30	1.51	0.00	−0.14	7.71	0.96	0.00	−0.14	0.00	−0.14
Chronic lymphocytic leukemia	1.62	1.06	0.84	−0.29	1.22	0.42	2.04	1.35	0.59	−0.51	0.76	−0.28	0.49	−0.97	0.28[a]	−1.45	0.50	−1.12	3.59	4.48	0.64	−0.64	1.23	−0.14	0.00	−1.82	0.92	−0.14	0.54	−0.95	4.82	7.34	0.00	−2.01
Acute non-lymphocytic leukemia	3.31[a]	2.89	5.29[a]	5.57	5.23[a]	6.05	10.72[a]	9.57	13.21[a]	11.71	4.87[a]	3.58	4.12[a]	4.32	5.92[a]	7.10	5.17[a]	6.80	0.00	−1.28	4.80[a]	5.07	5.97[a]	0.44	1.26	0.34	7.12[a]	8.28	2.98[a]	2.94	0.00	−1.40	3.76	4.07
Acute myeloid leukemia	2.48	1.65	5.59[a]	5.33	5.23[a]	5.49	6.00	4.40	13.01[a]	10.32	5.38[a]	3.67	2.30	1.61	5.72[a]	6.14	5.44[a]	6.58	0.00	−1.14	4.87[a]	4.63	6.00[a]	7.22	1.42	0.48	7.60[a]	7.98	3.29[a]	3.08	0.00	−1.26	4.18	4.22
Acute monocytic leukemia	11.32	0.63	6.09	0.31	7.67	0.41	55.42[a]	2.59	16.50	0.70	0.00	-0.04	28.62[a]	1.84	12.50[a]	0.76	5.36	0.30	0.00	−0.06	9.68	0.52	13.15	6.57	0.00	−0.06	6.84	0.37	0.00	−0.06	0.00	−0.06	0.00	−0.07
Chronic myeloid leukemia	1.43	0.21	0.74	−0.13	1.70	0.39	0.00	−0.39	1.96	0.36	7.21[a]	2.33	1.78	0.42	0.99	−0.01	1.77	0.48	0.00	−0.49	1.14	0.07	5.70[a]	0.73	0.00	−0.51	4.98[a]	2.10	3.83[a]	1.64	0.00	−0.54	0.00	−0.57

AER, absolute excess risk (per 10 000); SIR, standardized incidence ratio (observed cases / expected cases).

[a]Indicates statistical significance ($P < 0.05$).

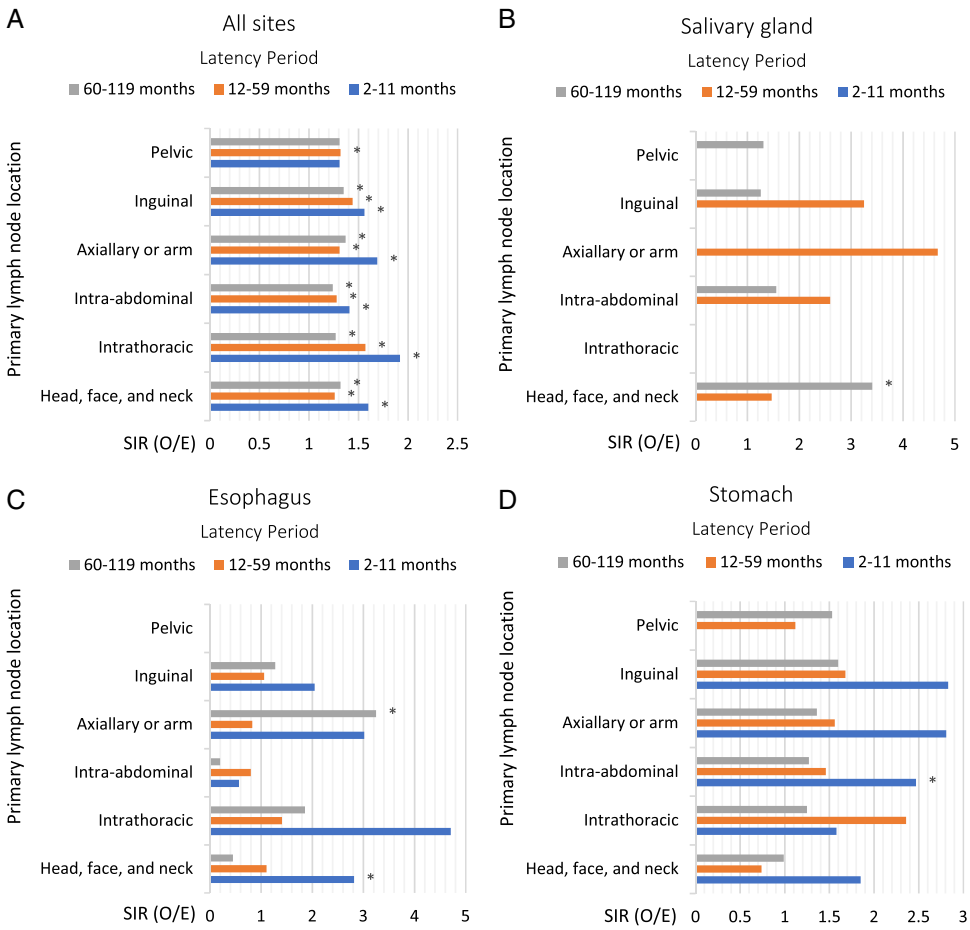

Figure 1. Standardized Incidence Ratios for second primary cancers in the sites: All sites (A), salivary gland (B), esophagus (C), and stomach (D) in NHL cases originating in different primary lymph node sites stratified across three latency periods. NHL, non-Hodgkin lymphoma; SIR, standardized incidence ratio (observed cases/expected cases). * indicates statistically significant SIRs.

registry-based study conducted in Germany[27]. The risk for some SPCs showed a significant SIR but the AER value was relatively low and thus were considered very rare SPCs and will not be given weight in our discussion.

In NHL patients of the head, face, and neck lymph node group, we demonstrated an elevated risk for thyroid and kidney cancers. The risk for thyroid cancer in NHL patients has been described previously in the literature. For instance, one study reported that 16.3% of patients treated for NHL developed thyroid malignancies[28]. Another study by Chattopadhyay *et al.*[4] indi cated an increased risk for thyroid cancer in NHL lymphoma with the prognosis remaining good. Another study by Chien *et al.*[29] conducted in Taiwan also showed an elevated risk for thyroid cancer in NHL patient. This increased risk for thyroid cancer in NHL patients of the head, face, and neck region could be attributed to receiving radiation to that area. Several studies have reported the development of thyroid cancer after radio therapy to the neck[30–32]. One particular study demonstrated a linear dependence of the rate of development of thyroid cancer on the radiation dose prescribed up to 20 Gy[33]. Kidney cancer risk in NHL patients has been very well described as well in the literature[19,27,34]. Our study is the first to demonstrate this asso ciation in the group of NHL originating in the head, neck, and face. While a biological mechanism is still lacking, we speculate that this association might be explained by the systemic effect of NHL treatment modalities. However, the results of previous stu dies in that regard were contradictory. Despite one study showing a lack of association between radiotherapy treatment and the development of renal cancer[34], another study showed a positive and significant association[35]. Kidney cancer was not related to cyclophosphamide treatment of lymphoma in another study[36]. This warrants more research in this area.

Patients with NHL originating in the intrathoracic lymph node group were at significant risk for thyroid, kidney, and lung cancers in the first year of NHL diagnosis. Lung cancer risk remained high in the next 12–59 months. Our study is the first to demonstrate an extremely high risk for cancer of the trachea in NHL patients of the intrathoracic lymph node, and also an elevated risk for lip cancer in the 12–59-month latency period. We were unable to find an explanation for these findings due to the lack of reporting for such SPCs in the literature. We speculate a role for common risk factors such as tobacco smoking. Furthermore, the AER values for trachea and lip cancer were low compared to the high SIR values, which can be explained by the fact these are unusually rare cancers or due to the large person-years risk for the Intrathoracic lymph node group, thus diluting the AER. On the other hand, lung cancers have been well described as SPCs in NHL survivors. A cohort study reported that NHL survivors

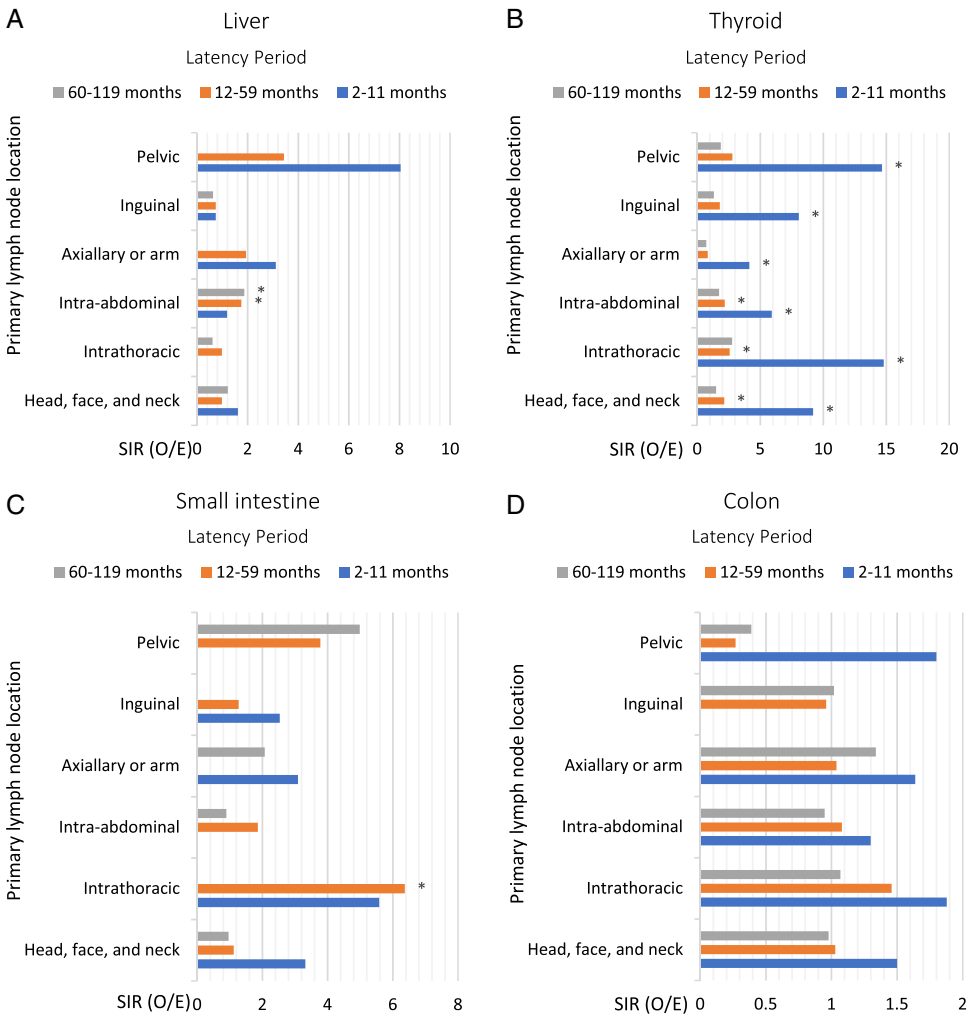

Figure 2. Standardized incidence ratios for second primary cancers in the sites: liver (A), thyroid (B), small intestine (C), and colon (D) in NHL cases originating in different primary lymph node sites stratified across three latency periods. NHL, non-Hodgkin lymphoma; SIR, standardized incidence ratio (observed cases/expected cases). * indicates statistically significant SIRs.

have a relative risk (RR) of 1.6 for developing lung cancer compared to the general population, with chemotherapy being a notable contributing factor[37]. Another study found that chemotherapy regimens for NHL containing alkylating agents and cyclophosphamide are particularly associated with an increased risk of lung cancer in NHL survivors[38]. Furthermore, lung cancer following radiation treatment has been described[39], although most other studies have denied such an association[40–43].

Patients with NHL originating in the intraabdominal region were at an increased risk for thyroid cancer during the first 2–11 months. Kidney cancer, stomach cancer, and melanoma were also significant SPCs in the 12–59-month latency period. Anal cancer was also a significant SP. In the 60–119-month interval, liver cancer showed a high significant risk. Melanoma risk in NHL survivors has been previously documented[44,45]. One study showed that the risk for melanoma was high in NHL and was associated with fludarabine-containing chemotherapy for patients with the chronic lymphocytic leukemia/small lymphocytic leukemia subtypes[46]. Other evidence points towards a common exposure mechanism such as ultraviolet radiation[47]. Our study is unique in that it showed a significant risk for melanoma only in NHL originating in the intraabdominal region during the first 10 years of NHL diagnosis. More research is required in order to understand the biological mechanism behind this intriguing association. Stomach cancer has been previously linked to NHL[41,48], and we are the first to report that this risk is only significant in patients with NHL originating in the intraabdominal lymph node group. This finding can be explained by the fact that, as Morton *et al.*[49] have demonstrated in their study, the risk for stomach cancer increased with increasing subdiaphragmatic radiation to the stomach, and also with increasing alkylating agents-containing chemotherapy, which was also demonstrated in another study[50]. Despite that, we also point out to the fact that the stomach is the most common location for extranodal NHL, and the possibility of misclassification should be kept in mind[51]. As for liver cancer, our results showed that the risk for second primary liver cancer is only significantly elevated in NHL patients with intraabdominal affected nodes. While we are the first to explicitly state the primary lymph node group of NHL to show an increased risk of liver cancer, several previous studies demonstrated an increased risk of liver cancer in NHL patients overall[11,52,53]. This association can be explained by the

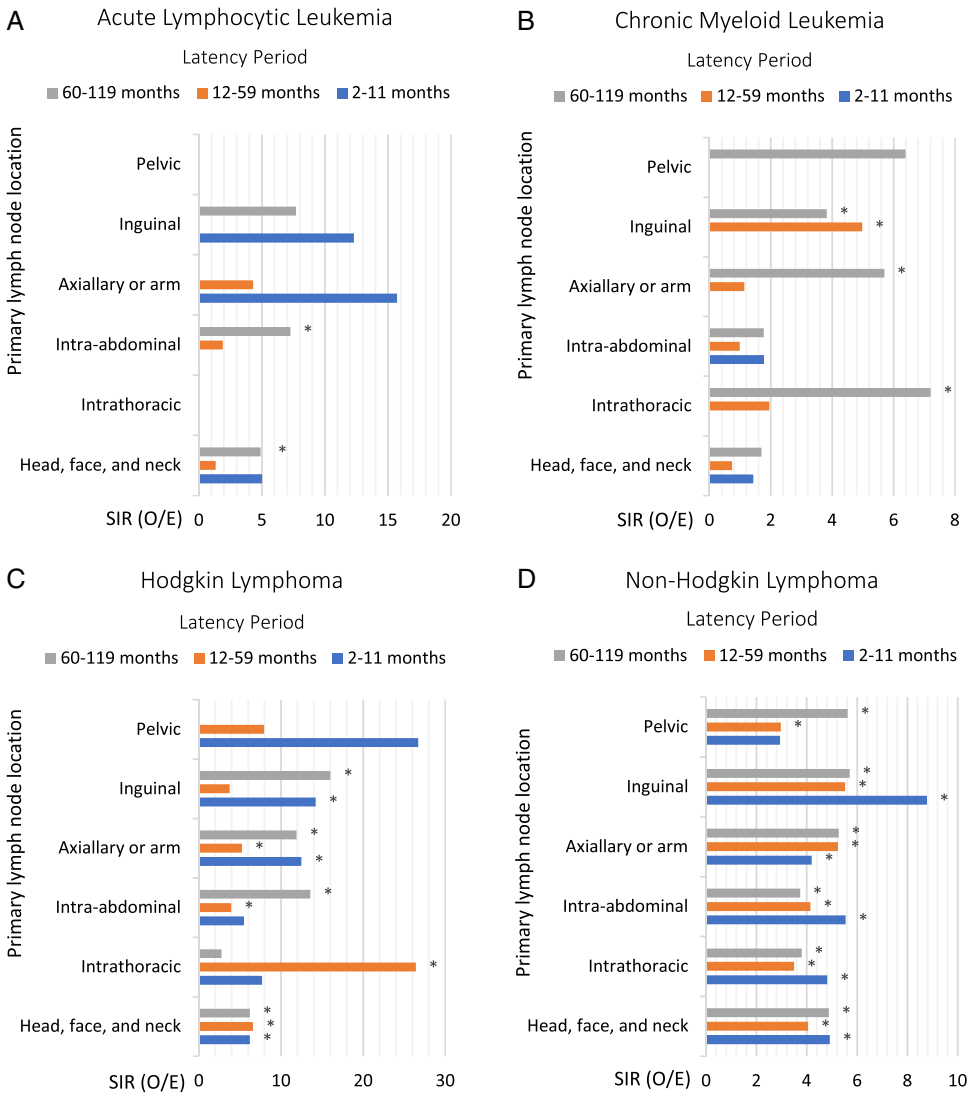

Figure 3. Standardized incidence ratios for second primary cancers in the sites: acute lymphocytic leukemia (A), chronic myeloid leukemia (B), Hodgkin lymphoma (C), and non-Hodgkin lymphoma (D), in NHL cases originating in different primary lymph node sites stratified across three latency periods. NHL, non-Hodgkin lymphoma; SIR, standardized incidence ratio (observed cases/expected cases). * indicates statistically significant SIRs.

fact that hepatitis C virus (HCV) is an important etiology for both NHL and liver cancer[54,55]. What is more intriguing is the fact that HCV was shown to be most strongly associated with the Marginal Zone Lymphoma subtype of NHL, commonly involving MALT, which is intra-abdominal[56]. The risk for anal cancer in NHL patients has not been extensively studied before. It is worth mentioning that one article linked this association to the shared etiology of human papillomavirus (HPV)[21].

As for NHL originating in the axillary region, kidney cancer, thyroid cancer, and lung and bronchus cancer in the 2–11-month latency period. For the inguinal lymph node NHL, the risk for kidney and thyroid cancers during the 2–11-month latency period was also significant. In the pelvic NHL group, during the 2–11 months latency period, thyroid cancer presented a significant risk, while in the 12–59 months latency period, lung and bronchus cancer showed a significant risk. While this is intuitive for thyroid and lung cancers that are in anatomical proximity to the axillary area and thus more likely to be affected by radiation treatment of NHL originating in that area, we are unable to provide an explanation for the elevated risk for kidney cancer in inguinal NHL with a higher SIR compared to the risk in inguinal NHL, despite the anatomical contradiction. One can only speculate as to the systemic effects of chemotherapy through mechanisms of DNA damage and mutagenesis[57]. For most SPCs, the location of the primary lymph node and that of the SPC was consistent, and the local effect of treatment to that area seemed the most plausible explanation to our findings. As biological mechanisms of second primary cancer development are still largely lacking, future studies are encouraged.

The risk for hematological malignancies in our study as a SPC in NHL patients was also significant. HL was significant in all primary NHL lymph node groups except the pelvic region. The risk was highest in the intrathoracic group during the 12–59-month latency period. Evidence of this association is ample in the literature[4,9,19,29,37,58]. The role of treatment-related factors has not been conclusive yet. One study indicated that

radiotherapy of a previous lymphoma increases the risk for subsequent second primary HL[59], while other studies argued that it is autoimmune conditions mediated by B-cell responses significantly increase the risk of NHL, particularly diffuse large B-cell lymphoma (DLBCL) and marginal zone lymphoma, and that this immune dysregulation can also predispose individuals to subsequent second primary lymphomas, not treatment-related factors[60].

Interestingly, the risk for ALL was only significant in the head, face, and neck and intraabdominal groups during the 60–119-month latency period. The risk for CLL was not significantly elevated in any of the groups of our cohort. The young age group and older age group for ALL and CLL, respectively, might play a role in our findings, but due to the descriptive nature of our study, we leave this inquiry for another study. Previous research has consistently shown that the risk for leukemia is elevated in NHL patients[4,9,42]. One study demonstrated that age, time since diagnosis, and receiving chemotherapy directly influence the risk of developing therapy-related acute myeloid leukemia in non-Hodgkin lymphoma survivors[61], while other studies indicated an elevated risk after auto-transplants for lymphomas[62].

Limitations

Our study has certain limitations. The SEER database has missing information concerning lifestyle factors, genetic predispositions, and family history of cancer, affecting our ability to control for confounding factors. The lack of detailed information about specific chemotherapy regimens, radiation doses, and newer treatment modalities like immunotherapy or targeted therapies restricts the evaluation of the impact of specific treatments on SPC risk. Increased surveillance and follow-up in NHL survivors may lead to earlier detection of SPCs, potentially inflating the observed incidence rates, especially in the first few years post-diagnosis and treatment. The broad classification of NHL in the study masks subtype-specific risks and nuances in SPC development due to the heterogeneity of NHL subtypes. Additionally, the findings, based on data predominantly from the United States, may not be generalizable to populations in other countries with different healthcare systems, treatment protocols, and genetic backgrounds.

Relevance and implications

The findings of this study have significant implications for clinical practice in the management and long-term care of NHL survivors. The study highlights the elevated risk of SPCs associated with different primary lymph node locations and various latency periods following the initial NHL diagnosis. Understanding these risk patterns enables clinicians to develop personalized surveillance strategies tailored to the primary lymph node site and the specific timing of increased risk. This targeted approach can facilitate early detection and timely intervention, potentially improving survival outcomes and quality of life for NHL survivors. Furthermore, the identification of specific cancers with high SIRs and AERs underscores the need for vigilance in monitoring these malignancies, thereby aiding in more effective patient management and reducing the burden of SPCs.

While this study provides valuable insights, it also underscores the need for further research to elucidate the underlying mechanisms driving the development of SPCs in NHL survivors. Future studies should aim to investigate the biological, genetic, and environmental factors contributing to these risks. Optimal study designs would include prospective cohort studies with detailed treatment data, including information on chemotherapy regimens, radiation doses, and newer modalities such as immunotherapy and targeted therapies. Additionally, incorporating genetic and molecular profiling could help identify specific patient subgroups at higher risk, facilitating the development of precision medicine approaches. Research should also explore the long-term effects of emerging treatments, such as CAR T-cell therapy and monoclonal antibodies, on SPC development. Comparative studies between different treatment modalities could provide insights into the relative risks and benefits, guiding therapeutic decision-making. Moreover, international collaborative studies could help generalize the findings to diverse populations and healthcare settings, enhancing the global applicability of the results.

Conclusion

Our study highlights the significant risk of second primary cancers in patients diagnosed with nodal NHL, varying by primary lymph node site and latency period. These results emphasize the need for personalized surveillance strategies tailored to the primary lymph node site to improve early detection and intervention. Further research is required to understand the underlying mechanisms and treatment-related factors contributing to SPC development. Such efforts are crucial to reducing the incidence and impact of SPCs, ultimately improving the long-term survival and quality of life for NHL survivors.

Ethical approval

As this study involves retrospective analysis of data deidentified and decoded by the Surveillance, Epidemiology, and End Results (SEER) Program and did not involve any direct or indirect patient contact or intervention, an Institutional Review Board (IRB) approval was not required.

Consent

Our study did not involve any direct or indirect human contact. We utilized a publicly available decoded database (SEER). This is in line with the guidelines by the **OHRP.**https://www.hhs.gov/ohrp/regulations-and-policy/guidance/research-involving-coded-privateinformation/ index.html

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None.

Author contribution

Conceptualization: A.H. Data curation: A.H. Formal analysis: A.H. Investigation: A.H. Methodology: A.H. Supervision: S.H. Writing—original draft: A.H. Writing—review: S.H. All writers agreed on the final manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

Our study used publicly deidentified data available online at https://seer.cancer.gov/. Our study not require any human contact whatsoever. As such, registering our study in a registry is not applicable.

Guarantor

Ali Hemade.

Data availability statement

Data utilized in our study are publicly available as part of the SEER database.

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