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Persistent Site-Specific Excess Risk of Second Primary Malignancies Among Diffuse Large B-Cell Lymphoma Survivors: A SEER-Based Analysis From 2000 to 2022

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INTRODUCTION

- Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin lymphoma subtype.
- Rituximab-based chemoimmunotherapy has markedly improved survival, producing a large and growing survivor population.
- Treatment genotoxicity and disease- and therapy-induced immune dysregulation both predispose to second primary malignancies (SPMs).
- The magnitude, site distribution and timing of SPM risk after DLBCL remain incompletely defined.

Which cancers, in whom, and for how long after DLBCL?

OBJECTIVE

- Quantify SPM risk in DLBCL survivors against the age-, sex-, race- and calendar-year–matched U.S. general population.
- Identify which cancer sites drive the excess.
- Determine whether the excess attenuates or persists with longer follow-up.
- Characterise variation by age, race and sex.

PRIMARY ENDPOINT

Standardized incidence ratio (SIR) — second primary malignancies observed ÷ expected, with Poisson 95% CI.

METHODS

Design — Retrospective population-based cohort

Source — SEER 17 Research Incidence Database, 2000–2022 (April 2025 release; November 2024 submission)

Cohort — Adults ≥18 y, histologically confirmed first primary DLBCL (ICD-O-3 9680/3)

Analysis — SIR = observed / expected; expected from general-population rates matched on age, sex, race and calendar year; Poisson 95% CIs; SIRs whose CI excludes 1.00 are significant

SEER 17 registries · 2000–2022
↓
Adults ≥18 y with first primary DLBCL
↓
Survived ≥2 months after diagnosis
↓
SPMs by SEER multiple-primary rules → SIR = O / E

CONCLUSIONS

- DLBCL survivors carry a significant excess of second cancers: SIR 1.29 (95% CI 1.27–1.32) — 2,338 more than expected.
- Hematologic SPMs dominate: lymphatic/hematopoietic 2.67, Hodgkin lymphoma 8.20, acute monocytic 6.42, AML 5.97.
- Solid-tumour excess is broad — salivary 2.69, thyroid 2.50, anus 2.50, liver 1.70, oral cavity 1.53, stomach 1.50, kidney 1.34, lung 1.22.
- Male genital cancers were significantly BELOW expectation (0.90, 0.85–0.96), likely reduced PSA screening in survivorship.
- Risk never returns to baseline — all-site SIR 1.27 beyond 10 years; AML remains 2.80.
- Steep inverse age gradient: all-site SIR 2.31 if <60 y vs 1.29 if >75 y; AML 25.48 in survivors <60 y.

RESULTS

DLBCL survivors · SEER 17 registries · 2000–2022 · SIR with 95% CI

1.29 — overall SIR (95% CI 1.27–1.32); 10,391 observed vs 8,053 expected

+2,338 — excess second cancers beyond population expectation

5.97 — SIR for acute myeloid leukemia (5.42–6.56) — 25.48 if aged < 60 y

2.31 — all-site SIR in survivors < 60 y vs 1.29 in those > 75 y

Figure 1. Site-specific SIRs for second primary malignancies after DLBCL

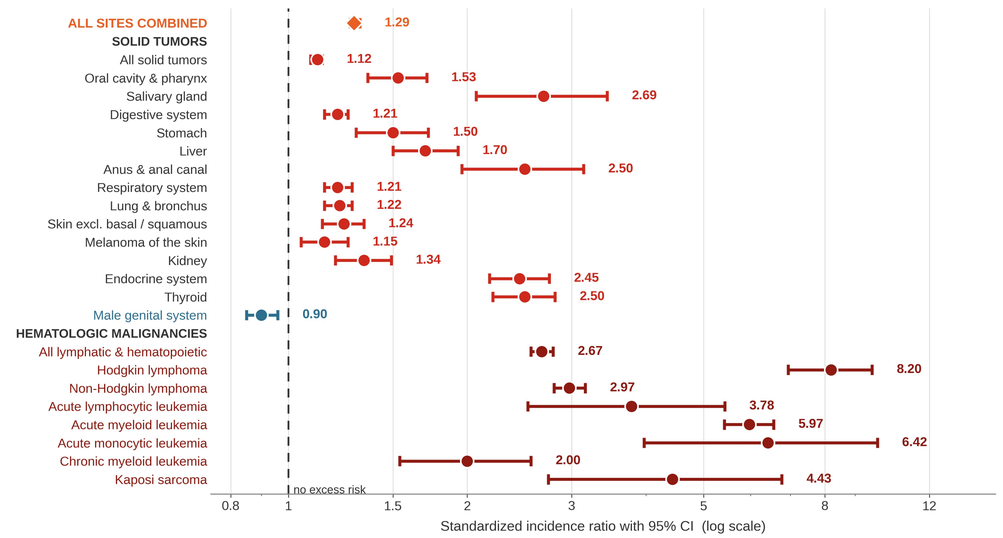
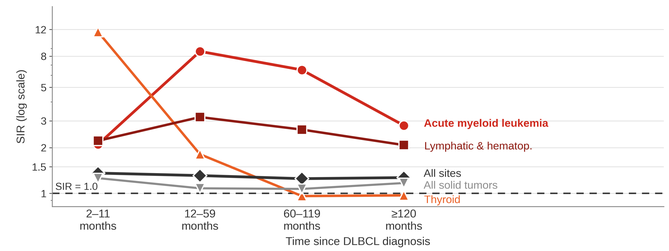


Table 1. Observed, expected and SIR by cancer site

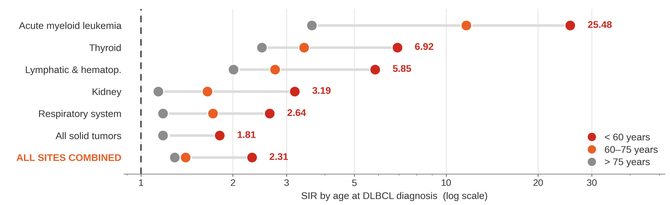
Cancer site / system	Obs.	Exp.	SIR (95% CI)
All sites combined	10,391	8,053.4	**1.29 (1.27–1.32)**
SOLID TUMORS			
All solid tumors	7,708	6,905.2	**1.12 (1.09–1.14)**
Oral cavity & pharynx	308	201.9	**1.53 (1.36–1.71)**
Salivary gland	63	23.4	**2.69 (2.07–3.44)**
Digestive system	1,855	1,535.6	**1.21 (1.15–1.26)**
Stomach	204	135.8	**1.50 (1.30–1.72)**
Liver	240	140.8	**1.70 (1.50–1.93)**
Anus & anal canal	74	29.6	**2.50 (1.96–3.14)**
Respiratory system	1,429	1,179.5	**1.21 (1.15–1.28)**
Lung & bronchus	1,351	1,109.5	**1.22 (1.15–1.28)**
Skin excl. basal / squamous	573	463.9	**1.24 (1.14–1.34)**
Melanoma of the skin	486	421.1	**1.15 (1.05–1.26)**
Kidney	343	256.2	**1.34 (1.20–1.49)**
Endocrine system	295	120.4	**2.45 (2.18–2.75)**
Thyroid	276	110.4	**2.50 (2.21–2.81)**
Male genital system	1,163	1,286.0	**0.90 (0.85–0.96)**
HEMATOLOGIC MALIGNANCIES			
All lymphatic & hematopoietic	2,003	749.4	**2.67 (2.56–2.79)**
Hodgkin lymphoma	152	18.6	**8.20 (6.94–9.61)**
Non-Hodgkin lymphoma	1,049	352.7	**2.97 (2.80–3.16)**
Acute lymphocytic leukemia	29	7.7	**3.78 (2.53–5.43)**
Acute myeloid leukemia	439	73.5	**5.97 (5.42–6.56)**
Acute monocytic leukemia	21	3.3	**6.42 (3.97–9.81)**
Chronic myeloid leukemia	63	31.5	**2.00 (1.54–2.56)**
Kaposi sarcoma	21	4.7	**4.43 (2.74–6.77)**

Figure 2. SIR by latency since DLBCL diagnosis



Hematologic risk peaks at 1–5 years and stays elevated. The thyroid spike at 2–11 months (SIR 11.57) reflects staging-driven detection, not sustained risk.

Figure 3. SIR by age at DLBCL diagnosis



LIMITATIONS

SEER captures no treatment-level data (regimen, cumulative dose, radiation fields) and no molecular covariates such as clonal haematopoiesis, so risk cannot be attributed to specific exposures. Multiple-primary rules may incompletely exclude histologic transformation. Residual confounding from tobacco, obesity and viral co-infection is possible, and lead-time / surveillance bias likely inflates early-latency SIRs (notably thyroid). Some strata rest on small observed counts.

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