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Incidence and time trends of second primary malignancies after non-Hodgkin lymphoma: a Swedish population-based study

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Key Points

- We observed stable excess rates of secondary malignancies over time among lymphoma patients compared with the general population.
- In follicular lymphoma, decreasing rates of secondary myelodysplastic syndrome and acute myeloid leukemia were observed after 2009.

Considering treatment changes and an improved prognosis of non-Hodgkin lymphoma (NHL) over time, knowledge regarding long-term health outcomes, including late effects of treatment, has become increasingly important. We report on time trends of second primary malignancies (SPMs) in Swedish NHL patients, encompassing the years before as well as after the introduction of anti-CD20 antibody therapy. We identified NHL patients in the Swedish Cancer Register 1993 to 2014 and matched comparators from the Swedish Total Population Register. The matched cohort was followed through 2017. By linking to the Swedish Lymphoma Register, subcohort analyses by NHL subtype were performed. Flexible parametric survival models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) of SPM among patients and comparators. Among 32 100 NHL patients, 3619 solid tumors and 217 myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) cases were observed, corresponding to a 40% higher rate of solid tumors ($HR_{\text{solid tumors}} = 1.4$; 95% CI, 1.4-1.5) and a 5-fold higher rate of MDS/AML ($HR_{\text{MDS/AML}} = 5.2$; 95% CI, 4.4-6.2) than for comparators. Overall, the observed excess risks for solid tumors or MDS/AML remained stable over the study period, except for follicular lymphoma, where the excess rate of MDS/AML attenuated with time (P for trend = .012). We conclude that NHL survivors have an increased risk of both solid tumors and hematologic malignancies, in particular MDS/AML. Stable excess risks over time indicate that contemporary treatment standards are not associated with modified SPM risk. Encouragingly, decreasing rates of MDS/AML were noted among patients with follicular lymphoma, possibly due to the increasing use of nonchemotherapy-based treatments.

Introduction

The population of non-Hodgkin lymphoma (NHL) survivors has grown substantially in recent decades due to the increasing incidence of many NHLs, aging populations in the Western world, and better treatment outcomes.¹⁻³ With the improved treatment outcomes and the growing population of patients cured for NHL or living with NHL as a chronic disease, the interest for research in late toxicities has increased.¹

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For data sharing, contact the corresponding author: sandra.eloranta@ki.se. Individual participant data will not be shared.

The full-text version of this article contains a data supplement.

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A highly relevant and potentially life-threatening complication following treatment of lymphoma is the occurrence of second primary malignancies (SPMs) (ie, a non-NHL cancer diagnosed subsequent to the NHL). This includes, but is not limited to, cancers that are related to the treatment given for the NHL (eg, caused by immunosuppression or DNA damage from chemotherapy or radiation therapy). Previous studies have consistently shown increased risks of SPM in general and of myeloid malignancies in particular.⁴⁻¹⁴ However, many of these studies have not investigated the most recent time periods with modern treatments, and have included small, sometimes selected, patient groups. The last 2 decades have brought several changes to the standard-of-care treatments for NHL. These include primary treatment escalation (eg, the addition of etoposide and methotrexate in aggressive lymphomas^{15,16}), increased use of consolidative autologous stem cell transplantation in transformed low-grade lymphomas and T-cell lymphomas,¹⁷ and additions of targeted therapies, most notably anti-CD20 antibody therapy such as rituximab, in B-cell lymphomas.¹⁸ Some of these changes could potentially lead to a higher risk of SPM, although the long-term impact of these changes remains uncertain. At the same time, the introduction of targeted therapies as single-agent primary treatment has led to reduced use of chemotherapy for low-grade B-cell lymphomas, which in turn could decrease the risk of SPM, in particular, treatment-related myeloid neoplasms.¹⁹

To address potential changes in the risk of SPM with changing treatment standards, we studied temporal trends in excess risks of SPM for NHL patients diagnosed from 1993 to 2014, followed through 2017, by comparing NHL survivors to matched population comparators using national Swedish register data.

Methods

Data sources and patient cohorts

We identified Swedish patients with NHL from 2 different national population-based registers. The Swedish Cancer Register (SCR) contains information on all cancers diagnosed in Sweden since 1958. The data are maintained by the National Board of Health and Welfare, and reporting to the register is mandatory by law for all health care providers.²⁰ Whereas the SCR contains basic demographic and diagnostic data, detailed clinical information about lymphoma, such as subtype and stage, is absent. The Swedish Lymphoma Register (SLR) was initiated by the Swedish Lymphoma Group in 2000 and contains detailed physician-reported clinical data. Although the reporting to the SLR is not mandated by law, the register covers around 95% of the cases in the SCR.² Dates of death, required for patient follow-up, was linked via the Swedish Cause-of-Death Register.

Two cohorts of NHL patients were created to address both long-term temporal trends and more detailed analyses of subtype-specific excess risks. The first cohort (SCR cohort) initially consisted of 33 062 cases with NHL (ICD-7 codes: 200, 202) diagnosed 1993 through 2014, aged ≥ 18 years. Exclusions were made for patients with WHO/HS/CANC/24.1 histology codes indicating nonlymphoma diagnoses ($n = 13$), uncertain basis for diagnosis (eg, without histopathological confirmation, $n = 58$), autopsy findings ($n = 567$), and missing information on birth year or death dates ($n = 34 + 4$). Further, by linkage to the Swedish National Patient Register, we excluded patients with a prior history of human immunodeficiency

virus (HIV) infection ($n = 86$) and allogeneic hematopoietic stem cell transplantation or solid organ transplantation ($n = 200$) since immunocompromised patients are known to have pronounced cancer risks for reasons related to the underlying disorders. The final SCR cohort encompassed 32 100 NHL patients (supplemental Figure 1).

The second cohort (SLR subcohort) consisted of patients diagnosed after 1 January 2000 and was created by further linking detailed NHL subtype data from the SLR. In the SLR subcohort, patients who were registered in the SCR but for whom no data had been reported to the SLR ($n = 1467$) or where inconsistencies were found between the SCR and SLR registrations ($n = 13$) were excluded, leaving 21 695 patients for analysis.

Our investigation focuses specifically on SPMs of myeloid origin since these have shown to be associated with chemotherapy agents commonly used in lymphoma care (eg, alkylating agents and topoisomerase II inhibitors).^{19,21,22} From the year 2000 and onward (SLR cohort), we assessed the risk of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) among high-grade vs low-grade NHL and among the most common NHL subtypes by morphology.

Population comparators

Comparators from the general population were identified by sampling with replacement from the Swedish Total Population Register. The comparators were individually matched to the NHL patients at the date of diagnosis by year of birth and sex (with 5 comparators per case except for 2 cases for whom only 4 comparators were available). On the matching date, the comparators had to be alive and free from previous history of NHL, HIV, or transplantation. The comparators included 160 498 individuals for the SCR cohort and 108 474 individuals for the SLR subcohort.

Follow-up and outcomes

The start of follow-up was set to 30 days (for MDS/AML outcomes) or 90 days (for solid tumor outcomes) after the date of NHL diagnosis (matching date for comparators) since cases occurring before that are unlikely to be related to the lymphoma or its treatment. Thus, by masking the immediate time period after NHL diagnosis, malignancies that were discovered incidentally during the lymphoma workup and unlikely to be true SPM outcomes were eliminated from the analyses. The matched cohorts were followed until diagnosis of a malignancy, date of death, or 31 December 2017, whichever came first. Based on the SCR cohort, 2 separate analyses were performed with MDS/AML and solid tumors as the main outcomes. Additional analyses were performed to assess the risk of other hematological malignancies, including myeloproliferative neoplasms (MPNs) and chronic myeloid leukemia (CML), Hodgkin lymphoma, multiple myeloma, lymphatic leukemia (excluding chronic lymphocytic leukemia [CLL]), and for different subtypes of solid tumors by anatomic location (with pooling of rare cancer forms and clinically relevant categorizations, eg, separating melanoma and nonmelanoma skin cancers) (supplemental Table 1). For each SPM group, time to the first SPM in that group was analyzed without censoring for other prior SPMs of a different type.

In the SLR subcohort with NHL patients diagnosed in 2000 or later, we focused the investigation on the risk of MDS/AML. Using morphological NHL subtype data from the SLR, separate analyses were performed by lymphoma aggressiveness (ie, high-grade and low-grade lymphomas) (supplemental Table 1) and by major subtypes

(diffuse large B-cell lymphoma [DLBCL], follicular lymphoma [FL], mantle cell lymphoma, marginal zone lymphoma, Burkitt lymphoma, and T/NK-cell lymphoma).

The study was approved by the Stockholm Regional Ethics Committee (Dnr 2012/298-31-1) and was performed in accordance with the Declaration of Helsinki.

Statistical methods

Demographic characteristics of NHL patients and population comparators were summarized descriptively. Incidence rates (IR) of SPMs and 95% confidence intervals (CIs) were calculated, stratified by age at diagnosis (<70 and ≥70 years), sex, calendar period of diagnosis (1993-1999, 2000-2004, 2005-2009, 2010-2014) and, in the SLR subcohort, by lymphoma aggressiveness and major morphological subtype.

In the SCR cohort, hazard ratios (HRs) with 95% CI contrasting rates of SPM between patients and comparators were estimated using flexible parametric survival models. These models use restricted cubic splines to model the baseline hazard rate but are otherwise similar to Cox regression models with respect to interpretation.²³ All models were adjusted for sex, age, and calendar period of diagnosis and parameterized such that comparators were the reference group. Likelihood ratio tests were used to sequentially test for interaction between case/comparator status and the variables included in the model.

For the analyses of temporal trends of SPM incidence (for NHL overall and stratified by subtype), we modeled the effect of calendar year using a restricted cubic spline (with internal knots placed at the 33rd and 66th percentiles of the calendar year distribution). We further included interaction terms between case/comparator status and the spline terms representing the calendar year of diagnosis. The models were used to estimate the HR of SPM, comparing cases to comparators for each point of calendar time, and summarize the trends graphically. To investigate temporal trends, we restricted the effect of the calendar year to be linear and tested if the effect of being a case (vs comparator) was modified by the calendar year.

To assess that the results for the temporal trends were not driven by the choice for number and location of knots in the restricted cubic spline, we also performed a sensitivity analysis with alternative knots configuration (with degrees-of-freedom ranging from 1 [linear spline] to 5).

All statistical analyses were performed using Stata (Stata Statistical Software, Release 16; StataCorp LLC, College Station, TX).

Third-party restrictions apply to the availability of the used data. The authors are therefore prevented from providing access or sharing the individual-level patient data.

Results

SCR cohort 1993-2014

Patient characteristics. In the SCR cohort with 32 100 NHL patients, the median age at diagnosis was 70 years (interquartile range [IQR], 60-78 years), with a slight male predominance (55.1%) (Table 1). The distribution of the NHL patients between calendar periods showed a gradual increase in the number of NHL

cases. The median follow-up time for the cohort was 7.1 years (IQR, 3.8-12.2 years).

Solid tumors

During follow-up, 3619 cases of solid tumors (first after NHL diagnosis) were observed among the NHL patients (IR, 20.6 per 1000 person-years; 95% CI, 19.9-21.3) and 22 485 cases among comparators (IR, 16.0 per 1000 person-years; 95% CI, 15.8-16.2). The median time from NHL diagnosis (or index date) to first solid tumor was 4.6 years (IQR, 2.1-8.5 years) for patients and 5.6 years (IQR, 2.7-9.9 years) for comparators.

The rate of solid tumors was 42% higher (HR, 1.4; 95% CI, 1.4-1.5) for patients than comparators when adjusted for matching factors and did not differ significantly by sex. NHL patients aged ≥70 years had a significantly higher rate (HR, 1.4; 95% CI, 1.4-1.5) of solid tumors than younger patients (HR, 1.3; 95% CI, 1.2-1.4) relative to comparators (*P* for interaction = .006). No significant effect modification was observed between different calendar periods of NHL diagnosis (*P* for interaction = .064) (Table 1; Figure 1).

Analyses of specific solid cancer types revealed that the rate of cancer was higher in NHL patients (than for comparators) for 9 of 13 types assessed (Table 2). The excess rate was most prominent for nonmelanoma skin cancers (HR, 3.6; 95% CI, 3.3-3.8) but also significantly higher for cancer of the oropharynx and upper airway, gastrointestinal tract, lower respiratory system, bones and soft tissue, malignant melanomas, urinary tract, endocrine system, and cancer of unknown primary site (Table 2). We observed a slightly lower rate of cancers in the female genital organs in NHL patients than comparators (HR, 0.8; 95% CI, 0.7-1.0).

Hematological malignancies

Among NHL patients, 217 cases of MDS/AML were observed, compared with 363 among comparators, corresponding to an IR of 11.1 per 100 000 person-years (95% CI, 9.9-12.9) for patients, and 2.4 per 100 000 person-years (95% CI, 2.2-2.7) for comparators. Fourteen out of 61 MDS patients found among NHL survivors subsequently developed AML (the latter was not included as an outcome in the analysis) with a median of 4.7 months between the MDS and AML diagnoses (range, 0.4-23.5 months). Among comparators, 91 MDS cases were found, out of which 9 progressed to AML (median interval 11.2 months; range, 2.8-17.5 months).

The rate of MDS/AML was 5-fold increased for the NHL patients (HR, 5.2; 95% CI, 4.4-6.2) than for comparators. The median time to MDS/AML diagnosis among NHL patients was 4.2 years (IQR, 2.2-8.0 years). Although the absolute rates of MDS/AML were similar for patients below and above 70 years at NHL diagnosis (Table 1), there was evidence of interaction (*P* ≤ .001) with respect to the relative rates (with young patients having significantly larger excess rates than old patients, reflecting the lower background incidence of MDS/AML in younger individuals). With regard to temporal trends in MDS/AML risk, a tendency toward a reduced excess rate among NHL patients was seen during the more recent years (Figure 1B). This pattern was, however, not statistically significant when applying a test for linear trend (*P* = .125).

Excess rates were also seen for MPN, including CML (HR, 1.4; 95% CI, 1.0-2.03), and for lymphatic leukemias (excluding CLL)

Table 1. IRs and HRs with 95% CIs of solid tumors and MDS/AML comparing lymphoma patients diagnosed 1993-2014, with follow-up through 2017, to matched population comparators in Sweden

			Solid tumors			MDS/AML		
	Lymphoma patients, n (%)	Comparators, n (%)	Events, n*	Rate* (per 1000 person-years)	HR (95% CI)†,‡	Events, n*	Rate* (per 1000 person-years)	HR (95% CI)†,‡
Comparators	—	160 498 (100)	22 485	16.0 (15.8-16.2)	1.00 (ref)	363	2.4 (2.2-2.7)	1.00 (ref)
Patients	32 100 (100)	—	3 619	20.6 (19.9-21.3)	1.4 (1.4-1.5)	217	11.3 (9.9-12.9)	5.2 (4.4-6.2)
Sex								
Male	17 691 (55.1)	88 454 (55.1)	2 242	23.8 (22.8-24.8)	1.40 (1.3-1.5)	127	12.2 (10.3-14.5)	5.0 (4.0-6.3)
Female	14 409 (44.9)	72 044 (44.9)	1 377	16.9 (16.0-17.8)	1.5 (1.4-1.5)	90	10.2 (8.3-12.5)	5.5 (4.2-7.2)
<i>P</i> §					.326			.602
Age at diagnosis/matching date								
<70 y	15 672 (48.8)	78 360 (48.8)	1 909	15.9 (15.2-16.6)	1.3 (1.2-1.4)	140	10.8 (9.2-12.8)	7.2 (5.7-9.1)
≥70 y	16 428 (51.2)	82 138 (51.2)	1 710	30.6 (29.1-32.0)	1.4 (1.4-1.5)	77	12.2 (9.8-15.3)	3.4 (2.6-4.4)
<i>P</i> §					.006			<.001
Year of diagnosis/matching date								
1993-1999	8 924 (27.8)	44 619 (27.8)	1 150	19.6 (18.5-20.8)	1.5 (1.4-1.6)	78	12.1 (9.7-15.1)	5.9 (4.4-7.7)
2000-2004	6 969 (21.7)	34 845 (21.7)	912	20.2 (18.9-21.6)	1.4 (1.3-1.5)	57	11.5 (8.9-14.9)	6.5 (4.6-9.1)
2005-2009	7 577 (23.6)	37 885 (23.6)	844	20.2 (18.9-21.7)	1.3 (1.2-1.4)	45	9.9 (7.4-13.3)	4.3 (3.0-6.2)
2010-2014	8 630 (26.9)	43 149 (26.9)	713	23.5 (21.8-25.2)	1.4 (1.3-1.6)	37	11.1 (8.1-15.4)	3.9 (2.6-5.9)
<i>P</i> §					.064			.154

*Events and rates by characteristics are presented for lymphoma patients only.
 †Mutually adjusted for matching factors sex, age at diagnosis, and calendar year of diagnosis.
 ‡Reference group: comparators.
 §From test for interaction.

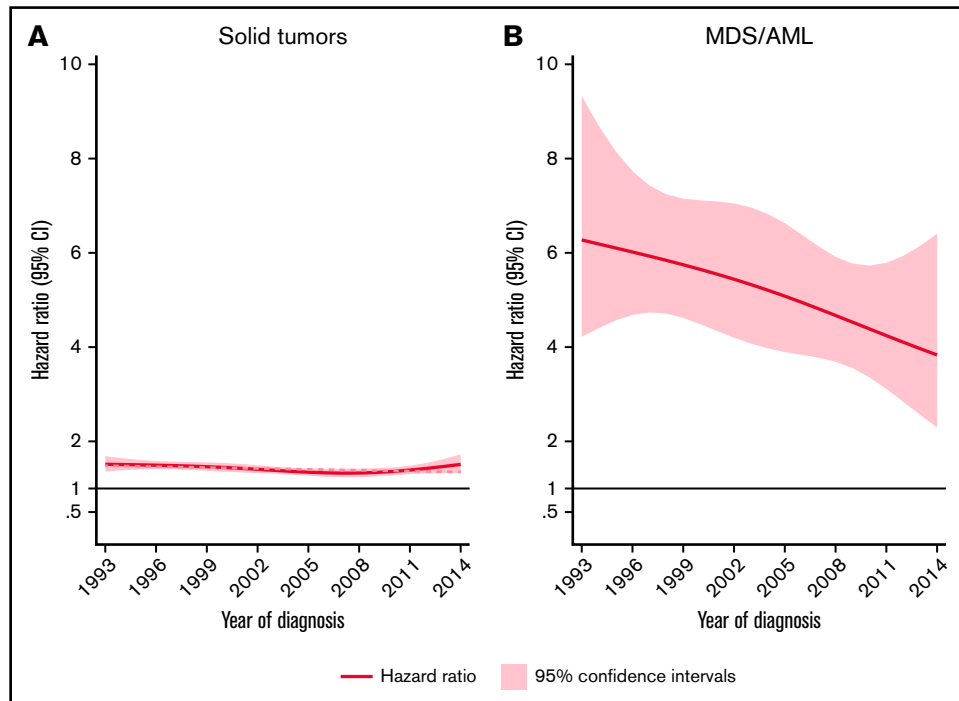


Figure 1. HRs and 95% CIs. Temporal trends of solid tumors (A) and MDS/AML (B), comparing lymphoma patients diagnosed 1993-2014 to matched population comparators.

Table 2. IRs and HRs with 95% CIs of different types of second primary solid tumors and hematological malignancies other than NHL and MDS/AML, comparing lymphoma patients diagnosed 1993-2014, with follow-up through 2017, to matched population comparators in Sweden

	Events, n	Median time to event years (IQR)	Rate (per 1000 person-years)	HR (95% CI)*	P
Solid tumors					
Lip, oral cavity, pharynx, upper respiratory system					
Comparator	560	5.8 (2.8-7)	0.4 (0.4-0.4)	1.0 (ref)	<.001
Case	117	4.3 (2.7-8.4)	0.6 (0.5-0.8)	1.8 (1.5-2.2)	
Gastrointestinal tract					
Comparator	5182	5.7 (2.6-10.0)	3.5 (3.4-3.6)	1.0 (ref)	<.001
Case	742	4.6 (2.1-8.5)	4.0 (3.7-4.3)	1.27 (1.2-1.4)	
Lower respiratory system					
Comparator	1926	5.6 (2.6-9.8)	1.3 (1.2-1.4)	1.0 (ref)	<.001
Case	331	5.2 (2.5-9.9)	1.8 (1.6-2.0)	1.5 (1.3-1.6)	
Thymus, bone cartilage and soft tissue sarcoma					
Comparator	215	4.5 (2.3-9.6)	0.1 (0.1-0.2)	1.0 (ref)	<.001
Case	43	5.2 (2.6-9.3)	0.2 (0.2-0.3)	1.7 (1.2-2.4)	
Melanoma					
Comparator	1136	6.2 (2.9-11.1)	0.8 (0.7-0.8)	1.0 (ref)	<.001
Case	224	4.8 (2.2-8.7)	1.2 (1.1-1.4)	1.7 (1.5-2.0)	
Nonmelanoma skin cancer					
Comparator	2691	6.1 (2.8-10.9)	1.8 (1.8-1.9)	1.0 (ref)	<.001
Case	952	4.3 (2.0-8.2)	5.2 (4.8-5.5)	3.6 (3.3-3.8)	
Breast					
Comparator	2265	5.6 (2.6-9.8)	1.5 (1.5-1.6)	1.00 (ref)	.252
Case	258	5.9 (2.8-10.7)	1.4 (1.2-1.6)	0.9 (0.8-1.1)	
Female genital organs					
Comparator	1041	5.2 (2.5-9.6)	1.5 (1.4-1.6)	1.00 (ref)	.047
Case	103	5.1 (1.5-8.5)	1.2 (1.0-1.5)	0.8 (0.7-1.0)	
Male genital organs					
Comparator	5574	5.6 (2.5-9.8)	7.2 (7.0-7.4)	1.00 (ref)	.578
Case	631	5.2 (2.3-9.3)	6.4 (5.9-6.9)	1.0 (0.9-1.1)	
Urinary tract					
Comparator	2156	5.5 (2.7-10.0)	1.5 (1.4-1.5)	1.0 (ref)	<.001
Case	328	4.0 (1.2-8.4)	1.8 (1.6-2.0)	1.3 (1.2-1.5)	
Central nervous system					
Comparator	435	5.5 (2.5-9.1)	0.3 (0.3-0.3)	1.0 (ref)	.087
Case	69	4.4 (1.5-8.9)	0.4 (0.3-0.5)	1.3 (1.0-1.6)	
Endocrine system					
Comparator	337	4.8 (2.3-8.5)	0.2 (0.2-0.3)	1.0 (ref)	<.001
Case	73	2.3 (1.3-6.4)	0.4 (0.3-0.5)	1.7 (1.3-2.1)	
Ill-defined/unknown primary site					
Comparator	796	5.0 (2.3-9.1)	0.5 (0.5-0.6)	1.0 (ref)	<.001
Case	145	4.2 (1.5-7.0)	0.8 (0.7-0.9)	1.6 (1.3-1.9)	
Hematological malignancies other than NHL and MDS/AML					
CML/MPN					
Comparator	226	5.9 (3.0-11.7)	0.2 (0.1-0.2)	1.0 (ref)	.036
Case	39	3.5 (2.1-5.4)	0.2 (0.2-0.3)	1.4 (1.0-2.0)	

*Mutually adjusted for sex, age at diagnosis, and calendar year of diagnosis.

†ALL and lymphoblastic/lymphocytic leukemia unspecified.

Table 2. (continued)

	Events, n	Median time to event years (IQR)	Rate (per 1000 person-years)	HR (95% CI)*	P
Hodgkin lymphoma					
Comparator	33	6.0 (2.6-9.2)	0.02 (0.02-0.03)	1.0 (ref)	<.001
Case	37	6.0 (3.3-7.7)	0.2 (0.1-0.3)	8.7 (5.4-13.4)	
Multiple myeloma					
Comparator	327	5.7 (2.6-9.4)	0.2 (0.2-0.2)	1.0 (ref)	.854
Case	37	4.9 (2.6-8.6)	0.2 (0.1-0.3)	1.0 (0.7-1.4)	
Lymphatic leukemia†					
Comparator	37	5.4 (2.9-8.6)	0.02 (0.02-0.03)	1.0 (ref)	<.001
Case	17	3.4 (1.2-5.9)	0.1 (0.1-0.1)	3.7 (2.1-6.6)	

*Mutually adjusted for sex, age at diagnosis, and calendar year of diagnosis.
 †ALL and lymphoblastic/lymphocytic leukemia unspecified.

(HR, 3.7; 95% CI, 2.1-6.6). A pronounced excess rate was also observed for Hodgkin lymphoma (HR, 8.7; 95% CI, 5.4-13.9).

SLR cohort 2000-2014

In the subcohort of 21 695 NHL patients diagnosed and registered in the SLR 2000-2014, we assessed MDS/AML as the sole outcome. The median age at diagnosis in this cohort and distribution of sex was virtually the same as in the SCR cohort (Table 3). The median follow-up time was 7.1 years (IQR, 4.3-10.11). A total of 131 cases with MDS/AML were observed among NHL patients and 206 among comparators. The median time to MDS/AML among the patients was 3.7 years (IQR, 1.8-6.2). The absolute incidence rates were similar to those estimated in the SCR cohort, as were the excess rate of MDS/AML in the patients (HR, 4.8; 95% CI, 3.9-6.0). The excess rate was stable across the study period (supplemental Figure 2). Moreover, we observed no global evidence of effect modification by NHL aggressiveness or by major NHL subtypes. However, the excess rate of MDS/AML was highest for T-cell lymphoma patients (HR, 8.5; 95% CI, 4.0-18.2) (Table 3).

The excess rate of MDS/AML was generally stable throughout the study period (Table 3; supplemental Figure 1). There was a tendency of a decreased excess rate among low-grade NHL, but the trend was not statistically significant (*P* for trend = .08) (Figure 2). No changes were observed over time in high-grade NHL. For morphological subtypes, a stable HR was seen for DLBCL and T-NHL, whereas in patients with FL, a significant linear trend toward normalization of risk was demonstrated in patients diagnosed after 2009 (*P* for trend = .012) (Figure 2).

Discussion

In this large, population-based matched cohort study, we demonstrated a 5-fold higher risk for MDS/AML and an excess risk of 1.4 for solid tumors among NHL patients, compared with the matched general population. Overall, the excess risk remained stable over time with the exception of patients with FL, for whom the excess risk of MDS/AML diminished in later time periods. This is the first study to show a clear decrease in risk of MDS/AML among contemporaneously treated FL patients.

The excess risk of SPM in NHL demonstrated in our study is in line with previous literature, although prior studies vary in terms of design and sources of the study populations and most often lack data regarding subtypes.⁴⁻¹⁴ In a 2011 meta-analysis, Pirani et al found pooled relative risks of 1.88 for any secondary cancer and relative risk of 1.32 for solid tumors among patients with NHL.¹¹ However, unlike the present study, none of the included studies covered the period after the introduction of rituximab into standard treatments for B-cell lymphomas. The fact that a similar risk of SPM was found in our study is thus reassuring, as there have been concerns that the B-cell depletion and decreased T-cell activity induced by rituximab may increase the risk of SPM.²⁴

Brennan et al found a similar increase in the overall SPM risk in a large multinational pooled-register study (standardized incidence ratios [SIR], 1.47).⁵ Here, the risks of myeloid malignancies were markedly lower than in our study, which could perhaps be attributed to advancements in the diagnostics and classification of these diseases.

In a more recent register study, using data from the Surveillance, Epidemiology, and End Results (SEER) program, Tward et al found an SIR of 1.14 for SPMs overall, which is considerably lower than our findings, perhaps partly explained by a longer follow-up.¹⁴ Moreover, Bermejo et al studied pooled register data from 3 Nordic countries between 1980 and 2006.⁹ They present a relative risk of 2.11 for solid cancers among NHL patients. However, median follow-up was limited to 2 years, which could explain the higher risk.

In our study, we observed a great variation in the risk of different types of SPM. The risk of nonmelanoma skin cancer was noticeably high, which may be caused by surveillance bias and/or immunosuppression from NHL treatment.²⁵ In contrast, increased risk for breast cancer was not seen, as is commonly shown in Hodgkin lymphoma survivors, where radiation therapy is part of standard therapy.²⁶ Further, no increased risks for male genital cancer (including prostate cancer) or female genital cancer were observed. This is in line with a risk reduction of uterine cancer reported in the meta-analysis by Pirani et al¹¹ and may imply protective antihormonal mechanisms following the NHL diagnosis and treatment, although the nature of epidemiological studies such as this precludes verification of causation and biological links.

Table 3. IRs and HRs with 95% CIs of MDS/AML comparing NHL patients in the SLR subcohort to matched population comparators

	Patients, n	Events, n	Rate(per 10 000 person-years)	HR(95% CI)*	P interaction
Comparators	108 474	206	2.4 (2.1-2.7)	1.00 (ref)	NA
All NHL combined	21 695	131	10.7 (9.0-12.7)	4.8 (3.9-6.0)	
Sex†					
Male	12 072	76	11.4 (9.1-14.2)	4.7 (3.5-6.3)	.750
Female	9 623	55	10.0 (7.7-13.0)	5.0 (3.6-7.1)	
Age at diagnosis†					
<70 y	10 770	81	10.1 (8.2-12.6)	7.8 (5.6-10.7)	<.001
≥70 y	10 925	50	11.9 (9.0-15.6)	3.1 (2.3-4.3)	
Period of diagnosis†					
2000-2004	6 600	51	10.8 (8.2-14.2)	6.0 (4.2-8.6)	.321
2005-2009	7 313	45	10.2 (7.6-13.7)	4.5 (3.1-6.5)	
2010-2014	7 782	35	11.4 (8.2-15.8)	4.0 (2.6-6.1)	
Lymphoma group†					
Low-grade NHL	10 091	57	8.8 (6.8-11.3)	4.1 (3.0-5.7)	.355
High-grade NHL	11 088	70	12.8 (10.1-16.2)	5.6 (4.2-7.6)	
Other/unknown	516	4	17.7 (6.6-47.1)	6.2 (1.7-21.8)	
Lymphoma subtype†					
Diffuse large B cell	8 144	46	11.0 (8.3-14.7)	5.1 (3.5-7.5)	.657
Follicular	3 593	27	10.2 (7.0-14.8)	5.4 (3.2-9.0)	
Mantel cell	1 360	9	15.1 (7.9-29.1)	4.9 (2.2-10.9)	
Marginal zone	1 298	6	7.0 (3.2-15.6)	3.0 (1.1-8.0)	
Burkitt	227	2	15.0 (3.8-60.2)	3.2 (0.6-16.5)	
T cell	1 648	13	17.0 (9.9-29.2)	8.5 (4.0-18.2)	
Other	5 425	28	9.3 (6.4-13.4)	4.1 (2.6-6.4)	

P values from tests for interaction.

*Mutually adjusted for sex, age at diagnosis, and calendar year of diagnosis.

†Restricted to NHL cases.

Regarding hematological malignancies other than MDS/AML, we found a prominent rate increase for Hodgkin lymphoma. However, this result should be interpreted with caution as some of these may represent initial misclassification or transformations with the same cell-of-origin as the original NHL.²⁷ The same applies to lymphatic leukemia, for which we also saw an increased risk among NHL patients.

At the subtype level, the incidence of MDS/AML did not differ significantly by NHL subtype, nor by stratification into high- and low-grade lymphoma. It is still noteworthy that T-cell lymphoma patients had a prominent >8-fold excess MDS/AML risk, although the number of events was small (n = 13).

During the study period, a gradual increase in the annual number of NHL cases was observed, reflecting previously described rising incidence and population growth.¹ In NHL overall, no statistically significant temporal trends for excess risks of either solid cancers or MDS/AML were found during the study period. However, by NHL subtype, the excess risk for MDS/AML among patients with FL diminished over time, with a risk for MDS/AML comparable to the risk in the general population for patients diagnosed after 2009. This could potentially be explained by the paradigm shift in the management of FL and other low-grade B-cell lymphoma subtypes, with

biological treatments such as rituximab monotherapy replacing or delaying chemotherapy and diminishing the need for radiation therapy in many cases.²⁸

The fact that we see no temporal trends for SPM risk in all NHL indicates that the changes in treatment protocols during the study period have not been associated with a general change in the risk for SPM. Still, it is generally accepted that DNA damage due to chemotherapy and radiation therapy can lead to the development of new cancers.²⁹ Furthermore, extensive investigations with medical imaging containing ionizing radiation may also increase cancer risk, although this causal relationship is less established.³⁰ However, comparison between calendar periods is complicated as modern front-line treatment, which could potentially cause more DNA damage, may, in turn, be more effective, avoiding second-line treatments and thus reducing overall treatment toxicity. Other potential explanatory factors for increased risk of SPM among NHL patients include the extensive medical investigations performed at lymphoma diagnosis and subsequent frequent health care contacts which may identify new cancers. To minimize this potential bias in our study, we excluded all cancer diagnoses made within 1 and 3 months from the time of NHL diagnosis for MDS/AML and other cancers, respectively. Still, surveillance bias may account for some of the increased risks for SPM seen for NHL survivors in our study.

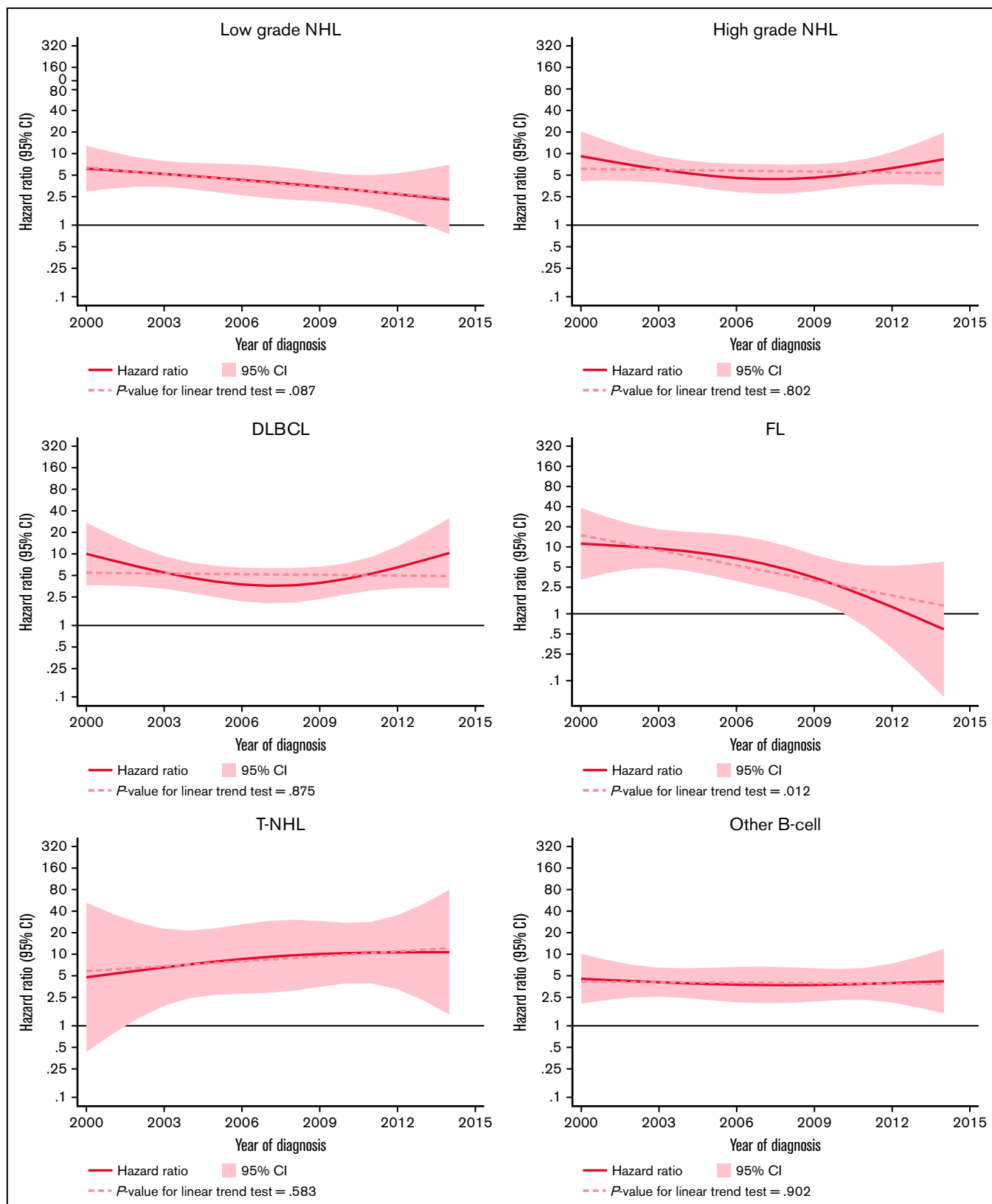


Figure 2. HRs and 95% CIs for temporal trends of MDS/AML, comparing lymphoma patients diagnosed 2000-2014 to comparators by lymphoma subtype in the Swedish Lymphoma Register cohort.

Another contributing factor to the increased risk of SPM among patients with NHL may be the immunosuppression, in particular T-cell suppression, caused by chemotherapy and steroids, a well-known risk factor for developing cancer.³¹ Biological links between the cells of origin of the NHL and SPM could in some cases also explain the excess risk observed in this study. An interesting example is the reported preexisting clonal hematopoiesis and common genetic aberrations linking some T-cell lymphoma subtypes to myeloid neoplasms,³² which could correspond to the excess rates of MDS/AML that were observed in T-cell lymphoma patients. Lastly, the data used to conduct this study did not include information on usual cancer risk factors, neither environmental nor genetic. Genetic predisposition to cancer is a potential risk factor for SPM, and, unfortunately, data regarding familial aggregation of cancer was not available in our NHL cohort, although the proportion of patients with familial predisposition to cancer in our study is likely low.

The strength of the present study is the large study population with unselected, consecutive patients with NHL, with subtype data available for a well-defined subcohort. Another advantage is the use of a matched (NHL-free) cohort for the calculation of cancer incidence rates in the general population rather than reported population statistics for cancer incidence. Further, a long tradition of collecting data in quality registers in Sweden enables the use of high-quality data sets with long follow-up times. Still, reliable subtype data are not available in the SCR,²⁰ limiting subtype analyses to 2000 and onward when the SLR was established.² Due to the rarity of SPMs, events are few despite our large study population, which hampered risk comparisons between subtypes. A limitation of the present study is the lack of detailed treatment data precluding us from analyzing associations between specific treatment and SPM risk (and even longer follow-up would be needed to fully evaluate risks of solid cancers, eg, in association with radiotherapy). Thus, further research is warranted to assess such associations to enable preventive measures such as adjustments in the treatment of

NHL or adapted follow-up strategies for patients at high risk for SPM.

To conclude, NHL survivors are still at an increased risk of SPMs, both solid cancers and MDS/AML, following contemporaneous treatment protocols. Encouragingly, for patients with FL, the risk for secondary MDS/AML has diminished during the most recent decade.

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Authorship

Contribution: S.E., K.E.S., T.W., and J.J. designed the study; J.J., K.E.S., and S.E. retrieved the data and performed data preparations and the statistical analyses; S.E., K.E.S., T.W., and J.J. led the writing of the manuscript; and all authors interpreted the data and edited the manuscript.

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References

1. Ekberg S, E Smedby K, Glimelius I, et al. Trends in the prevalence, incidence and survival of non-Hodgkin lymphoma subtypes during the 21st century – a Swedish lymphoma register study. *Br J Haematol*. 2020;189(6):1083-1092.
2. Ekstrom Smedby K. Swedish Lymphoma Registry 2000–2017: Regional cancer centers in collaboration; 2018.
3. Chiu BC, Weisenburger DD. An update of the epidemiology of non-Hodgkin's lymphoma. *Clin Lymphoma*. 2003;4(3):161-168.
4. Brennan P, Coates M, Armstrong B, Colin D, Boffetta P. Second primary neoplasms following non-Hodgkin's lymphoma in New South Wales, Australia. *Br J Cancer*. 2000;82(7):1344-1347.
5. Brennan P, Scélo G, Hemminki K, et al. Second primary cancers among 109 000 cases of non-Hodgkin's lymphoma. *Br J Cancer*. 2005;93(1):159-166.
6. Chien SH, Liu CJ, Hong YC, et al. Development of second primary malignancy in patients with non-Hodgkin lymphoma: a nationwide population-based study. *J Cancer Res Clin Oncol*. 2015;141(11):1995-2004.
7. Dong C, Hemminki K. Second primary neoplasms among 53 159 haematolymphoproliferative malignancy patients in Sweden, 1958-1996: a search for common mechanisms. *Br J Cancer*. 2001;85(7):997-1005.
8. Hemminki K, Lenner P, Sundquist J, Bermejo JL. Risk of subsequent solid tumors after non-Hodgkin's lymphoma: effect of diagnostic age and time since diagnosis. *J Clin Oncol*. 2008;26(11):1850-1857.
9. Lorenzo Bermejo J, Pukkala E, Johannesen TB, Sundquist J, Hemminki K. Age-time risk patterns of solid cancers in 60 901 non-Hodgkin lymphoma survivors from Finland, Norway and Sweden. *Br J Haematol*. 2014;164(5):675-683.

10. Morton LM, Curtis RE, Linet MS, et al. Second malignancy risks after non-Hodgkin's lymphoma and chronic lymphocytic leukemia: differences by lymphoma subtype. *J Clin Oncol*. 2010;28(33):4935-4944.
11. Pirani M, Marcheselli R, Marcheselli L, Bari A, Federico M, Sacchi S. Risk for second malignancies in non-Hodgkin's lymphoma survivors: a meta-analysis. *Ann Oncol*. 2011;22(8):1845-1858.
12. Tadmor T, Liphshitz I, Silverman B, Polliack A. Incidence and epidemiology of non-Hodgkin lymphoma and risk of second malignancy among 22 466 survivors in Israel with 30 years of follow-up. *Hematol Oncol*. 2017;35(4):599-607.
13. Tao L, Clarke CA, Rosenberg AS, et al. Subsequent primary malignancies after diffuse large B-cell lymphoma in the modern treatment era. *Br J Haematol*. 2017;178(1):72-80.
14. Tward JD, Wendland MMM, Shrieve DC, Szabo A, Gaffney DK. The risk of secondary malignancies over 30 years after the treatment of non-Hodgkin lymphoma. *Cancer*. 2006;107(1):108-115.
15. Wåsterlid T, Hartman L, Székely E, Jerkeman M. Impact on survival of addition of etoposide to primary chemotherapy in diffuse large B-cell lymphoma: a Swedish Lymphoma Registry study. *Hematol Oncol*. 2017;35(2):151-157.
16. Leppä S, Jørgensen J, Tierens A, et al. Patients with high-risk DLBCL benefit from dose-dense immunochemotherapy combined with early systemic CNS prophylaxis. *Blood Adv*. 2020;4(9):1906-1915.
17. Carlsten M, Jädersten M, Hellström A, et al. The Karolinska experience of autologous stem-cell transplantation for lymphoma: a population-based study of all 433 patients 1994-2016. *Exp Hematol Oncol*. 2019;8(1):7.
18. Mohammed R, Milne A, Kayani K, Ojha U. How the discovery of rituximab impacted the treatment of B-cell non-Hodgkin's lymphomas. *J Blood Med*. 2019;10:71-84.
19. Al-Juhaishi T, Khurana A, Shafer D. Therapy-related myeloid neoplasms in lymphoma survivors: reducing risks. *Best Pract Res Clin Haematol*. 2019;32(1):47-53.
20. Barlow L, Westergren K, Holmberg L, Talbäck M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta Oncol*. 2009;48(1):27-33.
21. Sugita K, Furukawa T, Tsuchida M, et al. High frequency of etoposide (VP-16)-related secondary leukemia in children with non-Hodgkin's lymphoma. *Am J Pediatr Hematol Oncol*. 1993;15(1):99-104.
22. Godley LA, Larson RA. Therapy-related myeloid leukemia. *Semin Oncol*. 2008;35(4):418-429.
23. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med*. 2002;21(15):2175-2197.
24. Fleury I, Chevret S, Pfreundschuh M, et al. Rituximab and risk of second primary malignancies in patients with non-Hodgkin lymphoma: a systematic review and meta-analysis. *Ann Oncol*. 2016;27(3):390-397.
25. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med*. 2003;348(17):1681-1691.
26. Hill DA, Gilbert E, Dores GM, et al. Breast cancer risk following radiotherapy for Hodgkin lymphoma: modification by other risk factors. *Blood*. 2005;106(10):3358-3365.
27. Janjetovic S, Bernd HW, Bokemeyer C, Fiedler W. Hodgkin's lymphoma as a rare variant of Richter's transformation in chronic lymphocytic leukemia: a case report and review of the literature. *Mol Clin Oncol*. 2016;4(3):390-392.
28. Karmali R, Kimby E, Ghielmini M, Flinn IW, Gordon LI, Zucca E. Rituximab: a benchmark in the development of chemotherapy-free treatment strategies for follicular lymphomas. *Ann Oncol*. 2018;29(2):332-340.
29. Alhmod JF, Woolley JF, Al Moustafa AE, Malki MI. DNA damage/repair management in cancers. *Cancers (Basel)*. 2020;12(4):1050.
30. Lin EC. Radiation risk from medical imaging. *Mayo Clin Proc*. 2010;85(12):1142-1146, quiz 1146.
31. Serraino D, Piselli P, Busnach G, et al; Immunosuppression and Cancer Study Group. Risk of cancer following immunosuppression in organ transplant recipients and in HIV-positive individuals in southern Europe. *Eur J Cancer*. 2007;43(14):2117-2123.
32. Lemonnier F, Gaulard P, de Leval L. New insights in the pathogenesis of T-cell lymphomas. *Curr Opin Oncol*. 2018;30(5):277-284.