Published in final edited form as:

Dermatol Surg. 2017 January ; 43(1): 116–124. doi:10.1097/DSS.0000000000000936.

Incidence and Clinical Features of Rare Cutaneous Malignancies in Olmsted County, Minnesota, 2000–2010

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Abstract

Background—The incidence of rare cutaneous malignancies is unknown. Current estimates of rare cutaneous malignancy incidences are based on broad epidemiologic data or single institution experiences, not population-based data.

Objective—To determine the incidence of several rare non-melanoma skin cancers.

Methods & Materials—We conducted a retrospective chart review of a population-based cohort between the years 2000 and 2010. Residents of Olmsted County, Minnesota, who were diagnosed with a biopsy-proven non-melanoma skin cancer - excluding basal cell carcinoma and squamous cell carcinoma - were included in this study. The primary outcome was tumor incidence. Additionally, we extracted patient demographics, tumor characteristics, treatment modalities, and outcomes.

Results—The age- and sex-adjusted incidences per 100,000 persons of multiple rare cutaneous malignancies were: atypical fibroxanthoma (1.8), sebaceous carcinoma (0.8), dermatofibrosarcoma protuberans (0.4), microcystic adnexal carcinoma (0.7), eccrine carcinoma (0.4), eccrine porocarcinoma (0.2), and leiomyosarcoma (0.2).

Conclusion—We report population-based incidences and clinical characteristics for these rare cutaneous malignancies. The immune status and smoking status of patients and the treatment and outcomes of these tumors are reported. Additional studies in a broader population are needed to further define the epidemiology and outcomes of these malignancies.

Introduction

Rare cutaneous malignancies are broadly categorized as non-melanoma skin cancer (NMSC) and exclude basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (SCC), the commonest forms of skin cancer. Among these tumors are atypical fibroxanthoma (AFX), eccrine carcinoma and porocarcinoma (EC and EPC, respectively), microcystic adnexal

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The authors have indicated no significant interest with commercial supporters.

carcinoma (MAC), leiomyosarcoma (LMS), dermatofibrosarcoma protuberans (DFSP), Merkel cell carcinoma (MCC) and sebaceous carcinoma (SC). Due to the rarity of the tumors and the absence of uniform reporting for all of these malignancies, the true incidence is unknown. The purpose of the present study was to calculate the incidence and tabulate clinical characteristics of these rare NMSC from a population-based cohort.

Methods

Study setting

This study took place in Olmsted County (OC), Minnesota. While the average socioeconomic status, proportion of college graduates, and proportion of non-Hispanic whites are higher than the national average, epidemiologic studies in OC have historically been consistent with available national data.(1) As of the 2010 United States (US) Census, the OC population was 84.0% white, 6.0% Asian, 5.5% black, 4.7% Hispanic, 0.3% Native American, 1.8% other race, and 2.4% two or more races.(2)

This study was approved by the Mayo Clinic and Olmsted Medical Center institutional review boards. Incident cases were identified through the Rochester Epidemiology Project (REP), a research infrastructure (R01 AG034676) which captures health care information for virtually all residents of OC since 1966.(3)

Study criteria

Using the REP, all medical records for OC residents who received an International Classification of Disease-9 code (ICD-9) diagnosis of 173.00–173.99 from January 2, 2000 to December 31, 2010 were identified. This code range identifies ‘unspecified’, and ‘other specified’ malignant neoplasms of the skin. The medical records of patients who had not denied access to their medical records for research purposes were reviewed for a histopathologic diagnosis of a NMSC. Exclusion criteria included: (1) <18 years of age; (2) no NMSC; (3) previous diagnosis of the incident tumor prior to January 2, 2000; (4) anogenital location; and (5) not an OC resident at the time of incident tumor diagnosis. An NMSC was considered incident if it was a patient’s first tumor of that type and was diagnosed during January 2, 2000 to December 31, 2010 while the patient was a resident of OC.

Data collection

Medical records were reviewed by an abstractor (AS & JM). The following data were collected: age at diagnosis, gender, race, previous diagnosis of melanoma, smoking history, and current immunosuppression. The number of incident tumors, location, and size were documented. Treatment type was recorded, as were recurrence and distant metastasis. Dates were collected for the last relevant clinical follow-up with a dermatologist or a primary care provider for a skin examination. All abstracted data were entered into REDCap (Research Electronic Data Capture) hosted at Mayo Clinic.

Analysis

Data were analyzed using SAS version 9.3 software package (SAS Institute, Inc.; Cary, NC). Continuous variables were summarized with means, standard deviations (SD), medians, and ranges; categorical variables were summarized with frequency counts and percentages. All tumor types were analyzed separately. Age- and sex-specific incidence rates per 100,000 persons in OC, MN, during 2000–2010 were calculated using the number of persons with the diagnosis of interest as the numerator and age- and sex-specific counts of the population of OC as the denominator. The denominators were obtained from the decennial census for OC with linear interpolation between census years. Rates were age- and sex-adjusted to the total population structure of the US in 2010. The 95% confidence intervals (CIs) for the rates were calculated assuming a Poisson error distribution.

Results

A total of 48 incident rare cutaneous malignancies were diagnosed among Olmsted County residents from 2000–2010. The patient demographics, treatment modalities, and outcomes for atypical fibroxanthoma, sebaceous carcinoma, dermatofibrosarcoma protuberans, microcystic adnexal carcinoma, eccrine carcinoma and porocarcinoma, and leiomyosarcoma are outlined in Table 1. Most tumors were diagnosed among the middle-aged or elderly, except for DFSP, where the mean age at diagnosis was 37.7 years. Forty-five of the 48 tumors (94%) occurred in Caucasian patients; one SC, one DFSP, and one EC were diagnosed in African American patients. The majority of tumors occurred in males (30/48, 63%), except for MAC and EC - both of which showed a female predominance – and EPC – which showed equal gender distribution. Mohs micrographic surgery (MMS) was the treatment modality of choice for most cases (30/48, 63%), followed by local excision (12/48, 25%). There were a total of 3 recurrences and no metastases. Table 2 illustrates the overall annual age- and sex-adjusted incidence for these tumors. AFX had the highest incidence with 1.8 cases per 100,000 persons. Other NMSC within our inclusion criteria encountered in this population are listed in Table 3.

Discussion

Atypical Fibroxanthoma

AFX is a fibrohistiocytic tumor with an intermediate malignant potential with metastases and death infrequently reported.(4-10) Other terms for AFX have been pseudocarcinoma, fibrosarcoma, paradoxical fibrosarcoma, pseudosarcomatous dermatofibroma, pseudosarcomatous xanthofibroma, and pseudosarcomatous reticulohistiocytoma.(11, 12) AFX has also been considered as a superficial, more benign variant of undifferentiated pleomorphic sarcoma, formerly known as pleomorphic malignant fibrous histiocytoma.(12)

To our knowledge, the incidence of AFX has not been reported. In a 10-year study period in New Zealand, of 50,411 NMSC AFX constituted 0.002%.(13) Our study shows an AFX incidence of 1.8 per 100,000 persons with a higher incidence in men compared to women (4.0 to 0.4 per 100,000 respectively).

Risk factors associated with AFX are male sex, older age, ultraviolet radiation exposure, x-ray radiation exposure, xeroderma pigmentosa, and a history of transplantation.(12) Depending on the modality of treatment, the recurrence rates range from 0–16%(11, 12, 14-17) but likely 7–9%.(12) Metastatic rate ranges from 0.5–4%.(12) A recent Canadian study demonstrated a local recurrence and distant metastasis up to 14% and 4%, respectively.(18) Both excision and MMS are used to treat AFX, with recurrence rates of 8.7% and 0–6.9%, respectively.(15-17, 19) All AFX in our cohort were on the head and neck with males being more commonly affected (84.2%), supporting the previously reported predilection of AFX for the head/neck of males. Fifteen (88%) of our patients were treated by MMS with a recurrence rate of 5% and without metastases.

Sebaceous Carcinoma

SC is a neoplasm derived from sebaceous glands.(20) These tumors occur most commonly on the eyelid,(21-23) comprising 0.2–5.5% of all periorbital malignancies and an estimated 0.05% of all cutaneous malignancies in the US.(24-27) SC is thought to behave aggressively, and has a propensity for recurrence and metastasis.(23, 24, 28)

A US SEER study (29) identified 1349 cases from 1973–2004 demonstrating 38.7% of SC on the eyelid, consistent with our finding of 37.5% eyelid cases and 87.5% on the head and neck. The SEER study found a significantly different incidence among whites (2.03 per million) versus Asian/Pacific Islanders (1.07 per million) and blacks (0.48 per million).(29) Previous case studies have identified a female predominance of SC,(30-32) but more recent epidemiologic data have revealed a lack of gender association, with perhaps even a slight male predominance.(22, 29) Similarly, we noted a majority of male patients (62%). SC is found primarily in the elderly;(22, 23, 29) our cohort's mean age at diagnosis was 80.1. There is an established relationship between Muir-Torre syndrome and SC,(22, 29, 33) and several studies have shown an association with immunosuppression or previous radiation to the tumor site.(23, 33, 34) One of 8 patients in our cohort (12.5%) was immunosuppressed at the time of diagnosis, and patients with Muir-Torre were excluded from our study.

Myriad treatment options have been employed,(26) though MMS appears to offer the lowest risk of recurrence and metastasis.(26, 35) Of the 2 recurrences observed in our population, 1 was treated with excision, while the other had no additional treatment beyond biopsy. Of the 3 patients treated with MMS, none experienced a local recurrence.

Dermatofibrosarcoma Protuberans

DFSP is a low-grade cutaneous soft tissue sarcoma that is locally aggressive and is associated with a high rate of recurrence.(36) DFSP has a low metastatic potential (1–5%) (37, 38); however, due to its recurrence potential, early surgical therapy is recommended. (39-43)

The reported incidence of DFSP ranges from 0.8 to 5 per million.(44, 45) A SEER study from 1972–2002 reported the incidence of DFSP at 4.2 per million,(46) while another from 1992–2004 estimated an incidence of 4.5 per million.(47) A recent population-based study from Denmark reported the overall incidence as 0.53 per 100,000 persons,(48) similar to our estimate of 0.4 per 100,000 persons. DFSP is found in similar frequencies in men and

women, although a slight male predominance has been suggested.(36, 49, 50) This was confirmed by our age-adjusted incidence of 0.3 per 100,000 in women and 0.5 per 100,000 in men. A significantly higher frequency has been suggested in blacks than whites with an incidence 6.5 per million and 3.9 per million, respectively,(46, 47, 51-53) though the incidence is increasing in among whites.(46)

Unlike most tumors investigated in our study, DFSP is typically seen in a younger demographic. It is most frequently diagnosed between the ages of 30 and 50.(36, 44, 48) The average age of diagnosis in our population was 37.7 years. The trunk is involved in 50% of published cases,(36) with the upper extremities being the next most common site (20–35%). In our population, the vast majority (80%) were located on the trunk.

Early studies demonstrated a recurrence rate of 10–60% with excision,(54-57) while more recent reports estimate a 4–7% recurrence.(48, 58) Surgical margins for DFSP have varied, but one study showed that 22% of tumors were removed with a 0.5 cm margin, 50% with a 1.0 cm margin, 67% with a 1.5 cm margin, and 89% with a 2.0 cm margin.(57) Today, MMS is often the preferred method for tumor clearance with an average recurrence rate around 0.6%.(57, 59-61) While 60% of patients with DFSP in our population underwent MMS, no recurrences or metastases were recorded at a median follow-up of 3.2 years.

Microcystic Adnexal Carcinoma

MAC is a neoplasm with pilar and eccrine differentiation first described by Goldstein et al in 1982.(62) MAC is locally aggressive and often extends beyond clinical margins, invading into nerves and muscle.(63-66) These tumors are typically asymptomatic, though they may present with numbness, tenderness, burning, anesthesia, or paresthesia.(64, 65, 67)

A 2008 literature review revealed just over 300 reported cases worldwide since 1982.(66) A SEER study from 1973 to 2004 found 223 cases,(68) an incidence of 6.5 per 10,000,000 for whites, 1.9 per 10,000,000 for blacks, and 1.6 per 10,000,000 for Asian/Pacific Islanders. Our population demonstrated an incidence of 0.7 (0.2 – 1.3) per 100,000 persons. Consistent with previous studies,(66) the rate of metastasis in the SEER study was very low (0.4%).(68) Similarly, we noted no metastases among those diagnosed with MAC in our population. An essentially equal gender distribution (51% male) was reported in a review of 105 cases in the English literature,(64) though the SEER study demonstrated a slight female predominance (57% female).(68) Our results, though limited, were more in line with the SEER study findings, with a 75% female predominance. A head and neck predilection of 74–88% has been reported,(66, 68) and 100% of our cases were on the head and neck.

While overall survival is excellent,(66, 68) significant morbidity may be associated with MAC due to its locally invasive nature. MMS has been demonstrated to offer a decreased likelihood of recurrence and metastasis, with tissue-sparing and fewer procedures for tumor clearance.(63, 64, 66, 69) In our cohort, 75% of MACs were treated with MMS without recurrence.

Eccrine Carcinoma and Eccrine Porocarcinoma

EC often designates a non-specific epithelial neoplasm with eccrine sweat gland differentiation or may include other eccrine tumors such as EPC, syringoid eccrine carcinoma, adenoid cystic, mucinous eccrine carcinoma, and clear cell eccrine carcinoma. (70) Accounting for the heterogenous appearance, nomenclature, and behavior of sweat gland carcinomas, EC represent an estimated 0.005% of all malignant epithelial neoplasms. (71, 72) A SEER study from 2001–2006 reported the overall US incidence of EC as 0.4 per million, with equivalent incidence among men and women. (73) A similar incidence of 0.4 per million was seen with EPC with men having a more frequent tumor burden of 0.5 compared to 0.2 per million in women. (73) Our study demonstrated an incidence of 0.4 (0 – 0.8) and 0.2 (0–0.4) per 100,000 for EC and EPC, respectively.

Both MMS and excisions with 2–3 cm margins have been utilized demonstrating a 20% recurrence and 20% metastatic rate to regional lymph nodes (LN) for EPC. (74–78) When LNs are involved, the rate of distant metastasis is estimated at 12% and the mortality rate of EPC has been reported as high as 67%. (72, 74, 79, 80) No cases of EPC recurrence with MMS have been reported, while 1 EPC metastasized to LN within 2 months of MMS. (74, 81, 82) In our study, MMS was performed in 2 EC and 1 EPC, and excision done in 2 EC and 1 EPC, respectively, with no recurrences or metastases.

Leiomyosarcoma

LMS is a rare smooth muscle tumor often presenting as a painful solitary nodule on the extensor surfaces of the extremities. (83–87) LMS is subdivided into dermal and subcutaneous forms. These classifications are often grouped, but evidence shows that these two subtypes behave very differently. (83, 86–88) Dermal LMS is thought to have a benign course with few studies showing metastatic potential. (89) Subcutaneous LMS invariably behaves more aggressively, with high recurrence, metastatic, and disease-specific mortality rates. (83, 87) In addition to subcutaneous classification, tumor size is independently associated with poor outcomes. (84, 86, 87, 90)

A study of 12,114 cutaneous soft tissue sarcomas (CSTS) in 13 SEER registries, (47) classified 270 LMS (2.2% of CSTS), occurring primarily among whites (91% of LMS). The overall incidence of LMS was 0.6 per million, with the incidence for men and women being 1.1 and 0.3 per million, respectively. Two incident cases of LMS were seen in our population with an age-adjusted incidence of 0.2 per 100,000. Reports have shown that cutaneous LMS tends to occur most commonly in male patients aged 50–80. (88, 90) The aforementioned SEER study showed a 3:1 male-to-female ratio. (47) Both LMS cases in our study were men aged 58 and 77 at the time of diagnosis.

Treatment of cutaneous LMS is typically surgical. Margin clearance status has been shown to be the most important predictor of recurrence. (83, 88) Wide local excision has demonstrated statistically lower rates of both recurrence and metastasis than surgery with narrow margins, (87) and no recurrences or metastases were seen among those treated with MMS. Our patients underwent local excision without recurrence or metastasis.

Conclusion—To our knowledge, this is the most inclusive report of population incidence of rare adnexal cutaneous malignancies and the first population-based report of the incidence of AFX, SC, MAC, EC, EPC, and LMS. The incidences of these tumors range from 0.2 per 100,000 for LMS and EPC to 1.8 per 100,000 for AFX. These data add to the understanding of the epidemiology of these rare tumors, the characteristics of the affected patients, and their outcomes by treatment modality. Additional studies in a larger population with a wider racial spectrum would contribute to better understanding of the true incidence and outcomes of these malignancies.

Acknowledgments

This study was made possible using the resources of the Rochester Epidemiology Project, which is supported by the National Institute on aging of the National Institutes of Health under Award Number R01 AG034676. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Abbreviations

NMSC	non-melanoma skin cancer
BCC	basal cell carcinoma
SCC	squamous cell carcinoma
AFX	atypical fibroxanthoma
MCC	Merkel cell carcinoma
SC	sebaceous carcinoma
DFSP	dermatofibrosarcoma protuberans
MAC	microcystic adnexal carcinoma
EC	eccrine carcinoma
EPC	eccrine porocarcinoma
LMS	leiomyosarcoma
SEER	Surveillance, Epidemiology, and End Results
REP	Rochester Epidemiology Project
OC	Olmsted county
MMS	Mohs micrographic surgery
PUVA	psoralen plus UVA
LMS	leiomyosarcoma
U.S.	United States

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Summary of characteristics of Olmsted County, Minnesota incident cases of rare NMSC diagnosed from January 2, 2000 through December 31, 2010

Table 1

	AFX (N=19)	SC (N=8)	DFSP (N=5)	MAC (N=8)	EC (N=4)	EPC (N=2)	LMS (N=2)
Male gender, n (%)	16 (84%)	5 (62%)	3 (60%)	2 (25%)	1 (25%)	1 (50%)	2 (100%)
Age at incident tumor (years)							
Mean (SD)	81.4 (11.7)	80.1 (10.7)	37.7 (5.4)	57.7 (15.6)	69.2 (19.2)	65.0 (22.8)	68.1 (13.1)
Range	45.6–107.8	57.2–90.2	31.1–45.6	38.4–90.4	45.6–86.0	48.9–81.1	58.9–77.4
Race							
Caucasian	19 (100%)	7 (88%)	4 (80%)	8 (100%)	3 (75%)	2 (100%)	2 (100%)
African American	0	1 (12%)	1 (20%)	0	1 (25%)	0	0
Smoking status at time of incident tumor, n (%)							
Never	8 (42%)	5 (62%)	4 (80%)	4 (50%)	2 (50%)	0	2 (100%)
Current	0	0	0	2 (25%)	1 (25%)	0	0
Former	11 (58%)	3 (38%)	1 (20%)	2 (25%)	1 (25%)	2 (100%)	0
Immunosuppression at time of incident tumor, n (%)	0	1 (13%) ^a	0	0	0	1 (50%) ^b	0
Treatment, n (%)							
Mohs Micrographic Surgery	15 (79%)	3 (38%)	3 (60%)	6 (75%)	2 (50%)	1 (50%)	0
Excision	2 (11%)	4 (50%)	0	1 (12%)	2 (50%)	1 (50%)	2 (100%)
Excision and radiation	0	0	1 (20%)	0	0	0	0
ED&C	1 (5%)	0	0	0	0	0	0
None	1 (5%)	1 (12%)	1 (20%)	1 (12%)	0	0	0
Outcomes							
Recurrence	1	2	0	0	0	0	0
Metastasis	0	0	0	0	0	0	0
Duration of relevant clinical follow-up (years): Median (range)	4.5 (<1–12.4)	2.0 (<1–5.4)	3.2 (<1–10.9)	6.7 (<1–14.5)	4.6 (3.3–6.8)	3.9 (3.8–3.9)	3.4 (1.6–5.1)

^a Prednisone and methotrexate for rheumatoid arthritis.^b Methotrexate, Prednisone, Hydroxychloroquine for inflammatory disease

Acronyms: SD, standard deviation; AFX, atypical fibroxanthoma; SC, sebaceous carcinoma; DFSP, dermatofibrosarcoma protuberans; MAC, microcystic adnexal carcinoma; EC, eccrine carcinoma; EPC, eccrine porocarcinoma; LMS, Leiomyosarcoma; ED&C, electrodissection & curettage; IQR, interquartile range

Table 2

Incidence of specific rare NMSC per 100,000 persons (95% CI) in Olmsted County, Minnesota, January 2, 2000 through December 31, 2010

	AFX	SC	DFSP	MAC	EC	EPC	LMS
Females, age-adjusted ^a	0.4 (0 – 0.8)	0.4 (0 – 0.9)	0.3 (0 – 0.8)	1.0 (0.2 – 1.9)	0.5 (0 – 1.1)	0.2 (0–0.4)	0
Males, age-adjusted ^a	4.0 (2.0 –5.9)	1.2 (0.1 – 2.2)	0.5 (0 – 1.0)	0.4 (0 – 1.0)	0.3 (0 – 0.8)	0.2 (0–0.5)	0.4 (0–1.0)
Overall, age- and sex-adjusted ^a	1.8 (1.0 – 2.6)	0.8 (0.2 – 1.3)	0.4 (0.05– 0.7)	0.7 (0.2 – 1.3)	0.4 (0 – 0.8)	0.2 (0–0.4)	0.2 (0 – 0.5)

^a Adjusted to the population structure of the total US population in 2010

Acronyms: CI, confidence interval; AFX, atypical fibroxanthoma; SC, sebaceous carcinoma; DFSP, dermatofibrosarcoma protuberans; MAC, microcystic adnexal carcinoma; EC, eccrine carcinoma; EPC, eccrine porocarcinoma; LMS, Leiomyosarcoma.

Table 3

Other NMSC in Olmsted County, Minnesota, January 2, 2000 through December 31, 2010

Tumor*	Number	Age	Gender (Male/Female)	Site(s)
Angiosarcoma	1	65.5	0/1	Chest
Extramammary Paget Disease	1	58.4	1/0	Scrotum
Hidradenocarcinoma	1	78.4	1/0	Lower leg
Kaposi's sarcoma	1	46.0	1/0	Thigh

^aBasal cell carcinomas and squamous cell carcinomas excluded