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## Second Primary Malignant Neoplasms and Survival in Adolescent and Young Adult Cancer Survivors

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### Article Information

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*Study concept and design:* Keegan, Goldfarb.

*Acquisition, analysis, or interpretation of data:* All authors.

*Drafting of the manuscript:* Keegan, Goldfarb.

*Critical revision of the manuscript for important intellectual content:* All authors.

*Statistical analysis:* Li.

*Administrative, technical, or material support:* Goldfarb.

*Study supervision:* Keegan, Bleyer, Goldfarb.

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## Key Points

### Question

Do second primary malignant neoplasms (SPMs) have a similar detrimental impact on survival for children, adolescents and young adults (AYAs), and older adults?

### Findings

In this cohort study, the impact of SPMs on survival was more pronounced in children and AYAs than older adults. Adolescents and young adults with a second Hodgkin lymphoma, sarcoma, or breast, thyroid, or testicular cancers had a greater than 2-fold increased risk of cancer-specific death than those with the same primary malignant neoplasms, but no prior cancer.

## Meaning

The adverse impact of SPMs on survival is substantial for AYAs and may partially explain the relative lack of survival improvement in AYAs compared with older adults with the same cancers.

## Abstract

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### Importance

Although the increased incidence of second primary malignant neoplasms (SPMs) is a well-known late effect after cancer, few studies have compared survival after an SPM to survival of the same cancer occurring as first primary malignant neoplasm (PM) by age.

### Objective

To assess the survival impact of SPMs in adolescents and young adults (AYAs) (15-39 years) compared with that of pediatric (<15 years) and older adult ( $\geq$ 40 years) patients with the same SPMs.

### Design, Setting, and Participants

This was a population-based, retrospective cohort study of patients with cancer in 13 Surveillance, Epidemiology and End Results regions in the United States diagnosed from 1992 to 2008 and followed through 2013. Data analysis was performed between June 2016 and January 2017.

### Main Outcomes and Measures

Five-year relative survival was calculated overall and for each cancer occurring as a PM or SPM by age at diagnosis. The impact of SPM status on cancer-specific death was examined using multivariable Cox proportional hazards regression.

### Results

A total of 15 954 pediatric, 125 750 AYAs, and 878 370 older adult patients diagnosed as having 14 cancers occurring as a PM or SPM were included. Overall, 5-year survival after an SPM was 33.1% lower for children, 20.2% lower for AYAs, and 8.3% lower for older adults compared with a PM at the same age. For the most common SPMs in AYAs, the absolute difference in 5-year survival was 42% lower for secondary non-Hodgkin lymphoma, 19% for secondary breast carcinoma, 15% for secondary thyroid carcinoma, and 13% for secondary soft-tissue sarcoma. Survival by SPM status was significantly worse in younger vs older patients for thyroid, Hodgkin lymphoma, non-Hodgkin lymphoma, acute myeloid leukemia, soft-tissue sarcoma, and central nervous system cancer. Adolescents and young adults with secondary Hodgkin lymphoma (hazard ratio [95% CI], 3.5 [1.7-7.1]); soft-tissue sarcoma (2.8 [2.1-3.9]); breast carcinoma (2.1 [1.8-2.4]); acute myeloid leukemia (1.9 [1.5-2.4]); and central nervous system cancer (1.8 [1.2-2.8]) experienced worse survival compared with AYAs with the same PMs.

### Conclusion and Relevance

The adverse impact of SPMs on survival is substantial for AYAs and may partially explain the relative lack of survival improvement in AYAs compared with other age groups. The impact of a particular SPM diagnosis on survival may inform age-specific prevention, screening, treatment, and survivorship recommendations.

## Introduction

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The increased incidence of second primary malignant neoplasms (SPMs) is a well-known late effect after cancer. Although pediatric cancer survivors are at a higher risk of developing an SPM compared with older cancer survivors, adolescent and young adult survivors (AYAs) have the highest absolute excess risk of SPMs among all age groups.

Studies have reported the increased late mortality after specific SPMs among young cancer survivors, but to our knowledge, no study has assessed the survival impact of various SPMs in AYAs compared with pediatric and older adult patients. It is possible that the detrimental effect of SPMs on survival accounts for some of the lack of survival improvement in AYAs compared with pediatric and older adult patients with cancer. Therefore, using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, we compared survival of patients with SPMs with their corresponding first primary cancer types and determined if there were age-specific differences in survival after SPMs.

## Methods

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### Patients

All patients diagnosed with an invasive first primary malignant neoplasm (PM) or SPM (with known type of PM) during 1992 to 2008 were identified from 13 SEER registries. Only 14 common AYA cancers (female breast cancer; thyroid, melanoma, and testicular cancers; Hodgkin lymphoma; non-Hodgkin lymphoma; acute lymphoid leukemia; acute myeloid leukemia; soft-tissue sarcoma; bone sarcoma; and colorectal, central nervous system, cervical, and ovarian cancers) were included in this study.

From SEER, we obtained clinical and demographic information, including race/ethnicity, routinely recorded in the medical record at diagnosis, and vital status, which for the deceased included underlying cause of death. Patients were divided into 3 age groups by the age of diagnosis of the PM or SPM: children (<15 years), AYAs (15-39 years), and older adults ( $\geq 40$  years). The PM group patients had a PM only, and the PM and SPM did not necessarily occur in the same age group.

Second primary malignant neoplasms diagnosed within 2 months of the PM were excluded to remove what were likely multiple primary tumors. Second primary malignant neoplasms with histologic characteristics similar to those of their corresponding PM were reviewed to verify that no SPMs would be considered recurrences according to the updated SEER multiple primary coding rules or best clinical practice. Patients with invalid survival time ( $n = 7585$ ) were excluded. This study was approved by the University of California, Davis, institutional review board.

### Statistical Analysis

Five-year relative survival and standard errors using the Ederer II method were calculated using SAS statistical software (version 9.3; SAS institute Inc) with National Center for Health Statistics expected survival life tables. Multivariable Cox proportional hazards regression at  $P < .05$  was used to evaluate associations of SPM with survival, controlling for age, race/ethnicity, sex, year of diagnosis, and stage at diagnosis (where applicable). For deceased patients, survival time was measured from diagnosis date of the PM or SPM to the date of death from any cause (all-cause death) and any cancer (cancer-specific death). Deaths from non-cancer-related causes were considered as competing risks in analyses of cancer death. Patients alive at the study end date (December 31, 2013) were censored at this date or at last known contact.

## Results

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A total of 15 954 pediatric, 125 750 AYA, and 878 370 older adult patients diagnosed as having 14 cancers occurring as a PM or SPM were included in the study. Children with cancer were predominantly male, whereas AYA and older adult patients were predominantly female (eTable 1 in the [Supplement](#)). The distribution of PMs and SPMs for each age group are presented in eTable 1 in the [Supplement](#), and the 3 most common PMs for those with an SPM are presented in eTable 2 in the [Supplement](#).

The 5-year relative survival for all selected cancers seems lower for those with SPMs than those with a PM, with the largest absolute difference in 5-year survival observed for children (33.1%) and AYAs (20.2%) compared with older adults (8.3%) (eTable 3 in the [Supplement](#)). In AYAs, 5-year relative survival for both a PM and SPM melanoma and testicular cancer was high. However, 5-year relative survival seems lower for all other SPMs compared with corresponding PMs in AYAs. For the most common SPMs in AYAs, the absolute differences in 5-year relative survival were 41.9%, 18.9%, 15.0%, and 12.6% lower for non-Hodgkin lymphoma, breast cancer, thyroid cancer, and soft-tissue sarcoma, respectively, than if these cancers occurred as a PM.

In multivariable-adjusted models, children with acute lymphoid leukemia, acute myeloid leukemia, and central nervous system cancer as an SPM were at a higher risk of cancer death than that of the same PM (Table). In AYAs, almost every SPM conferred a higher risk of death compared with the same PM. Secondary Hodgkin lymphoma and thyroid cancer had more than a 3-fold increased risk, and secondary breast cancer, testicular cancer, soft-tissue sarcoma, and bone sarcoma had more than a 2-fold increased risk of cancer-specific death. In general, SPMs in older adults were associated with higher mortality, but the magnitude of associations was less than in AYAs. All-cause and cancer-specific death by SPM status was significantly worse in younger patients for thyroid, Hodgkin lymphoma, acute lymphoid leukemia, acute myeloid leukemia, soft-tissue sarcoma, and central nervous system cancer; all-cause death by SPM status was significantly worse among younger patients for breast cancer, non-Hodgkin lymphoma, colorectal cancer, and cervical cancer.

## Discussion

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In this large, population-based study, the impact of an SPM on survival for the 14 cancers considered was most pronounced in AYAs and the relatively few SPMs that occurred in childhood compared with older adults. For the most common SPMs in AYAs, the absolute differences in 5-year survival were substantial.

To our knowledge, we are the first to report such large differences in 5-year survival after a second breast cancer or thyroid cancer by age. Possible explanations include a difference in aggressiveness of a PM vs SPM, the increased probability that younger patients harbor a genetic syndrome and different distributions of PM in younger patients. An initial thyroid carcinoma may also be a result of overdiagnosis (and thus not be clinically important) or related to the latency time from the PM to thyroid SPM. Testicular cancer; soft-tissue sarcoma; bone sarcoma; and central nervous system, colorectal, and cervical cancers as SPMs likewise conferred an increased risk of death in AYAs, although melanoma and ovarian cancer did not.

We are also the first to report a large difference in survival for PM and SPM Hodgkin lymphoma and non-Hodgkin lymphoma, particularly among children and AYAs. Treatment for any PM may have affected potential treatment options for a non-Hodgkin lymphoma SPM owing to cumulative toxic effects, thus having an impact on prognosis. In addition, in AYAs, 76% of PMs before non-Hodgkin lymphoma were Kaposi sarcoma, suggesting that an underlying diagnosis of HIV/AIDS is having an impact on the prognosis of second non-Hodgkin lymphoma. Compared with lymphomas, secondary acute lymphoid leukemia and acute myeloid leukemia portend an extremely poor prognosis across all age groups, which may be related to different biology, including cytogenetic or epigenetic features, that result in a poor response to therapy for secondary leukemias. The primary strength of the current study is the large number of patients from population-based registries, increasing the generalizability of our results.

## Limitations

Study limitations include a lack of detailed treatment information, comorbidities, health behaviors, and genetic information. Also, younger populations tend to be more mobile, which may underestimate the number of SPMs identified and lead to conservative (negatively biased) estimates of cancer survival.

## Conclusions

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The adverse impact of SPMs on both relative survival and cancer death seems greater for AYAs and pediatric patients compared with older patients with cancer. Our findings suggest that SPMs may partially account for the relative lack of improvement in 5-year relative survival in AYAs. As more young patients with cancer continue to live for many decades as survivors, the impact of a particular SPM diagnosis on survival may inform age-specific prevention, screening, treatment, and survivorship recommendations.

## Notes

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### Supplement.

**eTable 1.** Characteristics of patients diagnosed with selected primary malignant neoplasms (N= 950,954) and second primary malignant neoplasms (N= 69,120), by age group at diagnosis, SEER, 1992-2008

**eTable 2.** Frequency (percentage) of top three prior cancers occurring in children, adolescents and young adults (AYAs) and older adults by diagnosis, SEER, 1992-2008

**eTable 3.** 5-Year relative survival and standard error (SE) of selected first and second primary malignant neoplasms by age group at diagnosis, SEER, 1992-2008

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## Figures and Tables



**Table.**

**Hazard Ratios (HRs) for the Increased Risk of All-Cause and Cancer<sup>a</sup> Death After a Second Primary Malignant Neoplasm Compared With a Primary Malignant Neoplasm, by Age Group of Diagnosis, SEER, 1992-2008**

| Cancer site or type                        | Age at Diagnosis, HR (95% CI), y <sup>b</sup> |                   |                    |                     |                  |                  | P Value <sup>c</sup> |              |
|--|---|-------------------|--------------------|---------------------|------------------|------------------|----------------------|--------------|
|  | <15   |                   | 15-39              |                     | ≥40              |                  | All-Cause            | Cancer Cause |
|  | All-Cause                                     | Cancer-Specific   | All-Cause          | Cancer-Specific     | All-Cause        | Cancer-Specific  |                      |              |
| Breast carcinoma <sup>d</sup>              | NA  | NA                | 2.12 (1.86-2.41)   | 2.05 (1.76-2.39)    | 1.50 (1.47-1.53) | 2.06 (1.99-2.12) | <.001                | .35          |
| Thyroid carcinoma <sup>d</sup>             | NA  | NA                | 13.23 (9.06-19.32) | 31.62 (18.26-54.74) | 1.70 (1.57-1.83) | 2.42 (2.14-2.73) | <.001                | <.001        |
| Melanoma <sup>d</sup>                      | NA  | NA                | 1.46 (1.05-2.04)   | 1.46 (0.98-2.17)    | 1.19 (1.15-1.23) | 1.68 (1.59-1.77) | .13                  | .30          |
| Testicular cancer <sup>e</sup>             | NA  | NA                | 1.65 (0.91-3.00)   | 2.65 (1.23-5.71)    | 1.70 (1.24-2.34) | 3.12 (2.09-4.66) | .99                  | .72          |
| Hodgkin lymphoma <sup>d</sup>              | NA  | NA                | 3.69 (2.21-6.16)   | 3.50 (1.73-7.07)    | 1.14 (1.01-1.28) | 1.30 (1.12-1.52) | <.001                | .01          |
| Non-Hodgkin lymphoma <sup>d</sup>          | 3.15 (0.99-10.01)                             | 2.23 (0.44-11.17) | 2.97 (2.61-3.39)   | 0.70 (0.51-0.97)    | 1.02 (0.99-1.05) | 1.09 (1.05-1.13) | <.001                | .01          |
| Acute lymphoid leukemia <sup>d</sup>       | 4.00 (1.49-10.73)                             | 4.51 (2.16-9.41)  | 1.60 (1.00-2.56)   | 1.90 (1.20-3.01)    | 1.13 (0.96-1.33) | 1.10 (0.93-1.30) | .02                  | <.001        |
| Acute myeloid leukemia <sup>d</sup>        | 2.59 (1.70-3.92)                              | 2.96 (1.92-4.57)  | 2.07 (1.66-2.58)   | 1.91 (1.50-2.44)    | 1.08 (1.02-1.13) | 1.08 (1.03-1.14) | <.001                | <.001        |
| Soft-tissue sarcoma <sup>d</sup>           | 1.63 (0.71-3.74)                              | 1.20 (0.39-3.64)  | 2.06 (1.68-2.52)   | 2.80 (2.03-3.87)    | 1.16 (1.09-1.22) | 1.31 (1.21-1.41) | <.001                | .002         |
| Bone sarcoma <sup>d</sup>                  | 1.85 (0.86-3.96)                              | 1.95 (0.92-4.12)  | 1.97 (1.08-3.59)   | 2.26 (1.12-4.56)    | 1.34 (1.13-1.60) | 1.56 (1.26-1.93) | .16                  | .38          |
| Colorectal cancer <sup>e</sup>             | NA  | NA                | 1.77 (1.39-2.27)   | 1.74 (1.28-2.35)    | 1.14 (1.12-1.16) | 1.34 (1.31-1.37) | <.001                | .10          |
| Central nervous system cancer <sup>e</sup> | 3.69 (2.12-6.40)                              | 3.26 (1.75-6.07)  | 1.91 (1.40-2.61)   | 1.83 (1.22-2.75)    | 0.98 (0.93-1.04) | 1.09 (1.03-1.16) | <.001                | <.001        |
| Cervical cancer <sup>e</sup>               | NA  | NA                | 1.54 (1.03-2.29)   | 1.52 (0.86-2.70)    | 1.24 (1.19-1.29) | 1.62 (1.54-1.72) | <.001                | .93          |
| Ovarian cancer <sup>e</sup>                | NA  | NA                | 1.36 (0.89-2.08)   | 1.41 (0.92-2.14)    | 1.05 (1.00-1.11) | 1.08 (1.02-1.14) | .12                  | .15          |

Abbreviations: HR, hazard ratio; NA, not applicable; SEER, Surveillance, Epidemiology, and End Results.

<sup>a</sup>Cancer death refers to death from any type of cancer.

<sup>b</sup>Adjusted for 5-year age range, sex, race/ethnicity, year of diagnosis, and stage at diagnosis.

<sup>c</sup>P value for interaction of SPM status by age group for all-cause and cancer death. For cancers with all 3 age groups, all-cause death different between children and adolescent and young adults (AYAs) for central nervous system cancer, between children and older adults for non-Hodgkin lymphoma, acute lymphoid leukemia, acute myeloid leukemia and central nervous system cancer, and between AYAs and older adults for non-Hodgkin lymphoma, acute myeloid leukemia, soft-tissue sarcoma and central nervous

system cancer; cancer death different between children and AYAs for acute lymphoid leukemia and acute myeloid leukemia, between children and older adults for acute myeloid leukemia and central nervous system cancer, and between AYAs and older adults for non-Hodgkin lymphoma, acute lymphoid leukemia, acute myeloid leukemia and soft-tissue sarcoma.

<sup>d</sup>Cancer type based on the SEER AYA site recode.

<sup>e</sup>Cancer type based on SEER site recode.