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Risk of non-Hodgkin lymphoma after radiotherapy for solid cancers

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Abstract

Ionizing radiation increases risk for acute leukemia, but less is known about radiation and risk of other hematologic malignancies such as non-Hodgkin lymphoma (NHL). We compared second primary NHL incidence among patients who did and did not receive initial radiotherapy for first primary solid malignancy during 1981-2007 reported in nine SEER population-based cancer registries. We identified 5,590 second NHL cases among 1,450,962 one-year cancer survivors. NHL risk was increased after initial radiotherapy for all solid cancers combined (multivariate Poisson regression relative risk [RR]:1.13, 95% confidence interval [CI]:1.06-1.20), non-small cell lung cancer (RR:1.53, 95%CI:1.08-2.17), and prostate cancer (RR:1.19, 95%CI:1.09-1.32). NHL risk increased with longer latency after radiotherapy for non-small cell lung cancer (p_{trend}=0.003) but decreased for prostate cancer (p_{trend}=0.017). There was no clear NHL risk pattern by NHL subtype or age. Our study provides limited evidence that radiotherapy for solid malignancy is associated with increased risk of subsequent NHL.

Keywords

second malignancies; radiotherapy; non-Hodgkin lymphoma

Introduction

Ionizing radiation is known to cause a broad spectrum of malignant disease [1,2]. Among the hematopoietic malignancies (HM), ionizing radiation is an established risk factor for acute leukemia [1,3,4]. However, much less is known about the role of ionizing radiation in lymphomas, and results in the literature to date are inconsistent. Studies of atomic bomb survivors found a slight excess risk of lymphoma incidence only in men [3], but not lymphoma mortality [5]. Elevated non-Hodgkin lymphoma (NHL) risks have been reported after occupational ionizing radiation exposure in some [6-8] but not all studies [9-14]. Associations with medical radiation exposures also have been inconsistent. Several studies reported an increase in NHL risk following therapeutic radiation [15-23], whereas other studies found no evidence of an increased risk of NHL [24-29] and no association with diagnostic radiation has been reported to date [30,31].

To further investigate ionizing radiation and NHL risk, we compared second primary NHL incidence among patients who were initially treated with radiotherapy for a first primary non-hematologic malignancy versus those who were not during 1981-2007, as reported in nine Surveillance, Epidemiology, and End Results Program (SEER) population-based cancer registries in the United States [32]. The SEER registries cover a large population, allow for

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evaluation of long-term patterns of risk associated with ionizing radiation exposure, and allow for comparison across patient populations with different first primary malignancies.

Methods

Study Population

The cohort was derived from nine SEER population-based cancer registries covering approximately 9% of the US population (states including Connecticut, Hawaii, Iowa, New Mexico, and Utah; metropolitan areas including San Francisco, Detroit, Seattle, and Atlanta) [32]. SEER cancer registries collect information on patient demographics, tumor characteristics (site and morphology), extent of disease, and initial course of treatment in broad categories (surgery, radiotherapy, chemotherapy, immunotherapy, and hormonal therapy). Patients in this study comprised adults aged 20-84 years who were diagnosed with a first primary solid (non-hematological) cancer, restricted to patients diagnosed from 1981 through 2007 to reduce NHL subtype misclassification, as described further below. We excluded patients with a first primary hematological malignancy (leukemia or lymphoma) because of difficulty in distinguishing multiple hematologic malignancies in the same patient.

Case Ascertainment

Cases consisted of one-year survivors who developed a second primary NHL. Because NHL subtypes may have different etiologies, we evaluated risks for NHL overall as well as the two most common subtypes, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). We excluded patients diagnosed prior to the introduction of the Working Formulation Classification, which identified lymphoma subtypes more consistently than previous classifications [33]. Cases were identified using International Classification of Diseases for Oncology third edition (ICD-O-3) morphology codes (DLBCL: 9678-9680, 9684 [B-cell]; FL: 9690-9691, 9695 and 9698; Other NHL: 9590-9596, 9670-9671, 9673, 9675, 9687, 9689, 9699-9702, 9705, 9708-9709, 9714-9719, 9727-9729 or 9684 [non B-cell] or 9823, 9827 [primary site=420-421, 424]) [34,35].

Statistical Analysis

We evaluated second primary NHL risk following all first primary solid cancers (N=1,450,962). Patients for whom it was unknown whether they received an initial course of radiotherapy also were excluded (N=1,827). We considered separately 10 specific sites that are commonly treated with radiotherapy (>20% of patients received initial radiation treatment) and that had ≥10 NHL cases in each comparison group (received initial radiotherapy vs. did not receive initial radiotherapy) (Table I). Analyses of patients with first primary lung cancer were restricted to non-small cell lung cancer (NSC) because of potential confounding by chemotherapy for small cell lung cancer (SCLC), for which nearly all patients receive chemotherapy.

The follow-up time (person-years at risk) for each patient began one year after the date of the initial cancer diagnosis and ended at the date of diagnosis of any second cancer, last known vital status, death, age of 85 years, or the end of study (December 31, 2007), whichever occurred first. The first year of follow-up was excluded to minimize bias resulting from increased medical surveillance immediately following diagnosis with first primary cancer. Follow-up was censored at age 85 because of under-ascertainment of second malignancies at older ages [36].

The observed number of NHL cases was compared with that expected in the general population to calculate the standardized incidence ratio (SIR) for each first primary cancer

[32]. Poisson regression analysis were used to estimate the relative risk (RR) and 95% confidence intervals (CI) comparing patients who received initial radiotherapy to patients who did not receive initial radiotherapy. The RRs were adjusted for potential confounders including age at first primary cancer diagnosis, sex, stage, and initial chemotherapy. Adjustment for stage was included because of the potential importance of stage in relation to intensity of medical surveillance and thus, to second cancer ascertainment. The Poisson models were additionally adjusted for attained age and attained calendar year by using the expected number of second NHLs in the general population as an offset [37,38]. We also examined effect modification of the RR associated with radiotherapy under the multiplicative model by latency (time since initial primary diagnosis), sex, age at first primary cancer diagnosis, and NHL subtype. Trend tests were also conducted using ordinal categories as continuous variables for age and latency. Tests of homogeneity and linear trend were based on likelihood ratio tests. All analyses were conducted using the Amfit program in Epicure [39].

Results

The cohort included 1,450,962 one-year cancer survivors (Table I). Among the 10 specific sites commonly treated with radiotherapy, the percentage of patients who received initial radiotherapy ranged from 33.3% for first primary endometrial cancer to 78.3% for laryngeal cancer. Patients who were treated with initial radiotherapy were more likely to be diagnosed with a regional or advanced stage first primary cancer and more likely to have been treated with initial chemotherapy than patients who were not treated with initial radiotherapy. In general, initial radiotherapy was not strongly associated with sex or age at first primary cancer diagnosis, with the exception of patients treated with radiotherapy for cervical cancer, who were older on average than non-irradiated women.

We identified 5,590 cases of second primary NHL during a total of 8,833,038 person-years at risk (Table II). Patients treated with initial radiotherapy for any solid cancer had a significantly higher risk of developing second primary NHL as compared with those not treated with radiotherapy, after adjusting for age and other confounders (RR=1.13, 95% CI 1.06-1.20). Similar elevated risks for NHL associated with radiotherapy were observed after restricting the analysis to patients with solid cancers typically treated with radiotherapy (N=3,736, RR=1.14, 95% CI 1.07-1.22). Among specific first cancers, NHL risk was elevated significantly after initial radiotherapy for non-small cell (NSC) lung cancer (RR=1.53, 95% CI 1.08-2.17) and prostate cancer (RR=1.19, 95% CI 1.08-1.32), and nonsignificantly after radiotherapy for endometrial cancer (RR=1.26, 95% CI 0.96-1.65). Although NHLs after prostate cancer accounted for nearly one half of the second primary NHLs, elevated risks remained marginally significantly elevated for patients with a first primary other than prostate cancer (all solid cancers excluding prostate cancer: RR=1.09, 95% CI 1.00-1.20).

We observed no clear pattern to the second primary NHL risk by time since initial diagnosis after all first primary cancers combined. However there were some patterns for specific sites (Table III). The highest significant risks of second primary NHL were observed <5 years after prostate cancer (RR=1.30, 95% CI 1.13-1.50) and decreased to near unity among 10+ year survivors (p_{trend}=0.017). Although NHL risks were not elevated in any individual latency period, there were significant trends with latency after both female breast cancer (p_{trend}=0.002) and NSC lung cancer (p_{trend}=0.003).

Overall risks of second primary NHL associated with radiotherapy did not differ by NHL subtype after most first primary cancers (Table IV). However, higher risk of DLBCL compared with other NHL subtypes was observed among those treated with radiotherapy for

cancer of the rectum and rectosigmoid junction (RR=2.39, 95% CI 1.26-4.53, $p_{homogeneity}$=0.027), and higher risk of follicular lymphoma was observed after radiotherapy for thyroid cancer (RR=4.38, 95% CI 1.40-13.67, $p_{homogeneity}$=0.027). Similar results were observed after restricting the analysis to patients diagnosed since 1994, corresponding to changes in NHL subtype definitions with the introduction of the REAL classification [40].

Additional analyses demonstrated that risk of developing second primary NHL in relation to radiotherapy was not significantly different by gender (Supplementary Table I), age at first primary cancer diagnosis (Supplementary Table II), or stage (data not shown).

Discussion

In this large, long-term study of solid cancer survivors, initial radiotherapy treatment was associated with a weak, but statistically significantly, increased risk of NHL after all solid cancers combined, with significant elevations in risk for NSC lung cancer, and prostate cancer. We found no elevated risks for other sites that also typically involve radiotherapy to the chest (e.g., breast) or pelvis (e.g., cervical cancer). Thus our findings provide only limited evidence that radiotherapy may increase risk of second primary NHL.

Previous molecular studies have suggested that ionizing radiation may plausibly affect NHL risk either indirectly through immune alterations or directly by DNA damage in the lymphocytes. A range of radiation doses has been shown to cause acute and long-term immunosuppression [41,42], a well-established risk factor for NHL [43,44]. In addition, ionizing radiation has been associated with an increase in B-cell population [41,45], possibly leading to persistent inflammation, another well-established risk factor for NHL [43,44]. Also, observations of atomic bomb survivors have shown increased evidence of direct DNA damage to lymphoctyes, with persistent somatic mutations and chromosomal aberrations in lymphocytic and hematopoietic stem cell populations decades after exposure [45].

Despite some biologic plausibility that ionizing radiation could contribute to lymphomagenesis, the epidemiologic evidence in the literature has been equivocal [15-23], and our results differ in some critical aspects from certain findings. Specifically, previous studies have reported increased NHL risk following pelvic radiotherapy for gynecologic disorders [19,22] and cervical cancer [18,23], abdominal radiotherapy for peptic ulcer [20], spinal radiotherapy for ankylosing spondylitis [15,16], and abdominal/chest radiotherapy for Hodgkin lymphoma [17,21]. We report significantly increased risks after radiotherapy for NSC lung cancer and prostate cancer and non-significantly increased risks after radiotherapy for endometrial cancer, but we found no elevated risks for other sites that also typically involve radiotherapy to the chest or pelvis, and the reasons for these inconsistencies are unclear. In addition, several studies have reported that NHL risk associated with radiotherapy is expected to occur 5 or more years after exposure [2,15-21], but our findings did not show a consistent increase in risk among 5 year survivors.

A major strength of this study was the ability to quantify the risk of radiation-related NHL using multivariate analyses, adjusting for age and other potential confounders, in a large, population-based cohort of cancer survivors with long-term follow-up. Although we did not have complete treatment data, we evaluated risks separately by age, sex, age at first primary cancer diagnosis, latency, stage, and chemotherapy for the key first primary sites typically treated with radiotherapy. Previous studies have suggested differences in NHL etiology which we were able to examine in our dataset; however, we did not find any clear patterns by NHL subtype.

Despite these strengths several limitations of our study should be taken into account in the interpretation of our results. Radiotherapy is known to be under-reported in SEER registry

data [46], which may have attenuated our observed relative risk estimates. Under-ascertainment of initial radiotherapy may have increased in recent years with the increasing use of chemotherapy prior to radiotherapy [46]. In addition, we do not have information on subsequent courses of treatment; therefore, our latency findings should be interpreted with caution. The lack of radiotherapy randomization in these population-based data could introduce selection bias based on differences between the treatment groups with regards to specific factors that may be related to NHL risk (e.g., smoking, alcohol consumption, comorbid conditions), but SEER does not record information on these potential confounding factors. Another potential weakness derives from the fact that chemotherapy is known to be under-reported in SEER and our model adjustment for chemotherapy may be incomplete since we combined patients who did not receive chemotherapy with the patients for whom it is unknown whether they received chemotherapy into one group for the analysis. Further, for patients with combined therapy, chemotherapy may be reported in the radiotherapy records, making it easier to capture these data compared to patients that did not receive radiotherapy. Despite weak evidence relating chemotherapy to subsequent NHL, we controlled for chemotherapy in our analyses and excluded cancer sites (e.g., small cell lung cancer) for which a high percentage of patients are treated with chemotherapy. However, residual confounding by chemotherapy may have contributed to the findings [47]. Finally, the occurrence of second primary NHL may have been underestimated due to emigration from SEER registry areas.

Overall, our study provides limited evidence that radiotherapy for first primary solid cancers increases the risk of developing subsequent NHL. Our results and previous studies suggest that any role of ionizing radiation in lymphomagenesis is likely to be small. Future studies may need to address other considerations specific to NHL, such as the potential for immune dysfunction to contribute to the effects of radiation in developing NHL. Additional studies with detailed radiotherapy information and a large, well-defined study population may elucidate any potential association between ionizing radiation and NHL risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I

Selected characteristics of patients* by initial radiotherapy treatment for first primary solid cancer, ages 20-84, 9 SEER registries, 1981-2007

			Received initial radiotherapy					Did not receive initial radiotherapy				
	Total patients diagnosed	Female	Patients who received initial radiotherapy		Mean age at diagnosis	Mean person-years at risk	Localized stage	Patients who did not receive initial radiotherapy		Mean age at diagnosis	Mean person-years at risk	Localized stage
First primary cancer	N	%	N	%	Years	Years	%	N	%	Years	Years	%
All solid cancers	1,450,962	49.4%	481,163	33.2%	70.5	5.4	50.8%	969,799	66.8%	70.0	6.4	62.8%
All standard radiotherapy treated solid cancers†	982,404	51.4%	417,217	42.5%	72.3	5.7	55.7%	565,187	57.5%	72.6	6.8	66.1%
Oral cavity & pharynx	42,667	31.4%	24,212	56.7%	68.6	4.6	20.7%	18,455	43.3%	69.3	6.9	67.0%
Larynx	17,876	19.0%	13,994	78.3%	70.6	5.9	55.1%	3,882	21.7%	69.1	6.9	57.1%
Thyroid	35,229	76.1%	16,303	46.3%	62.1	7.6	47.8%	18,926	53.7%	62.5	9.5	70.4%
Lung & bronchus (NSC)	98,600	43.2%	43,559	44.2%	71.0	2.0	14.2%	55,041	55.8%	72.4	4.1	50.2%
Female breast	310,719	100.0%	138,499	44.6%	69.6	6.5	63.1%	172,220	55.4%	71.9	7.7	60.3%
Cervix uteri	22,820	100.0%	10,794	47.3%	67.0	6.5	29.9%	12,026	52.7%	59.9	10.7	84.3%
Endometrium	60,767	100.0%	20,216	33.3%	71.9	7.6	61.6%	40,551	66.7%	71.3	8.2	86.9%
Prostate	320,656	0.0%	121,490	37.9%	75.6	5.6	75.2%	199,166	62.1%	74.5	5.9	71.0%
Testis	15,356	0.0%	6,973	45.4%	53.2	10.8	83.4%	8,383	54.6%	50.6	10.4	59.2%
Rectum & rectosigmoid junction	57,714	42.5%	21,177	36.7%	72.1	4.9	25.9%	36,537	63.3%	73.9	6.0	62.1%

Abbreviations: NSC, non-small cell

*Study population was restricted to first prim ary cance r diagnosed betwee n ages 20-84 and survival at least one y ear followin g diagnosis .

Cohort follow-up was censored at age 85 years due to under-ascertainment of second cancers among older patients.

†Includes oral cavity & pharynx, rectosigmoid junction & rectum, larynx, lung & bronchus (NSC), female breast, cervix uteri, en dometrial, prostate, testis, and thyroid cancers.

Table II

Relative risk of non-Hodgkin lymphoma (NHL) after first primary solid cancer according to initial radiotherapy treatment

	Radiotherapy			No Radiotherapy			Radi otherapy vs. No Radiotherapy	
First Primary Cancer	**Obs**	**Exp**	**SIR**	**Obs**	**Exp**	**SIR**	**RR***	**95% CI**
All solid cancers	1.742	1,613.75	1.08	3,848	3,924.46	0.98	1.13	(1.06-1.20)
All standard radiotherapy treated solid cancers†	1,545	1,504.52	1.03	2,191	2,446.86	0.90	1.14	(1.07-1.22)
Oral cavity & pharynx	73	58.88	1.24	92	77.87	1.18	0.87	(0.60-1.25)
Larynx	59	57.70	1.02	23	18.59	1.24	0.89	(0.54-1.46)
Thyroid	45	32.81	1.37	47	51.00	0.92	1.29	(0.84-1.98)
Lung & bronchus (NSC)	62	52.93	1.17	135	151.85	0.89	1.53	(1.08-2.17)
Female breast	355	416.07	0.85	586	665.29	0.88	0.97	(0.84-1.10)
Cervix uteri	30	23.63	1.27	33	26.57	1.24	1.03	(0.57-1.86)
Endometrium	93	92.48	1.01	144	181.37	0.79	1.26	(0.96-1.65)
Prostate	728	684.60	1.06	991	1,102.58	0.90	1.19	(1.08-1.32)
Testis	22	17.46	1.26	10	14.99	0.67	1.57	(0.69-3.55)
Rectum & rectosigmoid junction	78	67.97	1.15	130	156.76	0.83	1.29	(0.88-1.88)

Abbreviations: NSC, non-small cell; Obs, observed; Exp, expected; SIR, standardi zed incide nce ratio; RR, relative risk; CI, confide nce interval

*Poisson regression modeling used to estimate RR of NHL comparing radiotherapy treatment groups for first primary cancer adjusted by sex, age, stage, and chemotherapy.

†Includes oral cavity & pharynx, rectosigmoid junction & rectum, larynx, lung & bronchus (NSC), female breast, cervix uteri, endometrial, prostate, testis, and thyroid cancers.

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Table III

Stratified relative risk of non-Hodgkin lymphoma (NHL) after first primary solid cancer according to initial radiotherapy treatment by latency

	Radiotherapy		No Radiotherapy			
First Primary Cancer	**Obs**	**SIR**	**Obs**	**SIR**	**RR* and 95% CI**	**Ptrend**
All solid cancers						
1-4.9 years	826	1.08	1,741	1.05	1.09 (1.00-1.20)	0.172
5-9.9 years	593	1.12	1,159	0.93	1.23 (1.11-1.36)	
10 + years	323	1.01	948	0.93	1.08 (0.95-1.23)	
All standard radiotherapy treated solid cancers†						
1-4.9 years	699	0.99	880	0.87	1.16 (1.05-1.28)	0.097
5-9.9 years	544	1.08	707	0.89	1.22 (1.09-1.37)	
10 + years	302	1.02	604	0.95	1.03 (0.89-1.19)	
Oral cavity & pharynx						
1-4.9 years	33	1.17	45	1.47	0.52 (0.31-0.87)	0.306
5-9.9 years	23	1.30	23	0.95	1.41 (0.68-2.93)	
10 + years	17	1.32	24	1.04	1.32 (0.65-2.70)	
Larynx						
1-4.9 years	30	1.25	10	1.47	0.86 (0.42-1.76)	0.166
5-9.9 years	20	1.09	3	0.52	2.08 (0.62-7.02)	
10 + years	9	0.59	10	1.67	0.39 (0.15-1.02)	
Thyroid						
1-4.9 years	12	1.00	16	1.06	0.90 (0.42-1.95)	0.350
5-9.9 years	18	1.76	15	1.04	1.44 (0.70-2.98)	
10 + years	15	1.42	16	0.74	1.62 (0.77-3.42)	
Lung & bronchus (NSC)						
1-4.9 years	31	0.85	77	0.98	1.20 (0.75-1.93)	0.003
5-9.9 years	18	1.59	38	0.86	1.94 (1.00-3.75)	
10 + years	13	2.43	20	0.69	2.23 (0.94-5.29)	
Female breast						
1-4.9 years	13 0	0.73	193	0.80	0.91 (0.73-1.15)	0.002

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	Radiotherapy		No Radiotherapy			
First Primary Cancer	**Obs**	**SIR**	**Obs**	**SIR**	**RR* and 95% CI**	**Ptrend**
5-9.9 years	128	0.92	179	0.86	1.05 (0.83-1.32)	
10 + years	97	1.00	214	1.00	1.01 (0.79-1.28)	
Cervix uteri						
1-4.9 years	5	0.61	10	1.55	0.30 (0.07-1.27)	0.137
5-9.9 years	12	1.77	7	0.92	1.88 (0.64-5.54)	
10 + years	13	1.49	16	1.28	1.17 (0.51-2.70)	
Endometrium						
1-4.9 years	37	1.17	51	0.83	1.43 (0.92-2.22)	0.207
5-9.9 years	31	1.08	43	0.75	1.38 (0.85-2.24)	
10 + years	25	0.78	50	0.80	0.99 (0.60-1.62)	
Prostate						
1-4.9 years	386	1.10	42 4	0.84	1.30 (1.13-1.50)	0.017
5-9.9 years	258	1.06	348	0.91	1.19 (1.01-1.41)	
10 + years	84	0.92	219	1.02	0.95 (0.73-1.23)	
Testis						
1-4.9 years	4	0.97	<3	0.56	1.07 (0.20-5.88)	>0.50
5-9.9 years	7	1.44	5	1.19	1.03 (0.28-3.75)	
10 + years	11	1.30	3	0.42	2.89 (0.71-11.71)	
Rectum & rectosigmoid junction						
1-4.9 years	31	0.95	52	0.78	1.50 (0.84-2.68)	>0.50
5-9.9 years	29	1.4	46	0.95	1.77 (0.96-3.27)	
10 + years	18	1.22	32	0.76	0.60 (0.27-1.32)	

Abbreviations: NSC, non-small cell; Obs, observed; SIR, stan dardized incidence ratio; RR, re lative risk; CI, confidence interval

Exact cell counts with <3 patients are suppressed to protect patient confidentiality.

*Poisson regression modeling used to estimate RR of NHL comparing radiotherapy treatment groups for first primary cancer stratified by sex, age, stage, and chemotherapy.

†Includes oral cavity & pharynx, rectosigmoid junction & rectum, larynx, lung & bronchus (NSC), female breast, cervix uteri, endometrial, prostate, testis, and thyroid cancers.

Table IV

Stratified relative risk of non-Hodgkin lymphoma (NHL) after first primary solid cancer according to initial radiotherapy treatment by NHL subtype

	Radiotherapy		No Radiotherapy			
First Primary Cancer*	**Obs**	**SIR**	**Obs**	**SIR**	**RR† and 95% CI**	**Phomogeneity**
All solid cancers						
FL	281	0.98	627	0.90	1.10 (0.95-1.27)	0.224
DLBCL	635	1.15	1,287	0.96	1.21 (1.09-1.34)	
Other NHL	826	1.07	1,934	1.03	1.09 (1.00-1.19)	
All standard radiotherapy treated solid cancers‡						
FL	264	0.99	408	0.94	1.05 (0.9 0-1.23)	0.497
DLBCL	559	1.08	735	0.88	1.20 (1.07-1.34)	
Other NHL	722	1.00	1,048	0.89	1.14 (1.03-1.25)	
Oral cavity & pharynx						
FL	17	1.59	20	1.45	0.79 (0.37-1.69)	0.389
DLBCL	36	1.83	30	1.14	1.29 (0.73-2.26)	
Other NHL	20	0.70	42	1.11	0.59 (0.32-1.10)	
Larynx						
FL	8	0.82	7	2.20	0.35 (0.13-0.98)	>0.50
DLBCL	23	1.19	8	1.29	1.15 (0.46-2.84)	
Other NHL	28	0.98	8	0.87	1.16 (0.53-2.56)	
Thyroid						
FL	14	2.03	4	0.37	4.38 (1.40-13.67)	0.027
DLBCL	14	1.27	20	1.18	0.76 (0.37-1.57)	
Other NHL	17	1.14	23	0.99	1.22 (0.63-2.34)	
Lung & bronchus (NSC)						
FL	11	1.17	21	0.78	2.08 (0.89-4.88)	>0.50
DLBCL	16	0.91	41	0.79	1.32 (0.70-2.52)	
Other NHL	35	1.35	73	0.99	1.51 (0.94-2.44)	
Female breast						
FL	80	0.91	129	0.96	0.95 (0.72-1.26)	>0.50

	Radiotherapy		No Radiotherapy			
First Primary Cancer*	**Obs**	**SIR**	**Obs**	**SIR**	**RR† and 95% CI**	**Phomogeneity**
DLBCL	120	0.85	192	0.85	1.01 (0.80-1.27)	
Other NHL	155	0.83	265	0.87	0.94 (0.77-1.15)	
Cervix uteri						
FL	5	1.01	8	1.3	1.17 (0.34-4.09)	>0.50
DLBCL	14	1.78	11	1.28	1.18 (0.45-3.08)	
Other NHL	11	1.02	14	1.19	0.85 (0.33-2.17)	
Endometrium						
FL	14	0.77	30	0.81	0.98 (0.51-1.90)	>0.50
DLBCL	37	1.17	55	0.88	1.28 (0.83-1.97)	
Other NHL	42	0.99	59	0.72	1.36 (0.90-2.06)	
Prostate						
FL	106	1.03	152	0.89	1.18 (0.91-1.52)	>0.50
DLBCL	261	1.09	341	0.90	1.20 (1.01-1.41)	
Other NHL	361	1.06	498	0.91	1.19 (1.04-1.37)	
Rectum & rectosigmoid junction						
FL	7	0.58	32	1.20	0.54 (0.19-1.55)	0.027
DLBCL	31	1.33	35	0.65	2.39 (1.26-4.53)	
Other NHL	40	1.22	63	0.83	1.14 (0.67-1.95)	

Abbreviations: NSC, non-small cell; Obs, observed; SIR, standardized incidence rati o; RR, relative risk; CI, confidenc e interval; FL, follicular lymphoma; DLBCL, diffuse large b-cell lymphoma; Other NHL, all other NHL subtypes combined

*Testis results removed due to small numbers and to protect patient confidentiality.

†Poisson regression modeling used to estimate RR of NHL following radiotherapy for first primary cancer stratified by sex, age, stage, and chemotherapy.

‡Includes oral cavity & pharynx, rectosigmoid junction & rectum, larynx, lung & bronchus (NSC), female breast, cervix uteri, endometrial, prostate, testis, and thyroid cancers.