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Subsequent primary malignancies after diffuse large B-cell lymphoma in the modern treatment era

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Summary

With the addition of rituximab and other treatment advances, survival after diffuse large B-cell lymphoma (DLBCL) has improved, but subsequent primary malignancies (SPMs) have emerged as an important challenge for DLBCL survivorship. We calculated standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for SPMs among 23,879 patients who survived at least 1 year after a first primary DLBCL diagnosed during 1989–2012, compared to the general population in California. Cumulative incidence (CMI) of SPMs, accounting for the competing risk of death, also was calculated. We found that the incidence of acute myeloid leukaemia (AML) nearly doubled in the post-rituximab era [SIR (95%CI) 4.39 (2.51–7.13) pre- (1989–2000) and 8.70 (6.62–11.22) post-rituximab (2001–2012)]. Subsequent thyroid cancer was rare pre-rituximab, but increased substantially after 2001 [0.66 (0.08–2.37) vs. 2.27(1.44–3.41)]. The 5-year CMI for all SPMs (4.77% pre- vs. 5.41% post-rituximab, P=0.047), AML (0.15% vs. 0.41%, P=0.003), thyroid cancer (0.03% vs. 0.15%, P=0.003) and melanoma (0.25% vs. 0.42%, P=0.020) were greater in DLBCL patients diagnosed in the post-versus pre-rituximab period. This study provides insight into the changing pattern of SPM occurrence after the introduction of rituximab,

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Author contributions: Tao and Keegan designed the study, interpreted the data, and led the writing and review of the manuscript. Tao performed the statistical analyses. Clarke, Rosenberg, Advani, Jonas, and Flowers participated in the interpretation of data and drafting and critical review of the manuscript. All authors read and approved the final manuscript.

which may elucidate the aetiology of SPMs and should guide future cancer surveillance efforts among DLBCL patients.

Keywords

lymphoma; diffuse large B-cell lymphoma; cancer; second primary malignancy; incidence

Introduction

Introduction of the monoclonal anti-CD20 antibody rituximab in the late 1990's represents one of the most important advances in the treatment of diffuse large B-cell lymphoma (DLBCL), followed by a 30% decrease in mortality among DLBCL patients.(Tao, *et al* 2014) With patients achieving longer-term survival, management of subsequent primary malignancies (SPMs) is an emerging challenge. While rituximab-induced B-cell dysfunction and immunodeficiency may lead to increased susceptibility to infections and progression of malignancies,(Chapel, *et al* 2003, Kaplan, *et al* 2014) there have been few reports of rituximab-related secondary cancers after DLBCL,(Aksoy, *et al* 2011, Cho, *et al* 2015, Fleury, *et al* 2015, Hua, *et al* 2015, Pfreundschuh 2006, Solal-Celigny 2006) with the exception of two reports of melanoma acceleration after rituximab treatment.(Peuvrel, *et al* 2013, Velter, *et al* 2014) A large Surveillance, Epidemiology, and End Results (SEER) analysis reported that DLBCL patients diagnosed 1992–2006 had 11% higher rate of overall SPM than the general population, with particularly elevated risks for second primary Hodgkin lymphoma (HL) and certain leukaemias.(Morton, *et al* 2010) However, no population-based studies have assessed whether the risk, or patterns, of SPMs changed after the introduction of rituximab in 2001.

In this study, we utilized sequential tumour data available from the large and high quality, population-based California Cancer Registry (CCR) to describe the incidence of SPMs before (1989–2000) and after (2001–2012) the routine use of rituximab was incorporated into standard first-line therapy for DLBCL.(Coiffier, *et al* 1998, Coiffier, *et al* 2002) We report the occurrence of SPMs overall and by cancer type, patient characteristics, use of chemotherapy and radiation therapy, and latency period between DLBCL and haematological SPMs in order to inform cancer surveillance efforts among DLBCL patients.

Methods

Patients

We identified 25,089 patients of all ages who survived for at least 1 year after diagnosis of a first primary DLBCL (International Classification of Diseases-Oncology, 3rd edition [ICD-O-3] morphology codes 9678–9680, 9684) between the years 1989 and 2012 in California. Among these patients, we excluded 1,210 who had evidence of human immunodeficiency virus infection or acquired immunodeficiency syndrome (Tao, *et al* 2014), resulting in a final study population of 23,879 DLBCL patients. We obtained information on age at diagnosis, race/ethnicity, stage at diagnosis, residential address at diagnosis and initial treatment modalities (chemotherapy and radiation therapy) for the first primary DLBCL based on the

routinely abstracted medical record. Over the period of our study, the receipt of rituximab was not recorded separately from chemotherapy and neither specific chemotherapy regimens nor radiation doses were available in the cancer registry. We used a multi-component index of neighbourhood socioeconomic status (SES) based on patients' residential census-block group at diagnosis.(Tao, *et al* 2014) The index is grouped into quintiles, based on the distribution of SES among all census block groups in California. We also obtained information regarding the occurrence of subsequent invasive cancers that developed at least 1 year after the initial DLBCL diagnosis, as done previously (Lam, *et al* 2015, Morton, *et al* 2010). All subsequent cases of non-Hodgkin lymphoma, lymphocytic leukaemia and Kaposi sarcoma were excluded from overall subsequent malignancy risk estimates because of the difficulty of distinguishing disease progression from the primary DLBCL.

The addition of rituximab to conventional chemotherapy started in the late 1990's(Coiffier 2007, Molina 2008) and became a consensus standard therapy after 2002.(Coiffier, *et al* 2009) Survival data on rituximab use in combination with chemotherapy for treatment of DLBCL were first presented in 2000 and its use was rapidly adopted in clinical practice. (Flowers, *et al* 2012, Sinha, *et al* 2012) Therefore 2001 was considered the beginning of the rituximab era. Patients in the pre- and post-rituximab treatment era were followed for the same period of time (study end date 31 December 2000 for patients diagnosed in pre-rituximab era and 31 December 2012 for patients diagnosed post-rituximab). All study protocols were overseen by the Institutional Review Board of the Cancer Prevention Institute of California.

Statistical Analysis

SEER*Stat version 8.2.1 (National Cancer Institute, Bethesda, MD) was used to calculate standardized incidence ratios (SIRs) and the corresponding 95% confidence intervals (CIs) for DLBCL patients by comparing these patients' subsequent cancer experience with the number of cancers that would be expected based on the 5-year age-, sex-, calendar year- and race/ethnicity-specific incidence rates for the general California population. SEER*Stat calculates observed (O) and expected (E) numbers of SPMs, the latter based on California state-wide cancer incidence rates applied to the total person-years of follow-up, weighted appropriately for cohort distributions of race and/or ethnicity, attained age, and attained calendar year. The SIR is a relative risk measure representing the ratio of O to E (O/E). We calculated SIRs for all invasive cancers and by invasive cancer type as well as by age group at diagnosis (<65, ≥65 years), sex, race/ethnicity, initial treatment, neighbourhood SES and latency. These age groups were chosen because of previously observed differences in survival patterns by age before and after the introduction of rituximab.(Tao, *et al* 2014) Statistics with fewer than three cases are not shown for privacy reasons.

The cumulative incidence of developing a SPM after the diagnosis of DLBCL was calculated using the life-test procedure for evaluating the Kaplan-Meier survival function using SAS software version 9.3 (SAS Institute, Cary, NC). Death was accounted for as a competing risk in these analyses. Person-years of observation were compiled from date of the first primary DLBCL diagnosis to the date of diagnosis of a SPM, the study cut-off date for each treatment era, or the date of death (before each study cut-off date), whichever

occurred first. Gray's K-sample test statistic was used to determine whether the difference in cumulative incidence of SPM was statistically significant (*P*-values that were <0.05) before and after the introduction of rituximab (Gray 1988) for all DLBCL patients, for all subsequent cancers and by SPM cancer site.

Results

Among 23,879 DLBCL patients in California who survived at least one year after diagnosis, the median (95% CI) person-years of follow-up was 3.61 (3.52–3.70) and 4.53 (4.43–4.61) for patients diagnosed before and after 2001, respectively. The mean age (±standard deviation) was 59.0 (±17.6) and 60.4 (±17.0) years for patients diagnosed in the two treatment eras, respectively. Most patients were non-Hispanic white, but, reflecting changes in the California population over time, the proportion of Hispanic and Asian patients increased in the later era (Table I). Relative to the pre-rituximab era, DLBCL patients diagnosed after 2001 were somewhat more likely to receive chemotherapy and less likely to receive radiation therapy (Table I), patterns that were similar in patients diagnosed with both localized/regional and advanced disease (data not shown).

Subsequent primary solid tumours were diagnosed in a total of 495 patients diagnosed in the pre-rituximab era (compared with 430 expected in the general California population, SIR 1.15, 95%CI 1.05–1.26), and in 773 in the post-rituximab era (compared with 713 expected in the general population, SIR 1.08, 95%CI 1.01–1.16; Table II). Subsequent thyroid cancers were rare in DLBCL survivors in the pre-rituximab era, but rates increased considerably during the post-rituximab era (SIR 2.27, 95%CI 1.44–3.41), regardless of radiation therapy use for the treatment of their DLBCL (SIR 2.13, 95%CI 0.78–4.63 for patients with radiation therapy and SIR 2.33, 95%CI 1.36–3.96 for patients without radiation therapy; Supplementary Table). By contrast, we found higher risks of subsequent primary colorectal and breast cancers in patients diagnosed in the pre-rituximab era (borderline significance), although the risks were comparable to the underlying population in rituximab era. The SIRs for lung cancer, liver cancer and melanoma were comparable in the pre- and post-rituximab era. For subsequent primary tumours, we did not observe notable differences in SIRs in each treatment era by age group at diagnosis, sex, race/ethnicity, initial treatment, neighbourhood SES or in latency (Supplementary Table). SIRs appeared to be either similar by stage at DLBCL diagnosis or more pronounced for DLBCL patients diagnosed with advanced (versus localized/ regional) stage disease (Supplementary Table).

Table III shows that rates of acute myeloid leukaemia (AML) among DLBCL patients doubled in the post-rituximab era (SIR 4.39, 95%CI 2.51–7.13 pre- vs. SIR 8.70, 95%CI 6.62–11.22 post-rituximab). Unlike patients diagnosed in the pre-rituximab era, DLBCL patients diagnosed in the post-rituximab era had persistently high rates of AML over time, particularly after 5 years (SIR 10.42, 95%CI 5.38–18.20 for ≥7 years from DLBCL diagnosis). For HL, the elevated rate persisted in both treatment eras, but was slightly lower in the post-rituximab era (SIR 10.38, 95%CI 5.36–18.13 pre- vs. SIR 7.99, 95%CI 4.57–12.98 post-rituximab); this difference was not statistically significant. For subsequent primary AML and HL, we did not observe notable differences in SIRs by age group at

DLBCL diagnosis, stage at DLBCL diagnosis, sex, race/ethnicity, or neighbourhood SES (Supplementary Table).

Overall, the cumulative incidence of all subsequent malignancies was greater in DLBCL patients diagnosed in the post-rituximab era than those diagnosed in the pre-rituximab era (cumulative incidence at 5- and 10-year after diagnosis was 4.77% and 9.67% in the pre-rituximab and 5.41% and 10.47% in the post-rituximab period, respectively; P= 0.047, Table IV and Fig 1). The 5-year cumulative incidence of AML (0.15% pre- vs. 0.41% post-rituximab, P=0.003), thyroid cancer (0.03% pre- vs. 0.15% post-rituximab, P=0.003) and melanoma (0.25% pre- vs. 0.42% post-rituximab, P=0.020), were significantly greater in DLBCL patients diagnosed in the post-versus pre-rituximab period (Table IV and Fig 2). No differences in the cumulative incidence of other cancers in the post-versus pre-rituximab period were observed (Table IV).

Discussion

To our knowledge, this is the first population-based study to describe the occurrence of SPMs in DLBCL patients before and after the common use of rituximab in the United States. Our findings suggest that DLBCL patients were more likely to develop a subsequent melanoma, thyroid cancer or AML in the post-rituximab than the pre-rituximab era. Further, we observed elevated rates of subsequent HL, lung cancer and liver cancer among DLBCL survivors as compared to the general population in the post-rituximab era. Overall, this study provides insight on the changing pattern of SPM occurrence after the introduction of rituximab, information that can guide cancer surveillance efforts among DLBCL patients.

Rituximab is a chimeric monoclonal antibody that targets the CD20 antigen expressed in more than 95% of normal and malignant B-cells, inducing complement-mediated and antibody-dependent cellular cytotoxicity.(Plosker and Figgitt 2003) In contrast to traditional chemotherapy agents, rituximab presents a favourable toxicity profile with the most frequently observed adverse events being infection, fever, and neutropenia (Neves and Kwok 2015). On the other hand, the prolonged duration of rituximab-induced B-cell depletion and T-cell inactivation might cause impaired immune-surveillance and the prolonged immunosuppressive state could provoke the development and progression of certain SPMs. (Aksoy, *et al* 2011, Tan and Coussens 2007) Furthermore, the use of rituximab has dramatically improved DLBCL outcomes,(Komrokji, *et al* 2011, Tao, *et al* 2014) with patients now surviving long after treatment. As a result, host susceptibility, shared aetiological elements, additional treatments and other exposures, and enhanced clinical surveillance(Morton, *et al* 2014) may lead to the occurrence of SPMs, an important cause of morbidity and mortality.(Travis, *et al* 1993, Tward, *et al* 2006)

Our study is the first to identify heightened risk for subsequent thyroid cancer in DLBCL patients diagnosed in the rituximab treatment era. While increased rates of incidental detection with more sensitive imaging tools and more frequent use of ultrasound could explain some of the incidence increase, we would also expect more sensitive imaging to detect other solid tumours, which we did not observe. Multiple studies have found positive associations between radiation therapy, but not chemotherapy (Meadows, *et al* 2009), and

the risk for subsequent thyroid cancer after a diagnosis of head and neck cancer, AML, or HL,(Meadows, *et al* 2009, Ron, *et al* 1995, Tolisano, *et al* 2015) and some studies have described thyroid disorders associated with rituximab use (Hartmann 2015, Raterman, *et al* 2009). Our findings suggest that the increased risk of thyroid cancer post-rituximab occurred in DLBCL patients with either localized/regional or advanced stage disease regardless of radiation therapy use. Further studies, particularly those focused on stimulation of thyroid function and risk of subsequent thyroid cancer after rituximab therapy, are warranted.

There is suggestive prior evidence for an association between rituximab-containing regimens and risk of secondary AML (Lam, *et al* 2016, Zhao, *et al* 2012, Zhou, *et al* 2012), but studies investigating the risk of SPMs during time periods when monoclonal antibodies were used widely for treatment of haematological malignancies are sparse.(Baldo 2013) Significant excesses of AML have been reported among lymphoma patients, and our SIR of 4.39 for secondary AML in the pre-rituximab era was very close to the SIRs reported in two SEER reports [4.83(Morton, *et al* 2010) and 4.96(Travis, *et al* 1993)]. However, it is important to note that the risk of AML was doubled (SIR 8.70) after the introduction of rituximab for DLBCL treatment. Rituximab-related immunodeficiency may last several years (Plosker and Figgitt 2003), which is consistent with our finding of the excess risk of AML over time. In the post-rituximab era, we observed an increase in the cumulative incidence of AML within 5 years of DLBCL diagnosis. This time-period for the onset of AML following treatment has been more commonly associated with topoisomerase II inhibitor use.(Allan and Travis 2005, Leone, *et al* 2001) These data raise the possibility that this risk may be potentiated by rituximab. A plateau in the cumulative incidence of AML was observed between 5 and 7 years after DLBCL, the time-period dominated by alkylator- or radiation therapy-related AML,(Allan and Travis 2005) suggesting that the impact of these therapies may not differ with the use of rituximab. It was followed by an increase in the cumulative incidence again after 7 years, which may be an ongoing late effect of alkylating agents or radiation.(Allan and Travis 2005, Leone, *et al* 2001) However, without details of DLBCL therapy available, we were unable to consider these specific treatment associations in this study.

Increased risks of malignant melanoma were previously recognized in patients with non-Hodgkin lymphoma subtypes other than DLBCL(Lam, *et al* 2015, Morton, *et al* 2010, Travis, *et al* 1993) treated with fludarabine-containing chemotherapy (with or without rituximab), highlighting the role of defective B-cell and T-cell function in some subtypes of lymphocytic malignancies.(Anderson, *et al* 1981, Fisher, *et al* 1980) We found an overall similar risk of melanoma in DLBCL patients compared with the general California population in both treatment eras. However, among DLBCL patients, the cumulative incidence or frequency of melanoma at specific time-points increased significantly in the post-rituximab treatment era, suggesting an association between immune perturbation and risk of melanoma in the context of prolonged survival in DLBCL patients and increased rates of melanoma in the general population of California. In addition, we found substantially higher risks of subsequent HL after DLBCL in both treatment eras, consistent with previous studies. (Hemminki, *et al* 2008, Moser, *et al* 2006, Tward, *et al* 2006)

Our study is unique in that it had a population-based design with sufficient size and statistical power to detect significant changes in SPM incidence in DLBCL survivors

diagnosed before and after the introduction of rituximab. A strength of our analysis is that we provide both SIR and cumulative incidence estimates, the latter of which takes into account the competing risk of death, to determine differences in the occurrence of SPM between the two time periods. Unlike clinical studies, this study was not subject to predefined inclusion criteria or treatment in specific hospitals/centres, and population-based cancer registries have low levels of pathological misclassification for cancers; thus, the results of our analyses are generalizable to the larger DLBCL patient population. One caveat that warrants consideration is the lack of available registry information on DLBCL-specific measurements, such as cell of origin, performance status and treatment details (i.e., use of rituximab and types/doses of chemotherapy or radiation), which limited our ability to characterize factors associated with SPMs. We also lacked treatment data beyond the first course of therapy, including potential additional treatment exposures due to relapse, resulting in the potential for treatment under-ascertainment. Furthermore, we did not have any other individual patient information regarding SPM risk factors (e.g., smoking history for lung cancer) that would allow us to rule out influences of patient selection on our results. Additional cohort studies, preferably involving large databases with more detailed medical history, are needed to evaluate the association of rituximab receipt with SPMs in other DLBCL or non-Hodgkin lymphoma survivor populations to confirm these findings.

In conclusion, we found a substantially elevated incidence of subsequent primary melanoma, thyroid cancer and AML in DLBCL patients diagnosed after the introduction of rituximab. Rates of subsequent HL, lung cancer and liver cancer were significantly elevated regardless of treatment era. To clarify the role of rituximab and other treatments on the risk of specific SPMs over time, further investigations should incorporate details of cancer treatment and other patient and clinical factors when evaluating factors associated with SPMs. The changing pattern of SPM occurrence before and after rituximab observed in our study can potentially elucidate the aetiology of SPMs and guide cancer surveillance efforts among DLBCL patients diagnosed in the modern treatment era, a growing patient population that is living longer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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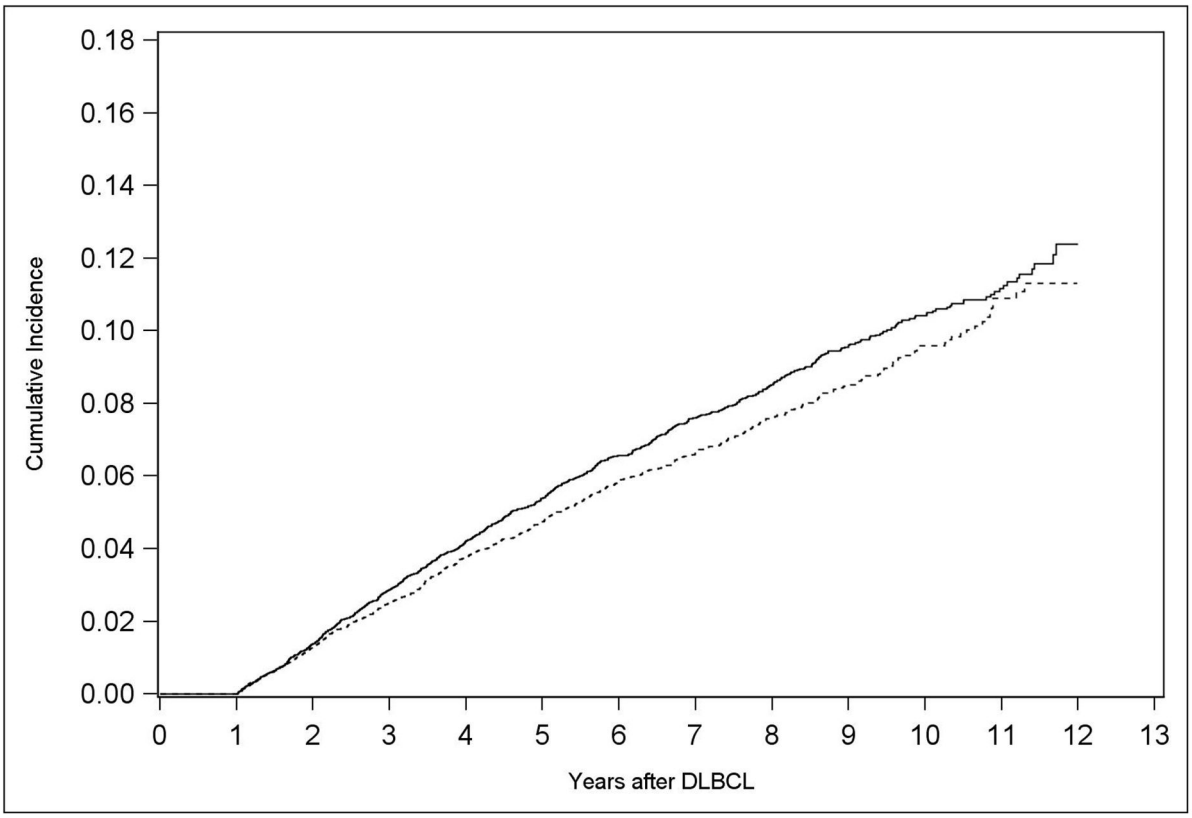

Fig 1.

Cumulative incidence of all subsequent primary malignancies for patients surviving at least 1 year after a first diagnosis of diffuse large B-cell lymphoma (DLBCL) by treatment era, California, 1989–2012

The vertical axis represents cumulative incidence; the horizontal axis represents time in years after DLBCL diagnosis. Pre-rituximab treatment era, 1989–2000 (dotted black line) and post-rituximab treatment era, 2001–2012 (solid black line).

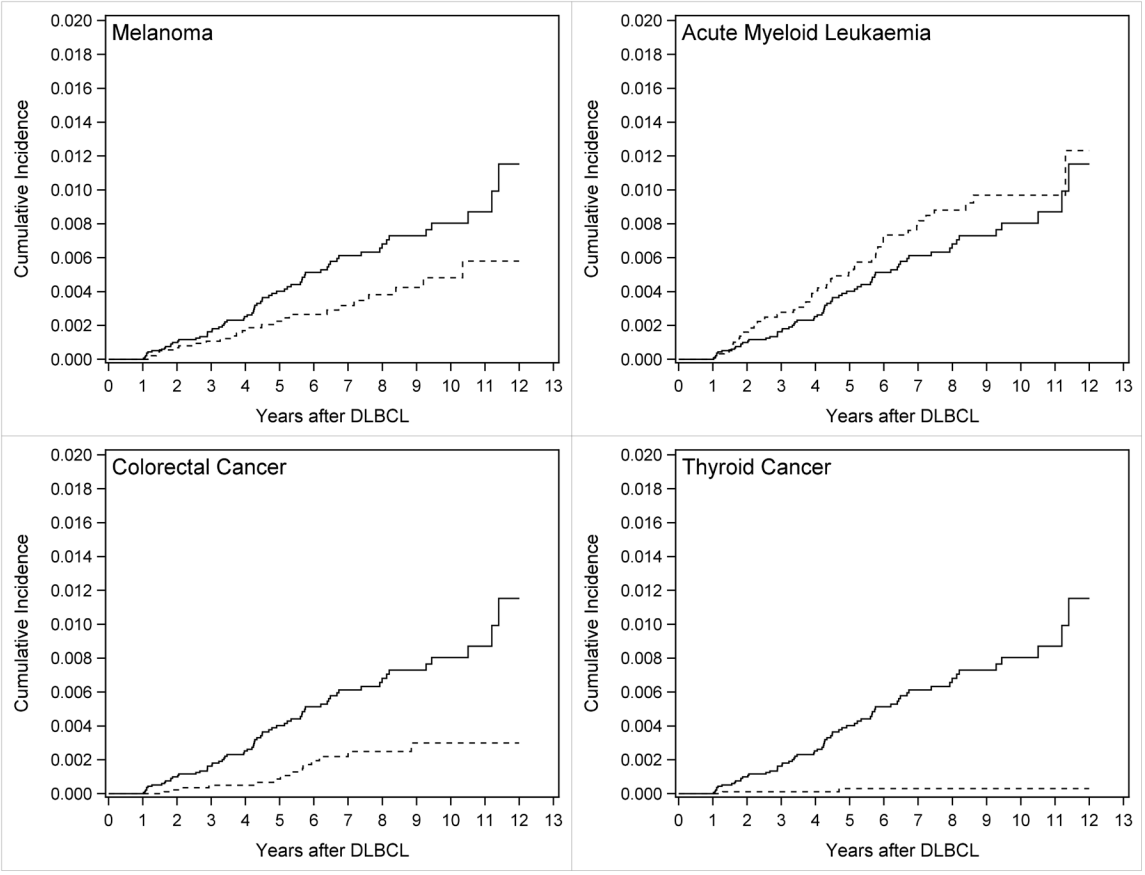

Fig 2.

Cumulative incidence of selected subsequent primary malignancies for patients surviving at least 1 year after a first diagnosis of diffuse large B-cell lymphoma by treatment era, California, 1989–2012

The vertical axis represents cumulative incidence; the horizontal axis represents time in years after DLBCL diagnosis. Pre-rituximab treatment era, 1989–2000 (dotted black line) and post-rituximab treatment era, 2001–2012 (solid black line).

Table I

Selected characteristics of patients surviving at least 1 year after an initial diagnosis of diffuse large B-cell lymphoma (DLBCL) in the pre- and post-rituximab treatment era, California

Characteristics	All		Pre-rituximab (1989–2000)		Post-rituximab (2001–2012)		P-value*
	N	%	N	%	N	%	
All	23879	100	9615	100	14264	100	
Age at DLBCL diagnosis (years)							<0.001
0–14	201	0.8	94	1.0	107	0.8	
15–39	3093	13.0	1443	15.0	1650	11.6	
40–64	9821	41.1	3727	38.8	6094	42.7	
65–79	8053	33.7	3396	35.3	4657	32.6	
80+	2711	11.4	955	9.9	1756	12.3	
Sex							0.686
Male	12697	53.2	5128	53.3	7569	53.1	
Female	11182	46.8	4487	46.7	6695	46.9	
Race/ethnicity							<0.001
Non-Hispanic White	15470	64.8	6870	71.5	8600	60.3	
Black	1008	4.2	381	4.0	627	4.4	
Hispanic	4395	18.4	1411	14.7	2984	20.9	
Asian/Pacific Islander	2685	11.2	862	9.0	1823	12.8	
Other	321	1.3	91	0.9	230	1.6	
Stage at DLBCL diagnosis							
Localized/regional	12930	54.1%	7321	51.3%	5609	58.3%	<0.0001
Advanced	9278	38.9%	6009	42.1%	3269	34.0%	
Unknown	1671	7.0%	934	6.5%	737	7.7%	
Chemotherapy for DLBCL							
Yes	19778	82.8	7884	82.0	11894	83.4	0.005
No/unknown	4101	17.2	1731	18.0	2370	16.6	
Radiation therapy for DLBCL							
Yes	6747	28.3	3153	32.8	3594	25.2	<0.001
No/unknown	17132	71.7	6462	67.2	10670	74.8	

Characteristics	All		Pre-rituximab (1989–2000)		Post-rituximab (2001–2012)		P-value*
	N	%	N	%	N	%	
Neighbourhood Socioeconomic status at DLBCL diagnosis							
Low (Quintiles 1–3)	12366	51.8	4996	52.0	7370	51.7	0.430
High (Quintiles 4–5)	11513	48.2	4619	48.0	6894	48.3	

*Chi-squared test for the difference in characteristics pre- and post-rituximab.

Table II

Observed incident cases (O) and standardized incidence ratios (SIR) with 95% confidence intervals (CIs) of selected subsequent primary solid tumours after an initial diagnosis of diffuse large B-cell lymphoma by treatment era, California, 1989–2012

Site of the subsequent primary solid tumour	Pre-rituximab (1989–2000)		Post-rituximab (2001–2012)	
	O	SIR (95% CIs)	O	SIR (95% CIs)
All solid tumours	495	1.15 (1.05–1.26)	773	1.08 (1.01–1.16)
Lung	88	1.25 (1.00–1.54)	129	1.23 (1.03–1.46)
Prostate	88	0.94 (0.75–1.16)	121	0.87 (0.72–1.04)
Breast	69	1.25 (0.98–1.59)	76	0.84 (0.66–1.05)
Colorectal	59	1.28 (0.97–1.65)	64	1.00 (0.77–1.27)
Urinary bladder	25	1.01 (0.65–1.49)	51	1.14 (0.85–1.50)
Melanoma of the skin	18	1.22 (0.72–1.93)	50	1.23 (0.91–1.62)
Head and neck	15	0.98 (0.55–1.61)	31	1.26 (0.86–1.79)
Liver	10	1.42 (0.68–2.62)	30	1.66 (1.12–2.37)
Pancreas	15	1.26 (0.71–2.08)	22	0.93 (0.59–1.41)
Kidney	6	0.60 (0.22–1.32)	23	0.95 (0.60–1.42)
Thyroid	<3	0.66 (0.08–2.37)	23	2.27 (1.44–3.41)

Table III

Observed incident cases (O) and standardized incidence ratios (SIR) with 95% confidence intervals (CIs) of subsequent primary acute myeloid leukaemia (AML) or Hodgkin lymphoma after an initial diagnosis of diffuse large B-cell lymphoma (DLBCL) by selected characteristics and treatment era, California, 1989–2012

Characteristics era	Treatment	Subsequent primary cancer			
		AML		Hodgkin lymphoma	
		O	SIR (95% CIs)	O	SIR (95% CIs)
All	**Pre-rituximab**	16	4.39 (2.51–7.13)	12	10.38 (5.36–18.13)
	Post-rituximab	59	8.70 (6.62–11.22)	16	7.99 (4.57–12.98)
Initial DLBCL treatment					
Chemotherapy					
Yes	**Pre-rituximab**	14	4.93 (2.7–8.28)	9	9.56 (4.37–18.14)
	Post-rituximab	48	8.80 (6.49–11.67)	14	8.52 (4.66–14.30)
No/unknown	**Pre-rituximab**	<3	2.48 (0.30–8.97)	3	14.01 (2.89–40.95)
	Post-rituximab	11	8.27 (4.13–14.8)	<3	5.57 (0.67–20.11)
Radiation therapy					
Yes	**Pre-rituximab**	6	5.06 (1.86–11.01)	3	7.73 (1.59–22.58)
	Post-rituximab	14	8.08 (4.42–13.56)	<3	3.64 (0.44–13.13)
No/unknown	**Pre-rituximab**	10	4.07 (1.95–7.49)	9	11.73 (5.36–22.26)
	Post-rituximab	45	8.91 (6.5–11.92)	14	9.64 (5.27–16.18)
Latency to subsequent primary, years					
1–3	**Pre-rituximab**	5	3.31 (1.07–7.72)	8	16.22 (7.00–31.95)
	Post-rituximab	21	8.18 (5.06–12.5)	7	8.80 (3.54–18.13)
3–5	**Pre-rituximab**	<3	2.09 (0.25–7.56)	<3	3.31 (0.08–18.43)
	Post-rituximab	13	7.18 (3.82–12.28)	4	7.39 (2.01–18.92)
5–7	**Pre-rituximab**	7	11.21 (4.51–23.1)	<3	5.11 (0.13–28.47)
	Post-rituximab	13	10.37 (5.52–17.73)	<3	5.48 (0.66–19.81)
≥7	**Pre-rituximab**	<3	3.63 (0.44–13.11)	<3	12.15 (1.47–43.9)
	Post-rituximab	12	10.42 (5.38–18.2)	3	10.00 (2.06–29.22)

The pre-rituximab treatment era was defined as 1989–2000 and post-rituximab treatment era was defined as 2001–2012

Table IV

Cumulative Incidence (%, percentage) with 95% confidence intervals (CI) of subsequent primary malignancies 5- and 10-years after an initial diagnosis of diffuse large B-cell lymphoma by treatment era*, California, 1989–2012

	5 years		10 years		P-value**
	Pre-Rituximab % (95% CI)	Post-Rituximab % (95% CI)	Pre-Rituximab % (95% CI)	Post-Rituximab % (95% CI)	
All	4.77 (4.29–5.28)	5.41 (4.99–5.84)	9.67 (8.77–10.61)	10.47 (9.74–11.22)	**0.047**
Lung	0.63 (0.47–0.84)	0.71 (0.57–0.89)	1.78 (1.35–2.30)	1.39 (1.12–1.72)	0.835
Prostate	0.93 (0.72–1.18)	0.75 (0.60–0.93)	1.63 (1.24–2.10)	1.40 (1.12–1.72)	0.365
Breast	0.66 (0.49–0.88)	0.53 (0.40–0.69)	1.58 (1.17–2.09)	1.23 (0.93–1.61)	0.165
Colorectal	0.53 (0.38–0.72)	0.43 (0.32–0.57)	1.24 (0.79–1.86)	0.77 (0.58–1.01)	0.099
Urinary Bladder	0.25 (0.15–0.39)	0.25 (0.17–0.36)	0.54 (0.27–1.00)	0.58 (0.41–0.81)	0.381
Melanoma of the Skin	0.25 (0.15–0.39)	0.42 (0.30–0.56)	0.58 (0.34–0.94)	0.87 (0.64–1.16)	**0.020**
Head and Neck	0.13 (0.07–0.25)	0.17 (0.11–0.27)	0.50 (0.23–0.98)	0.46 (0.30–0.68)	0.452
Liver	0.09 (0.04–0.19)	0.19 (0.11–0.29)	0.17 (0.07–0.36)	0.29 (0.18–0.44)	0.120
Pancreas	0.10 (0.04–0.20)	0.14 (0.08–0.24)	0.32 (0.17–0.55)	0.28 (0.17–0.44)	0.949
Kidney	0.08 (0.03–0.16)§	0.15 (0.09–0.24)	0.11 (0.05–0.24)	0.29 (0.16–0.50)	0.117
Thyroid	0.03 (0.01–0.11)	0.15 (0.09–0.24)	0.03 (0.01–0.11)	0.23 (0.13–0.36)	**0.003**
Acute myeloid leukaemia	0.15 (0.08–0.27)	0.41 (0.3–0.55)	0.39 (0.24–0.63)	0.85 (0.63–1.13)	**0.003**
Hodgkin lymphoma	0.17 (0.09–0.32)	0.10 (0.05–0.18)	0.30 (0.11–0.70)	0.18 (0.10–0.31)	0.614

*The pre-rituximab treatment era was defined as 1989–2000 and post-rituximab treatment era was defined as 2001–2012.

**Gray's K-sample test statistic for the difference in cumulative incidence of subsequent primary malignancies pre- and post-rituximab

§Cumulative incidence data at 3 years, as there were no events at 5 years