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Original Article

Trends in the risk of second primary malignances after non-Hodgkin's lymphoma

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Abstract: Patients with non-Hodgkin's lymphoma (NHL) have an increased risk of developing second primary malignances (SPMs). In the current study, we aimed to evaluate the trends and relative clinical variables of SPM risk among NHL survivors over the past four decades. Standardized incidence ratio (SIR) and cumulative incidence frequency (CIF) were assessed in patients diagnosed with first primary NHL between 1975-2016 from the Surveillance, Epidemiology, and End Results (SEER) database. As a result, the overall SIR was 1.13 for SPMs of all sites among NHL survivors. Risk factors included male patients, "other" races, chemotherapy and radiation, and younger age at the time of NHL diagnosis. The relative and cumulative risk for both hematological and solid second cancers after NHL increased over time, whereas the increasing trend was more remarkable for hematological malignances compared with solid tumors. For individual cancer sites, the trends of SIRs varied. A significantly increasing trend of SPM risk was observed in the group receiving chemotherapy and those younger than 40 years at the time of NHL diagnosis. Recent calendar years was not an independent risk factor after adjusting age, race, gender, and therapies in the multivariate Cox proportional hazard regression. To conclude, the current study showed that the relative and cumulative risk of developing SPMs significantly increased in patients diagnosed with NHL in recent years. The trend of SPM risk was associated with certain clinical and demographic variables, and might vary according to different cancer types.

Keywords: Non-Hodgkin's lymphoma, second primary malignancy, second malignant neoplasm, hematological second primary cancer, solid second primary cancer

Introduction

It has been recognized that the risk of developing SPMs increased after a primary tumor. Common risk factors include the genetic susceptibility, immunodeficiency, environmental and treatment exposure, and family history [1-4]. NHL is one of the most common hematological malignances. Over the past several decades, with the substantial development of NHL therapies, the survivorship of NHL patients has been largely improved. There have been studies about the risk of second malignances subsequent to NHL [5-8]. However, previous studies mainly focused on the development of SPMs among NHL patients with different clinical and demographic characteristics, without reporting the risk of SPMs in different study periods [9-11]. Besides, only a few studies included NHL patients who were diagnosed after 2000 [12]. It's important to analyze how the risk of SPMs changed over time and how clinical and demographic factors alter SPM risk in different time periods, especially in the rituximab era. Here, based on the large population with long-term follow-up data, we performed an analysis of the risk of SPMs among NHL survivors, taking into account race, gender, age at NHL diagnosis, treatments, SPM types, with regard to SPM development in different study periods, hoping to improve the current understanding of SPMs after NHL.

Methods

Study population

Patients diagnosed with first primary NHL between 1975 and 2016 were identified in the SEER database by the International Classi-

fication of Diseases for Oncology, 3rd Edition ("site recode ICD-0-3/WHO 2008"). We excluded the synchronous primary malignances by requiring a minimum of 1-year interval between cancer diagnoses. Subsequent NHL and lymphocytic leukemia were also excluded from the study considering the difficulty of distinguishing disease progression from primary malignances. Information regarding demographic and clinical variables, including SPM types, patient gender, race, treatment, age and calendar year at the time of NHL and SPM diagnosis, and survival time were abstracted. The calendar years were divided into four periods, including 1975-1989, 1990-1999, 2000-2009, and 2010+. We used the SEER 9 database for the calculation of SIR and absolute excess rate (AER) due to that the SEER Program used the SEER 9 database to calculate the relative risk of SPMs in the period from 1975 to 2016. Cohorts selected from the SEER 18 program were used for the analyses of the cumulative incidence of SPMs.

Statistical analysis

We evaluated the relative risk of SPMs among NHL survivors by SIR and corresponding 95% confidence interval (CI). SIR was calculated by the ratio of observed (O) to expected (E) events, which was estimated by the incidence rate of the general population after adjusting race, gender, age, and calendar year. The AER was calculated by dividing the subtraction of the observed and expected events by person-years at risk. Poisson distribution was used to estimate the 95% CI of observed events. The distribution of demographic and clinical variables in patients diagnosed with NHL in different periods was presented as number and frequency. The cumulative incidence of SPMs was assessed with death treated as a competing risk event. The effect of clinical variables on the cumulative risk was evaluated using the multivariate Cox proportional hazard regression. Patients who developed multiple second malignances were counted only once in the analyses of SPMs of all sites. When analyzing second malignances of specific sites, patients with multiple second cancers were included without regarding whether the cancer was preceded by another one or not.

SIR was calculated using SEER*Stat software version 8.3.8. Other analyses were performed in SPSS statistical software, version 25 (IBM Corp, Armonk, NK), and R software, version 4.03. All *P* values were two-sided, with the value less than 0.05 defined as statistically significant.

Results

A total of 110,701 patients with first primary NHL were identified in the SEER 9 database during the period between 1975-2016, with a follow-up time of 821,514.55 person-years at risk (**Table 1**). The cohort consisted of 59,135 male and 51,566 female patients. 85.67% were the white race. The mean age of patients at the time of NHL diagnosis was 60.32 years, and it increased across the study periods. During the whole study period, 23.21% patients received radiation, and 76.79% patients received chemotherapy for NHL. Patients who were diagnosed with NHL in the period from 1990 to 1999 had a higher proportion of receiving chemotherapy compared with other periods, whereas the ratio of receiving radiation successively declined, with the lowest ratio observed in the period 2010-2016.

Relative and absolute risk of SPMs among NHL survivors

After a follow-up of 821,514.55 person-years at risk, 12,169 people with first primary NHL were observed to develop SPMs. The risk of SPMs among NHL survivors was elevated compared with the general population, with a 13% higher risk of developing any SPM in the whole study period (95% CI: 1.11-1.15, $P<0.05$) (**Table 2**). The relative risk of developing second solid tumors was slightly higher among NHL survivors (SIR: 1.07, 95% CI: 1.05-1.09, $P<0.05$), while it was more significantly increased for hematological malignances (SIR: 2.72, 95% CI: 2.56-2.88, $P<0.05$). Solid tumors contributed to the absolute excess risk more than hematological malignances, with the AER being 8.96 and 7.87 for second solid and hematological cancers, respectively. For individual solid cancers, we noted a remarkably higher SIR of Kaposi sarcoma (KS) (SIR: 4.58, 95% CI: 3.5-5.88), followed by bones and joints carcinoma (SIR: 2.88, 95% CI: 2-4), salivary gland tumor (SIR: 2.25, 95% CI: 1.77-2.83). Increased SIRs were also observed in other cancer sites, including lip, tongue, stomach, cecum, ascending colon, liver, nose, nasal cavity and middle

Table 1. Characteristics of selected patients in the SEER 9 database

Characteristics	1975-2016 (N=110,701)	1975-1989 (N=24,959)	1990-1999 (N=27,059)	2000-2009 (N=35,482)	2010-2016 (N=23,201)
Person-years	821,514.55	247,674.93	256,062.37	259,054.51	58,722.75
Mean age, years	60.32	59.36	60	60.64	61.25
Gender, N (%)					
Male	59,135 (54.28%)	12,920 (52.75%)	14,396 (54.91%)	19,001 (54.01%)	23,201 (55.54%)
Female	51,566 (45.72%)	12,039 (47.25%)	12,663 (45.10%)	16,481 (45.99%)	12,818 (44.46%)
Age, N (%)					
<20	2,789 (2.52%)	722 (2.89%)	640 (2.37%)	848 (2.39%)	579 (2.50%)
20-39	10,687 (9.65%)	2,654 (10.63%)	2,974 (10.99%)	3,179 (8.96%)	1,880 (8.10%)
40-49	13,484 (12.18%)	2,821 (11.30%)	3,638 (13.44%)	4,640 (13.08%)	2,385 (10.28%)
50-59	22,081 (19.95%)	4,968 (19.90%)	4,812 (17.78%)	7,447 (20.99%)	4,854 (20.92%)
60-69	26,694 (24.11%)	6,590 (26.40%)	6,110 (22.58%)	7,787 (21.95%)	6,207 (26.75%)
70+	34,966 (31.57%)	7,204 (28.86%)	8,885 (32.84%)	11,581 (32.64%)	7,296 (31.45%)
Race, N (%)					
White	94,842 (85.67%)	22,629 (90.66%)	23,564 (87.08%)	29,840 (84.10%)	18,809 (81.07%)
Black	7,738 (7.0%)	1,310 (5.25%)	1,772 (6.55%)	2,704 (7.62%)	1,952 (8.41%)
Other[a]	7,291 (6.59%)	957 (3.83%)	1,607 (5.94%)	2,642 (7.45%)	2,085 (8.99%)
Unknown	830 (0.75%)	63 (0.25%)	116 (0.43%)	296 (0.83%)	355 (1.53%)
Chemotherapy, N (%)					
Yes	67,185 (60.69%)	15,025 (60.20%)	16,949 (62.64%)	21,386 (60.27%)	13,825 (59.59%)
No/Unknown	43,516 (39.31%)	9,934 (39.80%)	10,110 (37.36%)	14,096 (39.73%)	9,376 (40.41%)
Radiation, N (%)					
Yes	25,313 (23.21%)	7,087 (28.89%)	6,571 (24.66%)	7,464 (21.36%)	4,191 (18.26%)
No/Unknown	83,763 (76.79%)	17,445 (71.11%)	20,077 (75.34%)	27,484 (78.64%)	18,757 (81.74%)

[a]Include American Indian/AK Native, Asian/Pacific Islander.

ear, lung, thyroid, kidney, and skin melanoma during the whole study period 1975-2016. Additionally, the relative risk was lower for breast (SIR: 0.95, 95% CI: 0.9-1) and prostate (SIR: 0.94, 95% CI: 0.9-0.98, $P<0.05$) cancers. For hematological malignances, the relative risk was highest for Hodgkin's lymphoma (HL) (SIR: 7.44, 95% CI: 6.53-8.45), followed by acute myeloid leukemia (AML) (SIR: 4.76, SIR: 4.35-5.19).

We observed a successively increasing trend of the SIR for SPMs of all sites over time, with the highest SIRs seen in the period 2010-2016 (SIR: 1.31, 95% CI: 1.22-1.39) (**Figure 1**), and the lowest in the period between 1975 and 1989 (SIR: 1.11, 95% CI: 1.07-1.15). A more remarkably increasing trend was observed for hematological SPMs, with the SIR being 1.77 during the period 1975-1989 (95% CI: 1.54-2.03), and reaching 4.32 in the period 2010-2016 (95% CI: 3.60-5.13). For individual cancers, the SIRs for HL and AML was significantly increased across the study periods. We noted that the relative risk of developing second multiple myeloma was statistically higher among NHL survivors in the period from 2010-2016 (SIR: 2.11, 95% CI: 1.44-3). For second solid malignances, we noted the SIR was slightly decreased in the period 1990-1999 (SIR: 1.05, 95% CI: 1.01-1.09, $P<0.05$) compared with 1975-1989 (SIR: 1.09, 95% CI: 1.05-1.12), although it was highest during 2010-2016 (SIR: 1.17, 95% CI: 1.1-1.26). For specific cancers, we observed elevated SIRs for oral cavity and pharynx, ascending colon, stomach, liver, thyroid, and skin cancers, and decreased SIRs for cancers of bones and joints, prostate, bladder, lung, and breast in more recent years.

In the analysis of SIRs by various clinical and demographic variables (**Table 3**), we observed that the SIR was higher for those diagnosed with NHL at a younger age, while the maximum AER was observed in the group of 40-49 years (**Figure 2**). When stratified by study periods, SIR

Table 2. Standardized incidence ratio and absolute excess risk for individual second primary malignances after non-Hodgkin's lymphoma in the period 1975-2016

Second cancer or cancer sites	Observed	Expected	Standardized Incidence Ratio	Lower 95% CI	Upper 95% CI	Absolute Excess Risk
All sites, excluding NHL and lymphocytic leukemia	12,169	10,797.71	1.13*	1.11	1.15	16.69
Solid cancer	11,085	10,342.86	1.07	1.05	1.09	8.91
Lip	54	31.07	1.74*	1.31	2.27	0.26
Tongue	133	80.06	1.66*	1.39	1.97	0.60
Salivary gland	74	32.84	2.25*	1.77	2.83	0.46
Stomach	290	228.57	1.27*	1.13	1.42	0.69
Cecum	310	251.23	1.23*	1.1	1.38	0.66
Ascending colon	241	190.94	1.26*	1.11	1.43	0.56
Liver	185	154.8	1.20*	1.03	1.38	0.34
Nose, nasal cavity and middle ear	33	17.92	1.84*	1.27	2.59	0.17
Lung and bronchus	2,491	1,908.75	1.31*	1.25	1.36	6.56
Bones and joints	35	12.17	2.88*	2	4	0.26
Melanoma of the skin	657	509.67	1.29*	1.19	1.39	1.66
Breast	1,410	1,491.91	0.95*	0.9	1	-0.92
Prostate	2,076	2210.12	0.94*	0.9	0.98	-1.51
Bladder	949	741.6	1.28*	1.2	1.36	2.34
Kidney	411	333.91	1.23*	1.11	1.36	0.87
Endocrine system	241	150.62	1.60*	1.4	1.82	1.02
Thyroid	224	139.27	1.61*	1.4	1.83	0.95
Hematological diseases	1,102	405.76	2.72	2.56	2.88	7.87
Hodgkin's lymphoma	238	31.98	7.44*	6.53	8.45	2.32
Myeloma	198	188.67	1.05	0.91	1.21	0.11
Acute myeloid leukemia	497	104.51	4.76*	4.35	5.19	4.42
Acute monocytic leukemia	30	5.67	5.29*	3.57	7.55	0.27
Chronic myeloid leukemia	90	48.49	1.86*	1.49	2.28	0.47
Kaposi sarcoma	61	13.33	4.58*	3.5	5.88	0.54
Miscellaneous	397	289.61	1.37*	1.24	1.51	1.21

*$P<0.05$.

was seen elevated across the study periods for all age groups, and the most significantly increasing trend was noted in the group less than 20 years, with the SIR increasing about 2 times in the period from 2010 to 2016 (SIR: 6.78, 95% CI: 0.82-24.51) than that in the period 1975-1989 (SIR: 2.92, 95% CI: 2.13-3.9). Male patients had an overall higher SIR for any SPM compared with female in earlier periods, though it became opposite in the period 2010 through 2016. Besides, we noted a higher SIR in "other" races, which included Asians, Native Americans, and Pacific Islanders, compared with whites and blacks in the whole study period.

The relative risk of developing any SPM remained higher among NHL survivors for at least 30 years after NHL diagnosis (SIR: 1.17, 95% CI: 0.97-1.39) (**Figure 3**). We further stratified the relative risk of developing SPMs in different latency time by cancer types. The SIR for solid SPMs mirrored the trend of SPMs of all sites. Although it decreased slightly in the latency period of 180-239 months, it increased after that and reached the maximum after more than 30 years of follow-up (SIR: 1.18, 95% CI: 0.98-1.41). In the contrast, the SIR for second hematological malignances was highest in the first five years after NHL diagnosis (SIR: 3.24, 95% CI: 2.96-3.55).

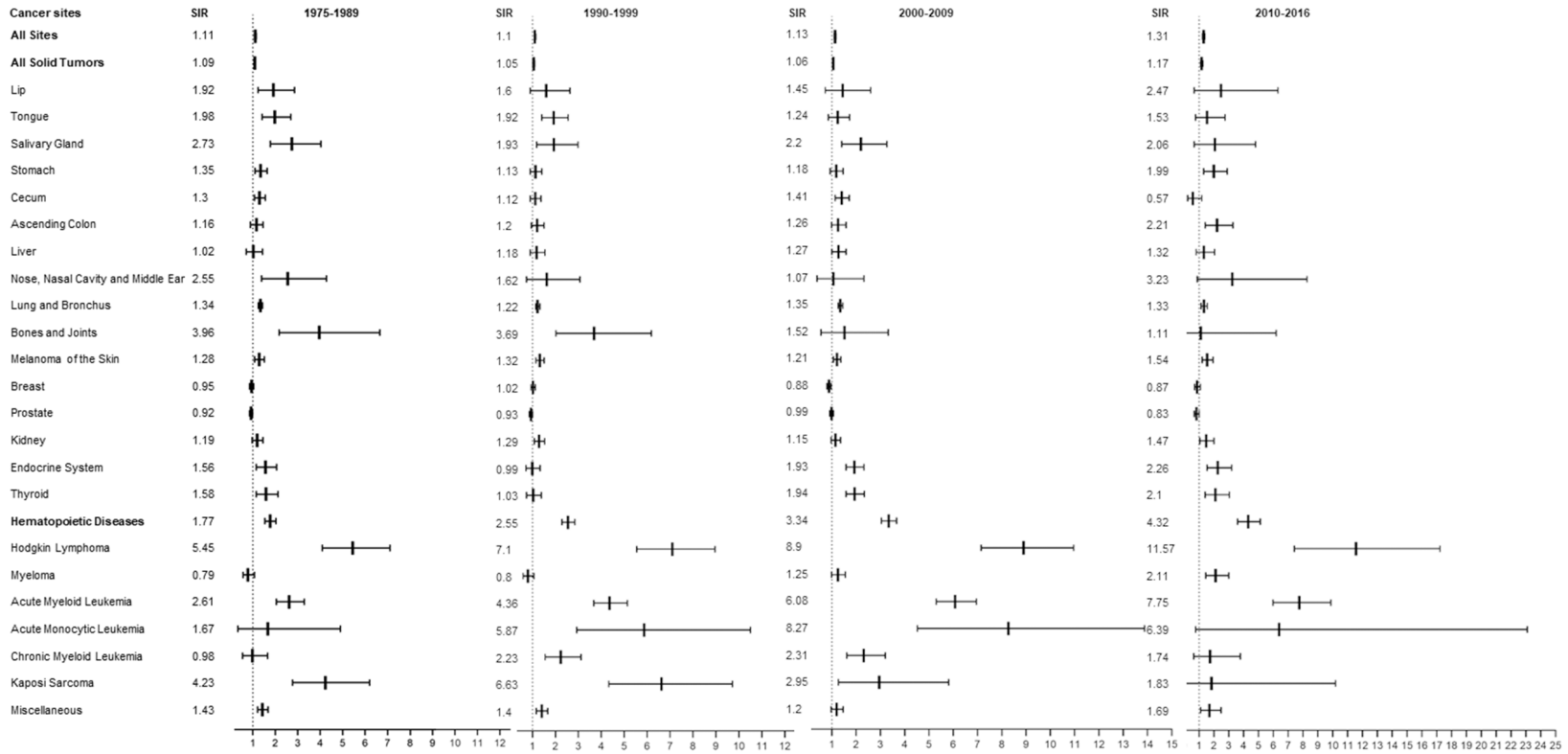

Figure 1. Standardized incidence ratios (SIRs) for individual second primary malignances (SPMs) after non-Hodgkin's lymphoma in different study periods. The SIRs in the four period 1975-1989, 1990-1999, 2000-2009, and 2010-2016 were compared. The SIRs for SPMs of all sites increased over time, with the highest SIR observed in the period 2010-2016. The SIRs for hematological malignances also increased during the whole studied period, but decreased for second solid tumors in the period 1990-1999 compared with 1975-1989. For specific cancer sites, the SIRs for oral cavity and pharynx, ascending colon, stomach, liver, thyroid, and skin cancers increased over time, while for cancers of bones and joints, prostate, bladder, lung, and breast, the SIRs decreased in more recent years.

Table 3. Standardized incidence ratio for any second primary malignances among non-Hodgkin's lymphoma (NHL) survivors by race, sex, chemotherapy, radiation, and age at the time of NHL diagnosis in different study periods

	1975-2016 (95% CI)	1975-1989 (95% CI)	1990-1999 (95% CI)	2000-2009 (95% CI)	2010-2016 (95% CI)
Age (years)					
<20	3.55 (2.83-4.4)	2.92 (2.13-3.9)	3.81 (2.33-5.89)	6.59 (3.77-10.7)	6.78 (0.82-24.51)
20-39	1.64 (1.51-1.77)	1.43 (1.28-1.6)	1.70 (1.48-1.95)	2.23 (1.84-2.68)	2.56 (1.46-4.15)
40-49	1.32 (1.25-1.4)	1.31 (1.2-1.43)	1.23 (1.11-1.35)	1.45 (1.3-1.62)	1.76 (1.28-2.37)
50-59	1.15 (1.1-1.19)	1.08 (1.01-1.16)	1.12 (1.04-1.2)	1.21 (1.13-1.29)	1.44 (1.23-1.68)
60-69	1.09 (1.06-1.13)	1.07 (1.01-1.14)	1.04 (0.98-1.11)	1.12 (1.05-1.18)	1.33 (1.19-1.48)
70+	1.02 (0.99-1.06)	0.97 (0.9-1.04)	1.03 (0.97-1.09)	1.01 (0.95-1.06)	1.19 (1.07-1.31)
Gender					
Male	1.14 (1.11-1.16)	1.11 (1.06-1.16)	1.12 (1.07-1.17)	1.15 (1.11-1.2)	1.29 (1.18-1.4)
Female	1.11 (1.08-1.14)	1.11 (1.06-1.17)	1.08 (1.03-1.13)	1.10 (1.05-1.16)	1.33 (1.21-1.47)
Race					
White	1.12 (1.1-1.14)	1.10 (1.06-1.13)	1.10 (1.06-1.13)	1.12 (1.08-1.16)	1.32 (1.23-1.41)
Black	1.23 (1.14-1.32)	1.25 (1.08-1.44)	1.18 (1.03-1.34)	1.27 (1.12-1.44)	1.16 (0.89-1.49)
Other[a]	1.33 (1.22-1.43)	1.35 (1,13-1.6)	1.23 (1.06-1.41)	1.33 (1.17-1.52)	1.60 (1.24-2.03)
Chemotherapy					
No/Unknown	1.05 (1.02-1.08)	1.03 (0.98-1.09)	1.03 (0.98-1.08)	1.06 (1.01-1.11)	1.13 (1.02-1.25)
Yes	1.19 (1.16-1.22)	1.17 (1.12-1.23)	1.16 (1.11-1.21)	1.19 (1.14-1.24)	1.44 (1.33-1.56)
Radiation					
No/Unknown	1.12 (1.1-1.14)	1.09 (1.05-1.14)	1.09 (1.05-1.13)	1.12 (1.08-1.16)	1.33 (1.24-1.43)
Yes	1.16 (1.12-1.2)	1.15 (1.08-1.22)	1.16 (1.09-1.23)	1.17 (1.09-1.25)	1.15 (0.97-1.35)

[a]Include American Indian/AK Native, Asian/Pacific Islander.

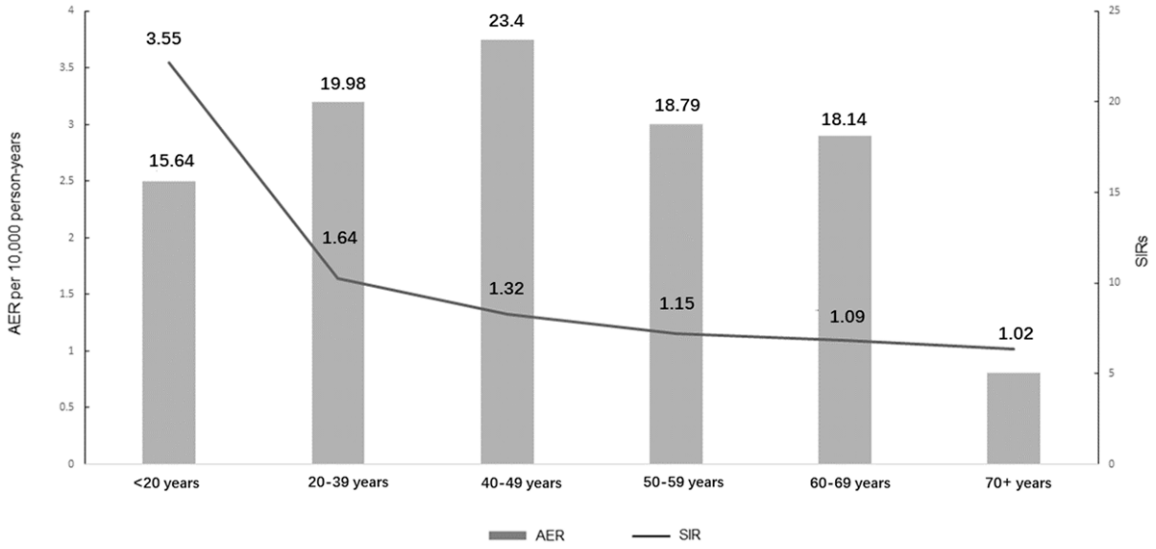

Figure 2. Standardized incidence ratios (SIRs) and absolute excess rates (AERs) for second primary cancers by patient age at the time of non-Hodgkin's lymphoma diagnosis. The SIR was higher for patients diagnosed with NHL at a younger age, while the maximum AER occurs in the group of 40-49 years.

The SIR was higher for those receiving chemotherapy compared with those not during the whole study period (SIR: 1.19, 95% CI: 1.16-1.22 vs. SIR: 1.05, 95% CI: 1.02-1.08) (**Table**

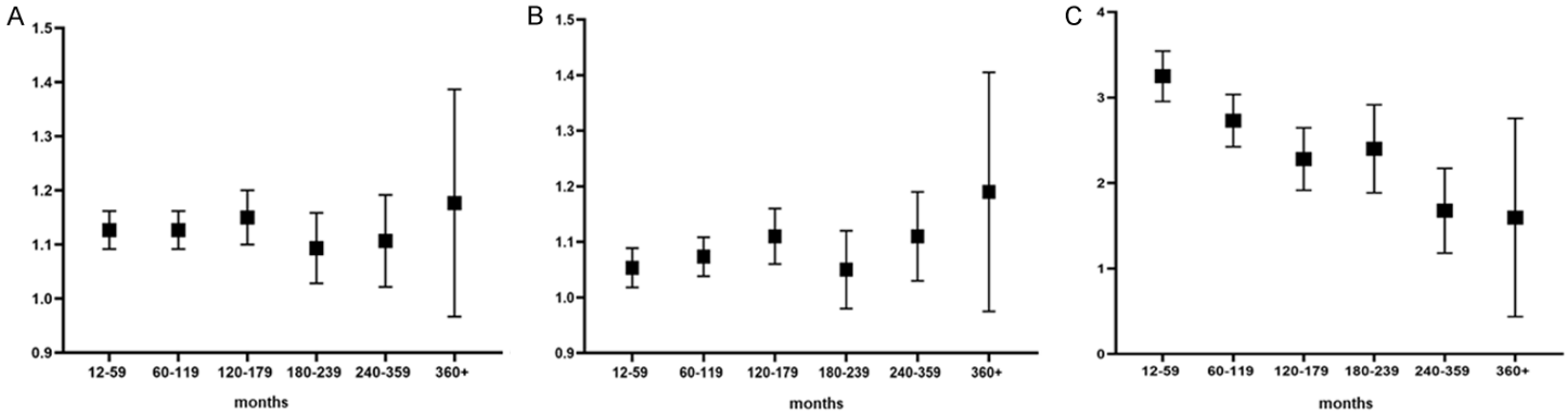

Figure 3. Standardized incidence ratios (SIRs) of second primary malignances (SPMs) during the follow-up after the diagnosis of non-Hodgkin's lymphoma (NHL). A. SIRs of any SPMs during the follow-up after the diagnosis of NHL. The SIRs for SPMs of any sites remained higher among NHL survivors for more than 30 years after the diagnosis, although there was not a progressively increasing or decreasing trend over time. B. SIRs of second solid malignances during the follow-up after the diagnosis of NHL, the trend was similar with that for SPMs of any sites. C. SIRs of second hematological malignances during the follow-up after the diagnosis of NHL. It can be observed that the SIR was highest in the first five years after the diagnosis of NHL.

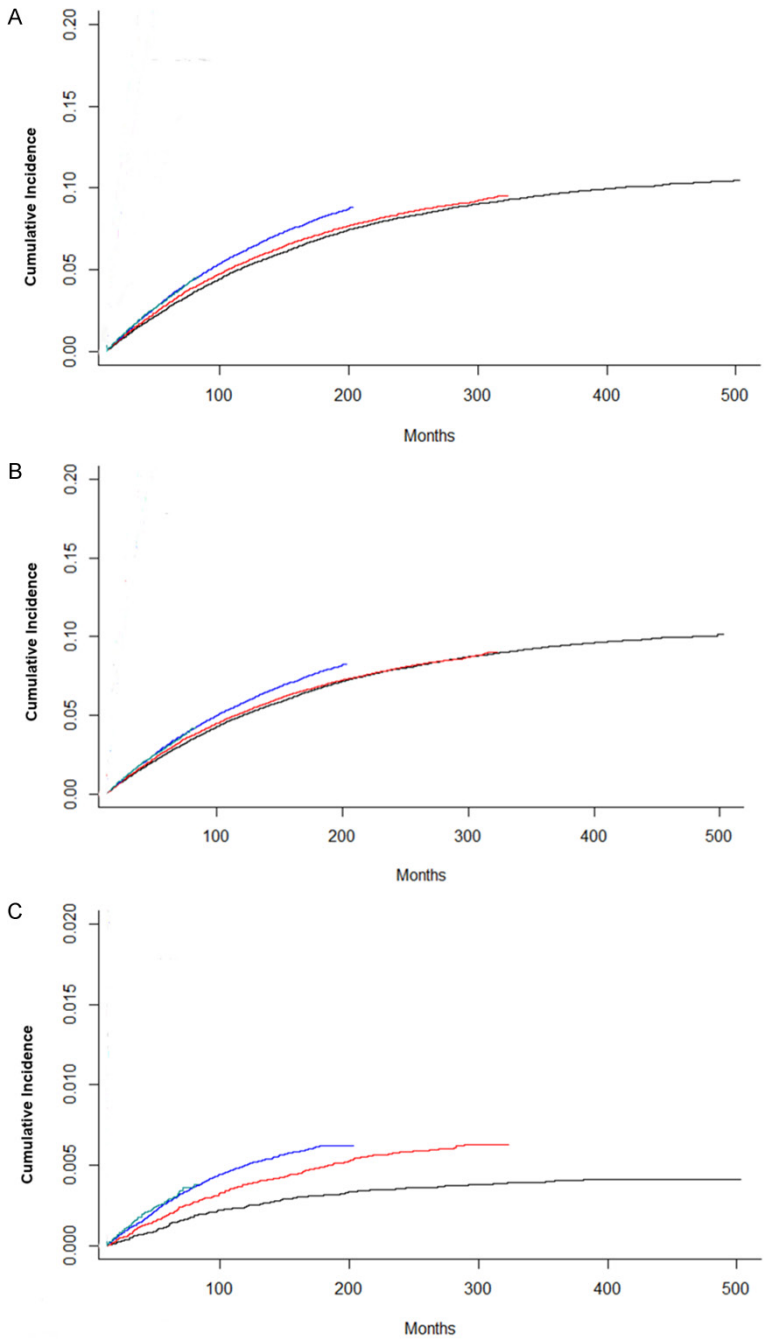

Figure 4. Cumulative incidence of second primary malignances (SPMs) with death treated as a competing event in different study periods. A. Cumulative incidence of developing any SPMs. The cumulative incidence for SPMs was higher in more recent years. B. Cumulative incidence of developing solid SPMs. C. Cumulative incidence of developing hematological SPMs, which increased more significantly than solid SPMs in recent years.

3). Although both groups had an increasing SPM risk over time, we observed a more significant increase in the group receiving chemotherapy. Patients receiving radiation had a higher risk of developing any SPM (SIR: 1.16, 95% CI: 1.12-1.2) compared with those not (SIR: 1.12, 95% CI: 1.1-1.14). However, the SIR in the group receiving radiation decreased in the period 2010-2016 (SIR: 1.15, 95% CI: 0.97-1.35), and became lower than that in the group not receiving radiotherapy (SIR: 1.33, 95% CI: 1.24-1.43).

Cumulative incidence according to different periods

As shown in **Figure 4**, we analyzed the cumulative incidence of SPMs in different time periods and observed a significantly increasing trend for both hematological and solid second malignances. Compared with solid tumors, hematological cancers showed a more remarkably increasing trend. In the multivariate Cox proportional hazard regression (**Figure 5**), which included race, gender, age and calendar year at the time of NHL diagnosis, we observed that patients who received chemotherapy for NHL had a significantly higher cumulative risk for second cancers than those did not (HR: 1.46, 95% CI: 1.42-1.5, $P<0.001$), whereas patients who were treated with radiation for NHL had a slightly increased risk of developing any SPM (HR: 1.05, 95% CI: 1.02-1.09, $P<0.001$). Compared with male patients, female had a lower cumulative risk for second cancers (HR: 0.85, 95% CI: 0.83-0.88, $P<0.001$). The "other" race was correlated with a lower hazard ratio (HR: 0.88, 95% CI: 0.83-0.9, $P<0.001$). To note that, after adjusting these clinical and demographic variables, we observed that the hazard ratio was lower for more recent study periods, which suggested that recent calendar years was not a risk factor of SPMs inde-

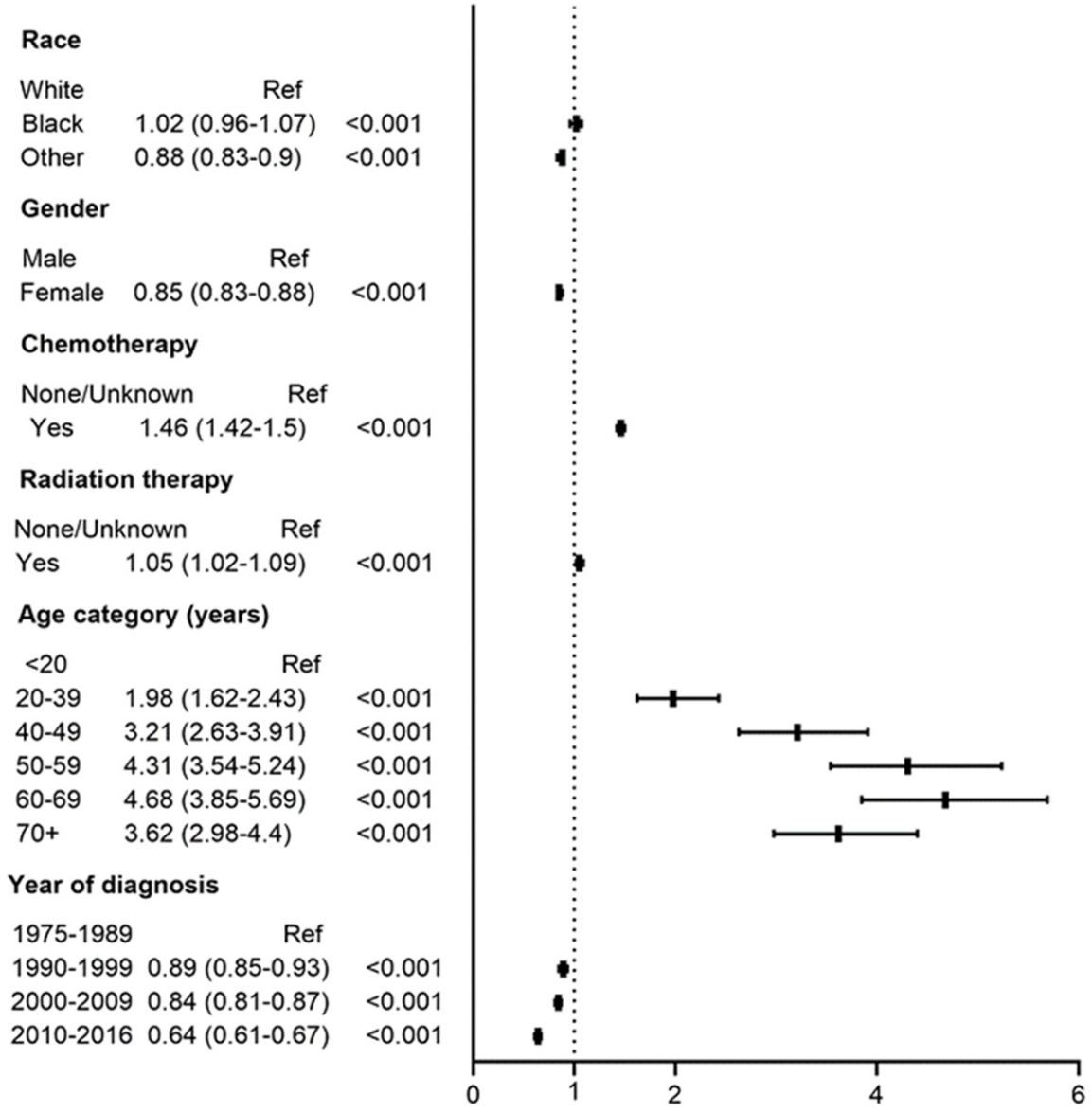

Figure 5. Hazard of developing any second primary malignance among NHL survivors in a multivariate competing risk model. Race, gender, age, and calendar year at the time of NHL diagnosis were included in the multivariate Cox proportional hazard regression. Patients who received chemotherapy or radiation, male patients, black people, and older age at NHL diagnosis were risk factors in the multivariate Cox regression analysis.

pendent of race, gender, treatments, and age at NHL diagnosis.

Discussion

In the current study, we observed a higher risk of developing any SPM among NHL survivors during the period 1975-2016. The SIR was more significantly increased for second hematological malignances, although solid tumors accounted for more absolute excess risk. During the follow-up, the SIR for solid second malignances increased and reached the maximum after more than 30 years of NHL diagnosis. This trend was similar with the development of radiogenic second tumors, which typically required a long latent period [13]. For second hematological malignances, the risk was highest in the first five years after NHL diagnosis. It was suggested that genomic alterations due to cytotoxic chemotherapies, and common risk factors such as EBV infection might be responsible for the higher rates of leukemic transformation within a short latency after NHL

diagnosis [14-17]. As previously reported, we observed that a younger age at NHL diagnosis was associated with a higher SIR of developing second cancers, which was consistent with previous studies [12], although those diagnosed at the age between 60-69 years had the highest cumulative risk of SPMs, which could be contributed by the substantial background cancer rates for NHL survivors when they reached an older age. Besides, male patients had a higher relative and cumulative risk of developing any SPM compared with female. This seemed to be associated with the increased risk for lung cancer and decreased risk for breast cancer, which were mainly contributed by male and female NHL survivors, respectively.

We observed significantly increasing risk for second cancers among NHL survivors diagnosed in more recent years. A previous study has reported a similar trend in SPM risk in CLL patients [18]. The SIR for second hematological malignances increased consistently and appreciably across the study periods, whereas for solid tumors, it decreased slightly in the period 1990-1999 compared with previous one, and then increased and reached the peak in the most recent study period. Similar results were also seen in the analyses for the cumulative incidence of SPMs, in which we observed a more significantly increasing trend of second hematological malignances compared with solid cancers. Treatments for NHL, mainly comprised of chemotherapy and radiation, have been confirmed as one of the causes for developing SPMs [2, 19, 20]. We observed a more significantly increasing risk among those receiving chemotherapy compared with those not, whereas the SIR in patients receiving radiation was slightly elevated across the study periods. To verify whether the relative risk of SPMs associated with treatment effect was outweighed by the reduction in mortality or was affected by other clinical variables, we performed the multivariate Cox regression analysis after treating death as a competing risk event, and still observed a significantly and remarkably higher risk for those receiving chemotherapy, whereas radiation did not remarkably increase the incidence of SPMs in the whole study period. Additionally, a dose response between chemotherapeutic agents and SPMs among cancer survivors has been reported [20]. Considering the higher ratio of receiving intensive chemotherapeutic regimens for NHL patients, it was suggested that the increasing risk of SPMs in recent years, was at least partly contributed by changes of the therapeutic methods, especially chemotherapies for NHL.

For individual cancer sites, we firstly reported an increasing trend of the risk for HL, myeloid leukemia, multiple myeloma, and cancers of the oral cavity and pharynx, ascending colon, stomach, liver, endocrine system, and skin, and decreased SIRs for cancers of bones and joints, prostate, bladder, lung, and breast in recent study periods. The current chemotherapeutic standard for NHL treatment has evolved with the introduction of rituximab from 2000s, and there was an increasing application of aggressive and dose-intensive treatment and HSCT [21]. Previous studies reported an elevated risk for myelodysplasia (MDS) and AML in patients receiving high-dose chemotherapy and HSCT for NHL [14, 22]. Besides, the use of G-CSF, which has been commonly applied in NHL patients receiving rituximab-containing multiple chemotherapy regimens, was suggested to increase the risk of MDS/AML in NHL survivors [15, 23, 24]. For certain radiogenic malignances, including breast and lung cancer [25, 26], the decreased risk in more recent study period might be associated with a lower ratio for NHL patients receiving radiation therapy, and the application of current radiotherapy strategies, such as low dose and 3D conformal radiation planning. The different trends for specific cancers could be attributed to the heterogeneities in etiology. We observed an increasing risk for certain cancers associated with immune suppression, including oropharynx and liver cancer, which were related to infection of HPV and hepatitis C, respectively [27]. This finding suggested that increased application of intensive chemotherapies and HSCT in recent years contributed to the elevated SPM risk [21]. The assumption was further confirmed by the remarkably increasing SIR for skin cancers over time, as previous studies have reported the strong correlation between extreme immune suppression and second skin cancer after NHL [28, 29]. Besides, we noted that the risk for Kaposi sarcoma and anal cancer, which were associated with HIV infection and AIDS related NHL [6, 30] was lowest in the most recent study period. The observation was consistent with the trend of the incidence rate of KS in the gen-

eral population, which was decreased due to the introduction of novel effective antiretroviral therapy in recent decades [31].

Additionally, the current study firstly reported that the SIR for SPMs in those younger than 40 years at the time of NHL diagnosis increased more significantly in recent years compared with other age groups, which could be due to typically more intense chemotherapies for younger patients and a higher ratio of aggressive NHL subtypes in younger patients. Compared with male patients, SPM risk in female patients increased more significantly in recent years. This could be partly attributed to the increased risk of second lung cancer among females compared with males, which mirrored the trend in smoking rates and lung cancer incidence in the general population. It was notable that after adjusting treatment, race, gender, and age at NHL diagnosis in the multivariate Cox regression model, the recent study period was no longer a risk factor for developing second malignances, while receiving chemotherapy or radiation for NHL, an older age at NHL diagnosis, male patients, black people were associated with a higher cumulative risk of SPMs. Causes of this observation can be multifactorial. It could be assumed that increased risk of SPMs after NHL in recent years was mainly attributed to the changes of treatment methods for NHL patients, including a higher ratio of receiving intensive chemotherapeutic regimens and HSCT. The increased proportion of older patients diagnosed with NHL in more recent study periods could also explain at least some of it, as observed in the current study. Besides, enhanced screening, decreased smoking rate, the application of current radiation strategies, and introduction of novel antiviral therapies might be associated with the lower hazard ratio of more recent study periods seen in the multivariate Cox regression.

The strengths of our study included the substantial samples identified in the large population-based setting from the SEER Program, which allowed the analysis of second malignances among NHL survivors with long-term follow-up. Besides, SEER database has extensive quality standards in the data collection to ensure the accuracy. Additionally, the current analysis included the period after 2000, during which the rituximab-based chemotherapeutic regimen has been widely applied in NHL patients, whereas the risk of SPMs in this period compared with previous ones has rarely been studied before [12, 32]. The limitations include the lack of details of the lymphoma staging, chemotherapeutic regimens, radiation fields and doses, whether the patients underwent HSCT, and some factors associated with SPM development, such as tobacco use and virus infection. Changes in the occurrence of different NHL subtypes may also contributed to SPM risk [9], which could be further analyzed. Besides, the history of treatment failure and recurrence status is not available in the SEER database. Additionally, the records of chemotherapy and radiation were incomplete in some patients, which might lead to the underestimation of their effects on the risk of developing SPMs.

To conclude, to our best knowledge, this is the first analysis for the trend in the risk of second malignances after NHL over the past four decades. We observed an elevated risk of developing SPMs among NHL survivors compared with the general population, which was altered by gender, race, SPM types, and age at the time of NHL diagnosis. We firstly reported an overall increasing risk for second hematological and solid malignances across the study period from 1975 to 2016, while the increasing trend was more significant and remarkable for hematological cancers compared with solid ones. For individual cancer sites, the trends were heterogeneous according to their etiologies. Compared with other risk factors, changes of chemotherapeutic methods and a higher proportion of receiving chemotherapy in recent years seemed to contribute more to the elevated SPM risk. Our analysis highlighted the importance of the screening for SPMs and optimal patient care in NHL patients in the era of rituximab. Future investigations incorporating the details of treatment, lymphoma staging, and specific factors associated with SPM etiology will be crucial to further address the current observations.

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Disclosure of conflict of interest

None.

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