

## Changing patterns of subsequent neoplasms in the Childhood Cancer Survivor Study cohort.

Background: Limited data exist on whether historical changes in therapeutic exposure have altered subsequent neoplasm (SN) risk after surviving childhood cancer.

Methods: Occurrence of SNs was evaluated in 23,603 5-year survivors diagnosed <21 years of age from 1970-99. Cumulative SN incidence and 95% confidence intervals (CI) at 15 years from diagnosis and standardized incidence ratios (SIRs - using SEER incidence rates) for subsequent malignant neoplasms (SMNs) were compared over treatment eras. Piecewise exponential models assessed changes in rates over treatment eras, adjusting for demographic and clinical characteristics.

Results: With 365,757 person-years at risk, a total of 3310 SNs (including 1026 SMNs, 233 benign meningiomas, 1855 non-melanoma skin cancers [NMSCs], 196 other) among 1760 survivors were reported and validated. Exposure to therapeutic radiation decreased by treatment decade (77.3%, 57.5%, 42.0%), while use of alkylating agents (41.5%, 53.6%, 55.3%) and epipodophyllotoxins (2.1%, 13.6%, 31.5%) increased. Cumulative incidence of SMNs at 15 years was lower for survivors diagnosed in the 1990s (1.6%, 95% CI 1.4-1.9) vs. 1970s (2.3%, 95% CI 2.0-2.7,  $p=0.001$ ). A similar decline was seen for NMSCs (0.1%, 95% CI 0.1-0.2 vs. 0.7%, 95% CI 0.6-1.0,  $p<0.001$ ). SIRs for SMNs declined significantly for survivors with attained age  $\geq 20$  (Table).

SIRs for SMNs by attained age and treatment era of primary diagnosis.							
	1970-74	1975-79	1980-84	1985-89	1990-94	1995-99	P-trend
5-19 y	10.9	10.2	9.7	9.7	10.2	6.3	0.077
20-29 y	6.4	5.2	5.0	4.5	3.6	3.6	0.002
30-39 y	6.3	5.0	5.5	4.2	2.7	4.8	0.006

After adjusting for demographics and cancer diagnosis, incidence rates declined every 5-year era by 7% for SMNs (95% CI 3%-12%,  $p=0.001$ ), 20% for NMSCs (95% CI 14% -25%,  $p<0.001$ ), and 17% for meningiomas (95% CI 8%-27%,  $p=0.001$ ). Inclusion of treatment exposures attenuated the treatment era-associated decline of SN rates, indicating the decline was at least partially attributable to changes in treatment exposure.

Conclusions: Although survivors remain at increased risk for SNs, risk is reduced for survivors diagnosed in more recent eras. Models suggest historical reductions in treatment exposure have contributed to the decreased risk.