SECOND PRIMARY MALIGNANCY RISK AMONG SURVIVORS OF CLASSICAL HODGKIN LYMPHOMA IN THE PRE- AND POST-PD-1 INHIBITOR ERAS

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INTRODUCTION

Classical Hodgkin lymphoma (cHL) survivors carry elevated second primary malignancy (SPM) risk from cytotoxic therapy and radiation. PD-1 checkpoint inhibitors (nivolumab, pembrolizumab) have reshaped cHL management since 2016, yet their impact on downstream SPM risk remains undefined.

AIM

To compare the risk and pattern of second primary malignancies (SPMs) among patients with classical Hodgkin lymphoma (cHL) diagnosed in the pre–PD-1 era (2000–2015) versus the post–PD-1 era (2016–2019) using SEER population-based data.

METHOD

Using the SEER database, we identified cHL patients in the pre-PD-1 era (2000–2015; n=10601) and post-PD-1 era (2016–2019; n=3166).

Observed-to-expected (O/E) ratios and excess absolute risks (per 10000 person-years) were calculated across 100+ cancer sites using age, sex, and calendar year-matched population rates.

Statistical significance was defined as $P<0.05$.

CONCLUSIONS

cHL survivors carry a persistently elevated and evolving SPM burden. The post-PD-1 era reveals a distinct SPM profile, with amplified risks of thyroid, melanoma, skin, kidney, and female genital malignancies, potentially reflecting dysregulation driven by immune checkpoint inhibition alongside shifting treatment exposures. Hematologic SPMs, particularly AML and NHL, remain prominent across both eras. Tailored, era-specific survivorship surveillance is warranted for cHL patients managed with modern immunotherapy. Limitations include the relatively short post-PD-1 follow-up window (2016 to 2019), which may underestimate latent SPMs.

RESULTS

Overall SPM risk was significantly elevated in both eras (O/E, 1.58;95% CI, 1.49–1.67 vs O/E, 1.75; 95% CI,1.48–2.06).

Non-Hodgkin lymphoma (NHL) remained the dominant SPM (O/E, 7.28 vs 7.21; both P<0.05), driven by nodal NHL (O/E, 8.19 vs 10.15).

Leukemia risk increased in the post-PD-1 cohort (O/E, 2.84 vs 4.67), particularly acute myeloid leukemia (O/E, 6.85 vs 8.93; both P<0.05).

Notably, several solid tumors showed amplified risk exclusively in the post-PD-1 era: thyroid cancer (O/E, 1.99 vs 5.04), melanoma (O/E, 1.20 vs 2.39), skin cancers excluding basal/squamous (O/E, 1.21 vs 2.22), female genital cancers (O/E, 1.14 vs 2.33), kidney cancer (O/E, 1.07 vs 2.54), and endocrine tumors (O/E, 1.96 vs 4.63); all P<0.05 in the post-PD-1 cohort.

Anal canal malignancies were markedly elevated in both eras (O/E, 8.48 vs 10.94; both P<0.05).

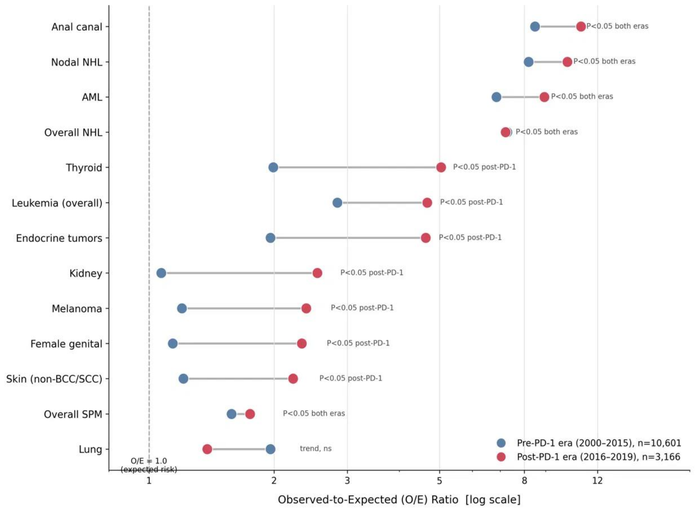
Lung cancer risk trended lower post-PD-1 (O/E, 1.96 vs 1.38), which maybe explained by reduced mediastinal radiation use.

Table. O/E Ratios and Reported P-values for Second Primary Malignancies in cHL Survivors, Pre-PD-1 vs Post-PD-1 Era (SEER)

Cancer Site (SPM)	Pre-PD-1 O/E (2000-2015, n=10,601)	Post-PD-1 O/E (2016-2019, n=3,166)	P-value
Overall SPM	1.58 (95% CI 1.49–1.67)	1.75 (95% CI 1.48–2.06)	**CI excludes 1 (both eras)**
Overall NHL	7.28	7.21	**P<0.05 (both eras)**
Nodal NHL	8.19	10.15	*NR*
Leukemia (overall)	2.84	4.67	*NR*
Acute myeloid leukemia	6.85	8.93	**P<0.05 (both eras)**
Thyroid	1.99	5.04	**P<0.05 (post-PD-1)**
Melanoma	1.20	2.39	**P<0.05 (post-PD-1)**
Skin (non-BCC/SCC)	1.21	2.22	**P<0.05 (post-PD-1)**
Female genital	1.14	2.33	**P<0.05 (post-PD-1)**
Kidney	1.07	2.54	**P<0.05 (post-PD-1)**
Endocrine tumors	1.96	4.63	**P<0.05 (post-PD-1)**
Anal canal	8.48	10.94	**P<0.05 (both eras)**
Lung	1.96	1.38	*NR (trend only)*

NR = not reported as a discrete P-value in abstract text (site-level significance not individually specified beyond grouped statements). CI = confidence interval.

Second Primary Malignancy Risk in cHL Survivors: Pre- vs Post-PD-1 Era (SEER)



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