From Hodgkin Lymphoma to Thymoma: A Comprehensive Map of Second Primary Malignancy Risk in 14,765 CTCL Patients

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1 Background

- Cutaneous T-cell lymphoma (CTCL) generally follows an indolent course, yet patients face elevated risks of second primary malignancies (SPMs).
- Prior studies vary in cohort size, follow-up duration, and subtype granularity; a meta-analysis reported a pooled SIR of 2.18 across studies from 1950–2019.
- Proposed mechanisms — shared biology, therapy, immune dysregulation, and surveillance bias — have not been separable in a single cohort.

2 Objective

To quantify SPM risk in CTCL using a bidirectional design that pairs the conventional forward analysis with a reverse analysis, separating biologically meaningful associations from bias.

3 Methods

- SEER 2000–2022, Multiple Primary – Standardized Incidence Ratio (MP-SIR) session; SEER*Stat 8.3.6.
- 14,765 patients with CTCL as a first primary (ICD-O-3 9700/3, 9701/3, 9702/3, 9708/3, 9709/3, 9718/3, 9719/3, 9726/3).
- SIRs (observed ÷ expected) with 95% CIs, referenced to age-, sex-, race-, and calendar-year–matched population rates.
- Reverse MP-SIR: risk of CTCL as a second primary after each of 131 index cancer sites. A 1-year latency exclusion was applied in both directions.

4 Cohort characteristics

	MF	SS	All CTCL
Patients, n	8,764	261	14,765
Person-years	66,987	947	112,335
Mean follow-up, y	7.64	3.63	7.61
Mean age, CTCL dx	57.6	67.8	58.7
Mean age, SPM dx	70.6	72.0	70.7
Observed SPMs	1,237	23	2,121
Expected SPMs	892.45	17.08	1,538.65
Overall SIR	**1.39†**	1.35	**1.38†**

MF, mycosis fungoides; SS, Sézary syndrome. † 95% CI excludes 1.0 (MF 1.31–1.47; all CTCL 1.32–1.44). The Sézary subgroup contributes only 23 SPMs and is underpowered for site-specific estimates.

1.38
Overall SPM risk
95% CI 1.32–1.44

+582
Excess cancers
51.8 per 10,000 PY

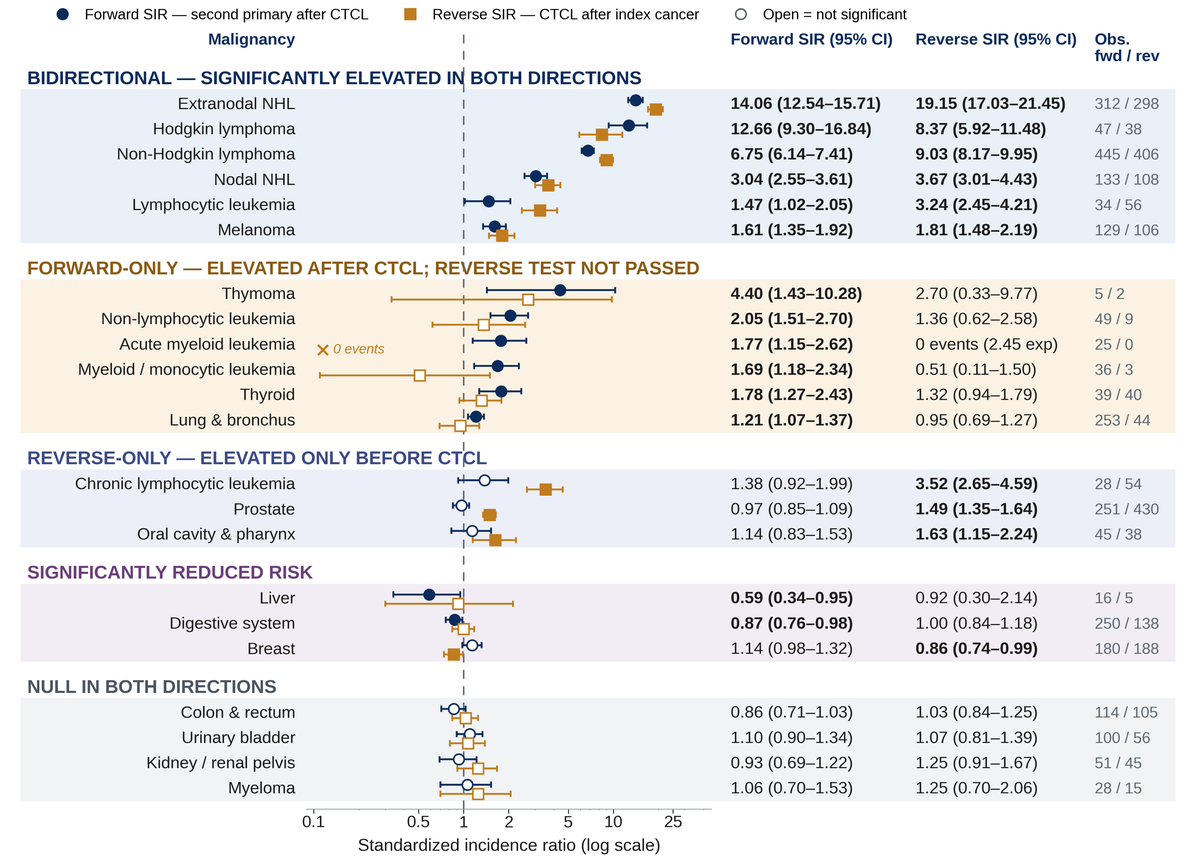
4.21
All lymphohematopoietic
95% CI 3.88–4.56

14.06 / 19.15
Extranodal NHL
forward / reverse

1.61 / 1.81
Melanoma
forward / reverse

4.40
Thymoma — novel
95% CI 1.43–10.28

5 Direction of risk separates biology from bias



Malignancy	Forward SIR (95% CI)	Reverse SIR (95% CI)	Obs. fwd / rev
BIDIRECTIONAL — SIGNIFICANTLY ELEVATED IN BOTH DIRECTIONS			
Extranodal NHL	**14.06 (12.54–15.71)**	**19.15 (17.03–21.45)**	312 / 298
Hodgkin lymphoma	**12.66 (9.30–16.84)**	**8.37 (5.92–11.48)**	47 / 38
Non-Hodgkin lymphoma	**6.75 (6.14–7.41)**	**9.03 (8.17–9.95)**	445 / 406
Nodal NHL	**3.04 (2.55–3.61)**	**3.67 (3.01–4.43)**	133 / 108
Lymphocytic leukemia	**1.47 (1.02–2.05)**	**3.24 (2.45–4.21)**	34 / 56
Melanoma	**1.61 (1.35–1.92)**	**1.81 (1.48–2.19)**	129 / 106
FORWARD-ONLY — ELEVATED AFTER CTCL; REVERSE TEST NOT PASSED			
Thymoma	**4.40 (1.43–10.28)**	2.70 (0.33–9.77)	5 / 2
Non-lymphocytic leukemia	**2.05 (1.51–2.70)**	1.36 (0.62–2.58)	49 / 9
Acute myeloid leukemia	**1.77 (1.15–2.62)**	0 events (2.45 exp)	25 / 0
Myeloid / monocytic leukemia	**1.69 (1.18–2.34)**	0.51 (0.11–1.50)	36 / 3
Thyroid	**1.78 (1.27–2.43)**	1.32 (0.94–1.79)	39 / 40
Lung & bronchus	**1.21 (1.07–1.37)**	0.95 (0.69–1.27)	253 / 44
REVERSE-ONLY — ELEVATED ONLY BEFORE CTCL			
Chronic lymphocytic leukemia	1.38 (0.92–1.99)	**3.52 (2.65–4.59)**	28 / 54
Prostate	0.97 (0.85–1.09)	**1.49 (1.35–1.64)**	251 / 430
Oral cavity & pharynx	1.14 (0.83–1.53)	**1.63 (1.15–2.24)**	45 / 38
SIGNIFICANTLY REDUCED RISK			
Liver	**0.59 (0.34–0.95)**	0.92 (0.30–2.14)	16 / 5
Digestive system	**0.87 (0.76–0.98)**	1.00 (0.84–1.18)	250 / 138
Breast	1.14 (0.98–1.32)	**0.86 (0.74–0.99)**	180 / 188
NULL IN BOTH DIRECTIONS			
Colon & rectum	0.86 (0.71–1.03)	1.03 (0.84–1.25)	114 / 105
Urinary bladder	1.10 (0.90–1.34)	1.07 (0.81–1.39)	100 / 56
Kidney / renal pelvis	0.93 (0.69–1.22)	1.25 (0.91–1.67)	51 / 45
Myeloma	1.06 (0.70–1.53)	1.25 (0.70–2.06)	28 / 15

Figure 1. Paired forward and reverse SIRs with 95% CIs, grouped by directional pattern. Surveillance after a CTCL diagnosis and CTCL-directed therapy can only raise risk in the forward direction; elevation in both directions therefore points to shared susceptibility. Filled markers indicate significance (95% CI excludes 1.0). Thymoma is elevated forward but rests on 5 forward and 2 reverse events, so its reverse CI (0.33–9.77) is uninformative rather than null. Acute myeloid leukemia had zero CTCL cases following it (2.45 expected), the pattern expected of therapy-related disease. Breast cancer was significantly elevated in the forward direction within mycosis fungoides (SIR 1.29, 95% CI 1.07–1.54) though not in the combined cohort. SEER 2000–2022; 14,765 patients; 112,335 person-years; 1-year latency exclusion in both directions.

6 Latency

Site	Obs.	Mean years to SPM
Chronic lymphocytic leukemia	28	1.62
Hodgkin lymphoma	47	2.19
Non-Hodgkin lymphoma	445	3.44
Lung & bronchus	253	3.24
Melanoma	129	4.65
Thyroid	39	4.69
All sites	**2,121**	**3.79**

Hematologic second primaries appear earliest; solid tumors follow years later. A therapy-induced leukemia would be expected to take longer, so the compressed hematologic timeline favors shared lymphoid biology over treatment causation.

7 Interpretation

Shared biology. Lymphohematopoietic malignancies and melanoma are elevated in both directions, most strikingly extranodal NHL (14.06 forward, 19.15 reverse). Neither surveillance nor CTCL therapy can raise the risk of CTCL in patients whose other cancer came first.

Therapy. The myeloid signals run one way only — acute myeloid leukemia is elevated after CTCL yet no CTCL followed AML (2.45 expected) — the asymmetry expected of therapy-related disease.

Detection. Forward-only elevations for thyroid, lung, and thymoma fit ascertainment during staging and shared exposures. Thymomas arise from thymic epithelium and share no lineage with malignant T cells, so a common cell of origin is implausible.

8 Where the design is limited

Survival. A null reverse SIR does not prove the absence of an association: patients with aggressive epithelial cancers accrue few person-years at risk for a later CTCL diagnosis, and the significantly reduced breast (0.86) and liver (0.59) estimates most likely reflect competing mortality.

Registry. SEER carries no treatment or clonality data, and the Sézary subgroup is underpowered.

9 Conclusions

- In the largest CTCL cohort analyzed to date, SPM risk is significantly elevated (SIR 1.38) and concentrated in lymphohematopoietic malignancies.
- The bidirectional design separates shared biology (lymphoma, melanoma) from therapy (myeloid neoplasms) and detection (thyroid, lung, thymoma).
- These estimates support targeted lifelong vigilance — nodal and total-body skin examination, attention to B symptoms, periodic blood counts, and smoking cessation — rather than broad screening across all sites.

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