Second primary malignancies after initial cutaneous pleomorphic sarcoma: A national database study

To the Editor: We read with great interest the publication by Ibanez and colleagues.[1] They analyzed data in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database to describe incidence of and prognostic factors affecting survival in cutaneous pleomorphic sarcoma (CPS). However, an important outcome not evaluated was risk of second primary malignancies (SPMs). Herein, we analyze data from SEER to determine the incidence of SPMs after CPS diagnosis and further stratify these findings by specific site, age group, and latency.

The SEER-18 data set pools cancer incidence and survival data from 34.6% of the US population.[2] Initial cases of CPS (during 2000-2016) were extracted via the International Classification of Diseases for Oncology, 3rd Edition, histology code 8830/3 (for malignant fibrous histiocytoma). Skin sites were selected via International Classification of Diseases for Oncology, 3rd Edition, topographical code C44.0-C44.9 (all skin sites). Standardized incidence ratios and excess absolute risks were computed for

Table I. Occurrence of second primary malignancies after cutaneous pleomorphic sarcoma diagnosis by specific site

Site or disease	O	E	O/E	LCL	UCL	Excess risk per 10,000 population
All sites	232	162.16	1.43*	1.25	1.63	98.65
All solid tumors	190	140.19	1.36*	1.17	1.56	70.36
Oral cavity and pharynx	8	3.89	2.06	0.89	4.05	5.8
Tongue	4	1.06	3.76*	1.02	9.62	4.15
Digestive system	41	32.64	1.26	0.9	1.7	11.81
Esophagus	7	2.26	3.09*	1.24	6.37	6.69
Respiratory system	34	27.25	1.25	0.86	1.74	9.54
Bones and joints	1	0.15	6.7	0.17	37.32	1.2
Soft tissue including heart	7	1.05	6.68*	2.68	13.75	8.41
Skin excluding basal and squamous	43	10.78	3.99*	2.89	5.37	45.51
Melanoma of the skin	29	9.53	3.04*	2.04	4.37	27.51
Other nonepithelial skin tumors	14	1.25	11.17*	6.11	18.75	18.01
Breast	5	5.73	0.87	0.28	2.04	−1.03
Female genitalia system	5	2.08	2.41	0.78	5.61	4.13
Vulva	2	0.17	11.47*	1.39	41.44	2.58
Male genitalia system	36	33.15	1.09	0.76	1.5	4.03
Urinary system	17	20.69	0.82	0.48	1.32	−5.21
Eye and orbit	2	0.27	7.32	0.89	26.44	2.44
Nonmelanoma	2	0.08	26.07*	3.16	94.17	2.72
Melanoma	0	0.2	0	0	18.77	−0.28
Brain and other nervous system	2	1.6	1.25	0.15	4.53	0.57
Endocrine system	3	1.27	2.37	0.49	6.91	2.45
Thyroid	1	1.14	0.87	0.02	4.87	−0.2
Thymus, adrenal gland, and other endocrine	2	0.12	16.14*	1.95	58.29	2.65
Thymus	1	0.07	14.49	0.37	80.74	1.32
Adrenal gland	1	0.04	26.83	0.68	149.5	1.36
Other endocrine	0	0.02	0	0	208.75	−0.02
All lymphatic and hematopoietic diseases	19	16.4	1.16	0.7	1.81	3.68
Lymphoma	11	8.02	1.37	0.68	2.45	4.21
Myeloma	3	2.65	1.13	0.23	3.31	0.5
Leukemia	5	5.73	0.87	0.28	2.04	−1.02
Mesothelioma	0	0.78	0	0	4.71	−1.11
Kaposi sarcoma	0	0.12	0	0	30.88	−0.17
Miscellaneous diseases	9	4.32	2.08	0.95	3.95	6.61

Confidence limits are from 95% confidence intervals.
E, Expected; *LCL*, lower confidence limit; *O*, observed; *UCL*, upper confidence limit.
*$P < .05$.

Table II. Site-specific second primary malignancies latency analysis after cutaneous pleomorphic sarcoma diagnosis

Site	2-11 months				12-59 months				60-119 months				≥120 months			
	O	O/E	LCL	UCL	O	O/E	LCL	UCL	O	O/E	LCL	UCL	O	O/E	LCL	UCL
All sites	40	1.54*	1.1	2.1	128	1.58*	1.32	1.87	57	1.36*	1.03	1.76	7	0.53	0.21	1.1
All solid tumors	34	1.51*	1.05	2.11	107	1.52*	1.25	1.84	44	1.22	0.89	1.64	5	0.44	0.14	1.04
Tongue	0	0	0	22.9	4	7.68*	2.09	19.7	0	0	0	13	0	0	0	37.5
Esophagus	1	2.77	0.07	15.5	6	5.29*	1.94	11.5	0	0	0	6.29	0	0	0	20.2
Soft tissue including heart	0	0	0	23.3	6	11.63*	4.27	25.3	1	3.52	0.09	19.6	0	0	0	40.8
Melanoma of the skin	6	4.26*	1.56	9.27	16	3.45*	1.97	5.61	6	2.3	0.84	5	1	1.14	0.03	6.36
Other nonepithelial skin tumors	2	10.83*	1.31	39.1	9	14.74*	6.74	28	3	8.63*	1.78	25.2	0	0	0	33.5
Vulva	0	0	0	155	1	12.2	0.31	68.1	1	20.5	0.52	114	0	0	0	185
Eye and orbit, nonmelanoma	0	0	0	313	1	26.3	0.67	147	1	48.54*	1.23	270	0	0	0	583
Thymus, adrenal gland, and other endocrine	1	51.90*	1.31	289	0	0	0	59.9	1	30.9	0.78	172	0	0	0	346

Confidence limits are from 95% confidence intervals.
E, Expected; *LCL*, lower confidence limit; *O*, observed; *UCL*, upper confidence limit.
*$P < .05$.

all SPMs relative to a control population matched by sex, race (white/unknown, black, other), age group (5-year interval), and calendar year of CPS diagnosis (5-year interval). Excess absolute risk was calculated per 10,000 individuals. We conducted a χ^2 analysis with SPSS (version 26, IBM Corp, Armonk, NY); a P value <.05 was considered statistically significant.

Of 1405 CPS patients, 232 developed SPMs across a mean follow-up of 67.3 (±50.9) months. Mean age at first malignancy was 74.2 (±12.7) years. Compared with the matched general population cohort, patients with CPS demonstrated increased incidence of new malignancies (standardized incidence ratio 1.43, 95% confidence interval 1.25-1.63; excess absolute risk 98.65; Table I).

Site-specific incidences differed across latency periods (Table II). Malignancies with increased risk in the first 2-11 months might be due to higher surveillance (eg, melanoma, recurrent CPS [most nonepithelial skin SPMs]) in the early postdiagnosis period. Malignancies with increased risk in the 12−59-month and 60−120-month periods might be due to increased genetic susceptibility, treatment-related sequelae, lifestyle or environmental factors, or shared etiology (eg, soft tissue, cutaneous malignancies).[3] Of note, after 120 months, no increased SPM risk was observed, suggesting only age-appropriate screening thereafter. In addition, statistical significance of rare SPMs (eg, 1 of 2 cases of nonthyroid endocrine cancer) might not translate to clinical significance. Although determining recurrence and metastasis is important for evaluating CPS aggressiveness,[1,4] SPM risk could also play a role.

Site-specific incidences differed across age groups. Additionally, the incidence of overall SPMs increased with age. These findings corroborate those of Ibanez et al, who noted increased age as a negative predictor of survival in patients with CPS.[1] SPMs might contribute to this worsened prognosis; survival of the SPM cohort was significantly lower than that of the overall cohort (28.9% vs 52.6%, respectively; $P < .001$). Of note, patients aged 0-49 years did not demonstrate increased SPM risk. Further investigation is required to elucidate and confirm these findings before further development of surveillance guidelines.

Our analysis has limitations. Tumor characteristics (eg, thickness, metastasis), treatment (eg, radiation, surgery type), and lifestyle factors (eg, smoking) might influence SPM risk but cannot be assessed by using SEER. In addition, once patients have cancer, they might receive increased surveillance; thus, surveillance bias might be responsible for a number of the observed cases, rather than there being a truly increased incidence.

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