SKIN

# RESEARCH LETTER

## Second Primary Malignancies After Initial Cutaneous Angiosarcoma: A SEER Population-Based Study

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### ABSTRACT

**Introduction:** The epidemiology of second primary malignancies is an under-investigated domain within dermatology. This notion is particularly true for more uncommon cutaneous oncologic diseases. While general epidemiological characteristics and survival data of patients with cutaneous angiosarcoma have been reported before, there is no investigation of the incidence and types of second primary malignancies (SPMs) that these patients face, which has relevance to screening and surveillance.
**Methods:** The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database was utilized in this study. Initial cases of CAS were extracted and analyzed using standardized incidence ratios (SIR) and excess absolute risks (EAR) for SPMs relative to a control population, which was matched by sex, race (white/unknown, black, other), age group (5-year interval), and calendar year (5-year interval). EAR was calculated per 10,000 persons. P-value <0.05 was deemed statistically significant.
**Results:** Compared to a matched cohort from the general population, patients with CAS demonstrated increased incidence of new malignancies (SIR 1.54; 95% CI, 1.05-2.17; EAR 107.02). Specifically, there was increased risk of soft tissue malignancies, and non-epithelial skin malignancies other than melanoma/basal cell/squamous cell.
**Discussion:** SPMs may be linked to many etiologies, including genetic susceptibility, treatment-related sequelae, lifestyle/environmental factors, or shared risk factors. Indefinite treatments may induce SPMs. Recently, immunotherapy/immune-modulating drugs have been used to treat CAS[4]; this therapy may increase the risk of SPMs via immunosuppression. Shared etiology (i.e. blood vessel or soft tissue-derived neoplasms) may also explain SPMs observed. Importantly, CAS is associated with high recurrence even after complete resection.

### INTRODUCTION

Conic and colleagues[1] provide an important epidemiologic study of cutaneous angiosarcomas (CAS) using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. They describe incidence rates and survival outcomes based on age, disease extent, and treatment. However, an important epidemiologic consideration after initial CAS is the risk of second primary malignancies (SPMs). SPMs may have implications on surveillance post-CAS diagnosis and prognosis.

## METHODS

To address this question, we used the SEER 18 dataset, which pools cancer incidence and survival data from 34.6% of the U.S. population.[2] Initial cases of CAS (2000-2016) were extracted using the International Classification of Diseases for Oncology 3rd edition (ICD-O-3) histology code 9120/3 ("Hemangiosarcoma"). Skin sites were isolated using ICD-O-3 topographical code C44.0-C44.9 (all skin sites). Standardized incidence ratios (SIR) and excess absolute risks (EAR) were computed for SPMs relative to a control population, which was matched by sex, race (white/unknown, black, other), age group (5-year interval), and calendar year (5-year interval). EAR was calculated per 10,000 persons. P-value <0.05 was deemed statistically significant.

## RESULTS

Overall, 358 CAS cases were extracted. Of these, 8.9% (32/358) developed SPMs. Mean follow-up period was 39.4 (+/- 40.8) months and mean age at diagnosis of first neoplasm was 74.6 (+/- 13.0) years. At study end, 31.8% of the cohort remained alive. Compared to a matched cohort from the general population, patients with CAS demonstrated increased incidence of new malignancies (SIR 1.54; 95% CI, 1.05-2.17; EAR 107.02) (Table 1).

Specifically, there was increased risk of soft tissue malignancies, and non-epithelial skin malignancies other than melanoma/basal cell/squamous cell. Of the soft tissue SPMs, 75% (3/4) were blood vessel neoplasms (2 angiosarcomas, 1 malignant epithelioid hemangioendothelioma) and 25% (1/4) was sarcoma (sarcoma, NOS). Of the non-epithelial skin malignancies other than melanoma/basal cell/squamous cell SPMs, 100% (8/8) were angiosarcomas.

## DISCUSSION

The mechanisms underlying the association of CAS with SPMs remain unclear. It is known that underlying risk factors for CAS include radiation therapy as well as exposure to arsenic, polyvinyl chloride and viral hepatitis.3 However, these are also common risk factors for various other cancers. Of note, in our study the risk was highest for non-epithelial skin cancers as highest risk of SPMs in patients with initial CAS. We postulate this risk may also be partly attributed to treatment-related sequelae, such as chemotherapy and radiation. For CAS, there is no clear treatment regimen; surgical resection appears to be the mainstay, and some patients receive adjuvant radiation therapy or chemotherapy.[4] These indefinite treatments may induce SPMs.

Recently, immunotherapy/immune-modulating drugs have been used to treat CAS;[4] this therapy may increase the risk of SPMs via immunosuppression. Furthermore, the literature reveals that particular mutations and pathophysiologic pathways may be implicated in angiosarcomas (e.g. KDR, TP53, and PIK3CA. PIK3CA).5 It is plausible that these pathways may be implicated in SPMs in patients with initial CAS as they serve as a genetic predisposition that may become unmasked, especially when the SPM is of vascular etiology. Future studies would benefit from collaboration with translational researchers to elucidate the genetic sequencing and molecular characterization of malignant tissue in these patients via bio-banking. This may lead to more targeted therapy options

for the management of this challenging malignancy as well. The Angiosarcoma Project, for instance, is an example of such an effort.5 Our analysis of CAS within the SEER database is constrained by several limitations. We were unable to study the tumor site, tumor characteristics, type of treatment received, and socioeconomic factors. Additionally, lifestyle/modifiable risk factors cannot be assessed through SEER, which also limited our analysis. Data entry errors and physician-dependent factors (e.g. surgical technique) are also unable to be accounted for.

## CONCLUSION

In conclusion, patients who have been diagnosed with CAS should be continuously monitored post initial diagnosis and treatment not only for recurrence but also for SPMs.

**Conflict of Interest Disclosures:** None

**Funding:** None

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**Table 1.** Second primary malignancy occurrence following cutaneous angiosarcoma diagnosis by specific sites.

| | Observed | Expected | O/E | CI Lower | CI Upper | Excess Risk |
|---|---|---|---|---|---|---|
| **All Sites** | 32 | 20.85 | 1.54* | 1.05 | 2.17 | 107.02 |
| **Oral Cavity and Pharynx** | 1 | 0.49 | 2.04 | 0.05 | 11.34 | 4.88 |
| **Digestive System** | 3 | 4.36 | 0.69 | 0.14 | 2.01 | -13.02 |
| **Respiratory System** | 3 | 3.42 | 0.88 | 0.18 | 2.56 | -4.03 |
| **Bones and Joints** | 0 | 0.02 | 0 | 0 | 191.08 | -0.19 |
| **Soft Tissue including Heart** | 4 | 0.13 | 30.58* | 8.33 | 78.3 | 37.12 |
| **Skin excluding Basal and Squamous** | 9 | 1.24 | 7.26* | 3.32 | 13.78 | 74.45 |
| **Melanoma of the Skin** | 1 | 1.1 | 0.91 | 0.02 | 5.09 | -0.91 |
| **Other Non-Epithelial Skin** | 8 | 0.14 | 55.28* | 23.87 | 108.93 | 75.37 |
| **Breast** | 2 | 1.4 | 1.43 | 0.17 | 5.16 | 5.75 |
| **Female Genital System** | 0 | 0.53 | 0 | 0 | 6.95 | -5.1 |
| **Male Genital System** | 4 | 3.71 | 1.08 | 0.29 | 2.76 | 2.77 |
| **Urinary System** | 2 | 2.39 | 0.84 | 0.1 | 3.02 | -3.74 |
| **Eye and Orbit** | 0 | 0.03 | 0 | 0 | 109.1 | -0.32 |
| **Brain and Other Nervous System** | 0 | 0.2 | 0 | 0 | 18.04 | -1.96 |
| **Endocrine System** | 0 | 0.19 | 0 | 0 | 18.95 | -1.87 |
| **All Lymphatic and** | 2 | 2.05 | 0.98 | 0.12 | 3.53 | -0.45 |

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|---|---|---|---|---|---|---|
| **Hematopoietic Diseases** | | | | | | |
| **Lymphoma** | 1 | 1.02 | 0.98 | 0.02 | 5.49 | -0.15 |
| **Myeloma** | 1 | 0.33 | 3.03 | 0.08 | 16.87 | 6.43 |
| **Leukemia** | 0 | 0.7 | 0 | 0 | 5.26 | -6.73 |
| **Mesothelioma** | 0 | 0.09 | 0 | 0 | 43.33 | -0.82 |
| **Kaposi Sarcoma** | 0 | 0.01 | 0 | 0 | 246.1 | -0.14 |
| **Miscellaneous** | 2 | 0.57 | 3.48 | 0.42 | 12.57 | 13.67 |

Excess risk is per 10,000,
Confidence intervals are 95%
* P < 0.05