

### Short Communication

## The Influence of Subsequent Neoplasms on Incidence Trends in Childhood Cancer<sup>1</sup>

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### Abstract

**The purpose of this analysis was to evaluate to what extent subsequent malignant neoplasms account for the increasing rates of cancer occurrence among children. Data from the population-based Surveillance, Epidemiology, and End Results program were used to calculate age-standardized annual incidence rates from 1974–1989 for 10 common cancers among children 14 years of age or younger. Mean rates and linear trends were evaluated using least squares regression, first for all neoplasms and then excluding subsequent neoplasms, to determine if the removal of subsequent neoplasms would attenuate increasing trends. Increasing annual incidence rates were found for all childhood cancers combined, acute lymphoid leukemia, and brain tumors, but not for other cancer types. Excluding subsequent neoplasms from the analysis had a negligible effect on the trends we observed. Although it remains largely undetermined why childhood cancer incidence rates are increasing in the United States, this study presents evidence that subsequent primary neoplasms do not substantively contribute to these observed trends.**

### Introduction

A gradual but continuous increase in incidence rates of childhood neoplasms have been observed over the past two decades, especially for the two most common categories of childhood cancer, acute lymphoid leukemia and malignant tumors of the brain (1, 2). Rate increases from 1973 through 1989 have averaged 1.9%/year for acute lymphoid leukemia and 1.6%/year for brain tumors among children 0–14

years of age in the United States (2). Whether these trends reflect an actual increase in cancer occurrence rather than a data or diagnostic artifact remains largely unexplored. In adults 65 years of age and older, increases in brain tumor incidence and mortality rates have been reported in the United States, Canada, Europe, and New Zealand (3–7); temporal changes with diagnostic procedures, disease classification, and access to medical care, account for part, but not all, of the observed trends (6–12). It is unclear if this is true for childhood cancer as well.

In contrast to incidence rates, case fatality rates have been decreasing substantially for many types of childhood cancer (1, 2, 13). Five-year relative survival rates for acute lymphoid leukemia, for instance, have improved from 18% during the period of 1967–1973 (13) to over 72% during the period of 1983–1988 (2). For children with non-Hodgkin's lymphoma, 5-year relative survival rates improved from 24–69% during the same periods. Survival has also improved, although to a lesser extent, for children with acute myeloid leukemia, bone tumors, and soft tissue sarcomas.

Given the trend toward improving survival among children diagnosed with cancer, we hypothesized that the apparent increase in childhood cancer incidence rates may be due in part to increased survival, leading to subsequent neoplasms from treatment effects and/or a predisposition to cancer. The purpose of this analysis was to evaluate to what extent subsequent malignant neoplasms account for the increasing incidence rates of cancer among children younger than 15 years of age at diagnosis.

### Methods

Incident cancer data were obtained from nine population-based cancer registries of the National Cancer Institute's SEER<sup>4</sup> program for the years 1974 through 1989. Only primary malignant neoplasms, as defined by the International Classification of Diseases-Oncology 5th digit morphology behavior code (14), were included in this analysis. First (or only) neoplasms and subsequent neoplasms were distinguished by sequence codes as recorded by SEER. These data are abstracted from medical records according to a coding manual that provides specific rules to distinguish subsequent neoplasms from remissions or metastases.

Annual incidence rates were standardized to the 1980 SEER population of children 0–14 years of age using the direct standardization method (15) and are reported per 1 million children per year. The National Cancer Institute contracts with the United States Census Bureau to provide yearly population estimates for the specific catchment areas served by the individual SEER registries, and these are the

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<sup>4</sup> The abbreviation used is: SEER, Surveillance, Epidemiology, and End Results.

Table 1 A comparison of childhood cancer trends between all primary malignant neoplasms and first or only primary malignant neoplasms from least squares regression, SEER registries, 1974–1989

	All sites	ALL <sup>a</sup>	Brain
Total number of primary neoplasms	10,555	2,484	1,934
Number of subsequent primary neoplasms	76	7	12
Annual mean rate, <sup>b</sup> all neoplasms	133.3	30.9	24.3
Slope of the fitted line	1.26	0.47	0.46
Test for linear trend, <i>P</i>	0.001	0.006	0.009
Annual mean rate, <sup>b</sup> first or only neoplasms	132.1	30.8	24.0
Slope of the fitted line	1.22	0.45	0.44
Test for linear trend, <i>P</i>	0.001	0.006	0.007

<sup>a</sup> ALL, acute lymphoid leukemia.

<sup>b</sup> Per 1 million children, standardized to the 1980 SEER population.

data that were used for denominators for the rate calculations. Rates were first calculated for all neoplasms and then recalculated after excluding subsequent tumors, thus allowing comparison of all neoplasms with first or only neoplasms. Rates were compared for all cancer types combined and separately for 10 common childhood cancers (acute lymphoid leukemia, brain, neuroblastoma, non-Hodgkin's lymphoma, Wilms' tumor, acute myeloid leukemia, Hodgkin's disease, bone, rhabdomyosarcoma, and retinoblastoma). Age-standardized rates were plotted by the year of diagnosis, and linear trends were estimated from least squares regression (16).

## Results

There were 10,555 primary malignant tumors recorded by SEER registries from 1974 through 1989 among children 0–14 years of age at diagnosis. Of these, only 76 tumors (from 74 children) were identified as subsequent primary neoplasms (Table 1). Thus, 76 records comprised the subsequent neoplasms for this analysis.

The mean age-standardized incidence rate for all malignant cancers combined was 133.3/1 million children/year, and there was evidence of an increasing trend ( $P = 0.001$ ). Removing subsequent neoplasms from the analysis reduced the slope of the line only slightly (slope, 1.26 versus 1.22, respectively) and revealed no meaningful attenuation of the trend. Additionally, mean rates for the two groups were almost identical. There was also evidence of an increasing linear trend for both acute lymphoid leukemia ( $P = 0.006$ ) and brain tumors ( $P = 0.009$ ); however, in neither case did subsequent neoplasms influence the trend or the mean rate. Bone tumors had the highest number of subsequent neoplasms ( $n = 11$ ) other than brain tumors, but did not appear to be increasing linearly with time ( $P = 0.13$ ); removing subsequent bone neoplasms from the bone tumor analysis also had no effect on the mean rate of 6.4/1 million children/year (data not shown). No other cancer type demonstrated an increasing trend or had enough subsequent neoplasms to warrant further analysis.

## Discussion

These results suggest that subsequent malignant neoplasms do not meaningfully contribute to the increasing incidence rate trends observed for acute lymphoid leukemia, brain tumors, or for all childhood cancers combined. Likewise,

subsequent neoplasms do not contribute perceptibly to incident rates of other childhood cancers. Although there is convincing evidence that cancer treatment can lead to subsequent primary neoplasms among childhood cancer survivors (17–19), apparently this residual effect does not occur frequently enough during the first 14 years of life to influence cancer trends among children in this age group in the United States.

Although the SEER program seeks to identify all individuals who have been diagnosed with cancer in specific geographical areas, individuals are not followed outside these areas to record subsequent cancer diagnoses. Thus, subsequent primary neoplasms among children who move to non-SEER reporting areas after diagnoses of their first primary neoplasms were not included in this analysis. Likewise, children identified with subsequent primary neoplasms in our analysis may have had their first primary neoplasms diagnosed outside a SEER reporting area. It is also conceivable, although unlikely, that a second primary neoplasm could be incorrectly coded as a first primary neoplasm if the prior primary is not mentioned in the medical record. Despite these limitations, given the small number of subsequent neoplasms relative to first or only neoplasms, it is unlikely that missed subsequent neoplasms could change the results we have reported here.

Epidemiological studies of childhood cancer have not, in general, been particularly successful in identifying etiological risk factors that are likely to account for a substantial proportion of cases. As such, the increasing incidence rates, which appear to be most pronounced since 1983, remain largely unexplained. Rate increases could be due to unidentified environmental exposures, diagnostic improvements, increased registry reporting, improved access to medical care, or other reasons yet to be identified. This study has presented evidence that subsequent malignant neoplasms are not a substantive factor in the observed rate increases of childhood cancer.

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