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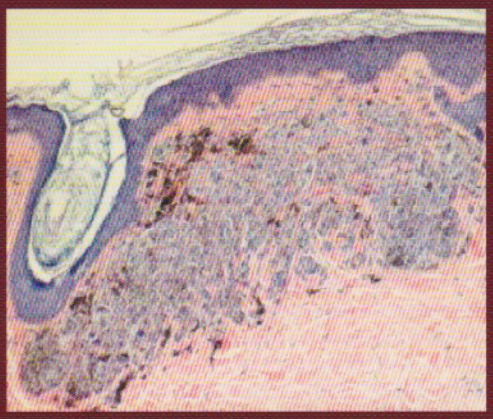

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Demographic and Tumor Characteristics of NMSC

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ANTI-AGING · AESTHETIC · MEDICAL DERMATOLOGY

Demographic and Tumor Characteristics of Patients Younger Than 50 Years With Nonmelanoma Skin Cancer Referred for Mohs Micrographic Surgery

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ABSTRACT

Background: An increase in nonmelanoma skin cancer (NMSC) in younger patients has been reported. Many are treated with Mohs micrographic surgery (MMS).

Objective: Investigate patient and tumor characteristics in patients <50 years undergoing MMS for NMSC at a large, referral-based practice.

Methods & Materials: Retrospective chart review of 1,332 tumors occurring in 1,018 consecutive patients over a five-year period.

Results: 81.7% of tumors were BCC and 55.3% occurred in women. Patients <30 years were more likely to be female (P=0.016) and women were more likely to have BCC (P=0.010). SCCs were more likely with increasing age (P<0.001). Of all tumors, 3.6% were recurrent, 2.7% had diameters ≥ 2 centimeters, and 5.5% of all BCCs had a high-risk histologic subtype. Women were more than twice as likely as men to be referred to plastic surgery for repair (P=0.020).

Conclusion: Patients <50 years with NMSC may represent a growing population referred for MMS, especially young women with BCC. High-risk tumor features were rare among young patients, and female gender was associated with an increased rate of referral for repair by a plastics subspecialty.

Study was performed at the Laser & Skin Surgery Center of New York.

IRB status: Approved by Essex Institutional Review Board, Protocol #MOHS40-65

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INTRODUCTION

Nonmelanoma skin cancer (NMSC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is the most common malignancy in Caucasian populations worldwide. However, because NMSC are typically not reported to national and state registries, the exact incidence rates are unknown and are likely underestimated. In the United States, it is estimated that over 5.4 million cases of NMSC are treated in more than 3.3 million people annually and that the incidence is increasing each year.[1] A significant increase in NMSC diagnosed in patients younger than 40 years, particularly in women diagnosed with BCC, has been reported.[2-4] Yet, little is known about this patient population beyond age and gender. Additionally, as many of these patients are being treated with Mohs micrographic surgery (MMS), the surgical implications of both patient and tumor characteristics in this patient population become of greater clinical interest. The purpose of this study was to further investigate patient demographics and tumor characteristics in patients younger than 50 years undergoing MMS for NMSC at a large, referral-based practice. Differences in tumor characteristics based on gender, age range, smoking status, immunosuppression, and hormonal influence in this patient population were also considered. In particular, this study aimed to elucidate patient characteristics that may predispose to high-risk tumor characteristics or more extensive surgical intervention.

METHODS

After institutional review board approval, a retrospective chart review was performed on consecutive patients younger than 50 years treated with MMS for BCC or SCC from January 2009 to December 2013. This population was treated at the Laser & Skin Surgery Center of New York, a referral-based, private practice, outpatient surgical center, where nearly 3,000 MMS are performed annually. Given the relative infrequency of NMSCs such as dermatofibrosarcoma protuberans (DFSP), merkel cell carcinoma, and atypical fibroxanthoma, patients undergoing MMS for treatment of these tumors were excluded. Data were collected on patient age, gender, Fitzpatrick skin type (FST), personal and family history of NMSC or malignant melanoma, and smoking, immunosuppression, and hormonal status at the time of initial presentation for MMS within the study period. Family history was considered positive if the patient reported a parent with NMSC or MM. Patients were considered immunosuppressed if they

reported taking immunosuppressive medications including corticosteroids, biologics, tacrolimus, azathioprine/6-mercaptopurine or cyclosporine, or an immunosuppressive condition including human immunodeficiency virus or an active hematologic malignancy. Patients with conditions that inherently predispose to cutaneous malignancies, such as xeroderma pigmentosum (XP) and Gorlin's syndrome, were also included in this group. Hormonal influence was considered positive if the patient reported active pregnancy, or taking oral contraceptives or other hormonal medications including tamoxifen and anastrozole.

Tumor diagnosis, high-risk histologic features, recurrence status, anatomic location, tumor diameter, number of MMS stages, post-operative defect diameter, and repair technique were recorded. Tumors occurring in patients with an unusually high number of NMSC, defined as 10 or more within the study period, were eliminated from the tumor characteristic data. Keratoacanthomas were categorized as SCC. A BCC was considered to have high-risk histologic features if one of the following sub-types was reported: morpheaform, sclerosing, infiltrative, micronodular, or basosquamous.[5] The high-risk histologic features considered for SCC included poorly differentiated histology, perineural invasion, or tumor invasion beyond subcutaneous fat.[6] Extensive MMS was defined as tumors requiring 5 or more stages for clearance.

Chi-squared tests and t-tests were used to compare categorical and continuous variables, respectively. Multivariate regression model included gender, age range, and tumor diagnosis. The variables chosen to include in the multivariate analysis were selected based on those that were significant in the univariate analyses. Analysis was conducted in Stata 11.0 for Mac (StataCorp, College Station, TX).

RESULTS

During the five-year study period, 1,018 patients younger than 50 years with BCC or SCC were treated with MMS by eight different Mohs micrographic surgeons within the practice. Five patients younger than 50 years underwent MMS for treatment of DFSP during the study period, constituting less than 0.5% of all treated tumors, and were excluded from data analyses. Patient demographics upon first presentation for MMS are summarized in Table 1. Smoking status was available for 400 of the patients. A total number of 1,332 NMSCs occurring in 1,014 patients were included in the tumor data (Table 2). Of these tumors, 81.7% were histologically confirmed BCC and 18.3% were SCC. Only 5.5% of BCCs had high-risk histologic subtypes. High-risk histologic features recognized for SCC were not observed in our tumor population.

Gender

Of the 1,332 MMSs performed in patients younger than 50 years, 55.3% were performed on women. BCC was the most common tumor in both genders, representing 81.7% of all treated tumors. When compared to men, women were more likely to have BCC (Table 3). After controlling for age range, women had a 1.4 higher odds ratio of developing BCC than men (P=0.024). There was no significant difference between genders in terms

TABLE 1.

Demographic Characteristics of Patients Younger Than 50 Years With NMSC Referred for MMS, Laser and Skin Surgery Center, 2009-2013[a]

Characteristic	Finding (N=1,018)[b]
Age, y	
Mean (SD)	42 (6)
Median (range)	43 (20-49)
Age group, y	
<30	51 (5)
30-39	262 (25.7)
40-49	705 (69.3)
Sex	
Female	566 (55.6)
Male	452 (44.4)
FST	
1	448 (44)
2	498 (48.9)
3	64 (6.3)
4	2 (0.2)
5	2 (0.2)
Personal history of SCC	
No	957 (94)
Yes	61 (6)
Personal history of BCC	
No	805 (79.1)
Yes	213 (20.9)
Personal history of melanoma	
No	976 (95.9)
Yes	42 (4.1)
Family history of NMSC[c]	
No	601 (59)
Yes	417 (41)
Family history of melanoma[c]	
No	900 (88.4)
Yes	118 (11.6)
Smoking (N= 400)	
No	368 (92)
Yes	32 (8)
Immunosuppression[d]	
No	976 (95.9)
Yes	42 (4.1)

TABLE 3.

Tumor Diagnosis and Age Range by Gender		
	Female, n (%)	Male, n (%)
Tumor Diagnosis*		
BCC	620 (84.12)	468 (78.66)
SCC	117 (15.88)	127 (21.34)
Age Range (yrs)**		
<30	37 (6.54)	14 (3.1)
30-39	153 (27.03)	109 (24.12)
40-49	376 (66.43)	329 (72.79)

*P=0.010
**P=0.016

defect diameters did not statistically differ based on smoking status.

Immunosuppression

Patients with immunosuppression were more likely to have SCC (28.57% vs 17.81%, P=0.031). Among the tumors, 7.38% of SCCs and 5.96% of BCCs occurred in immunocompromised patients (P=0.031). Mean tumor diameter was larger in immunosuppressed patients (8.1 vs 6.9 mm, P=0.041). There was no difference in mean defect diameter based on immunosuppression status.

Hormonal Influence

Women with hormonal influences were more likely to have BCC than women without hormonal influence (91.89% vs 82.75%, P=0.015). However, when this was adjusted for age, there was no statistically significant difference in tumor type based on hormonal status (P=0.059).

High-Risk Tumor Features and Surgical Implications

Tumor characteristics of particular interest given their clinical relevance included recurrent tumors, tumors ≥ 2 centimeters in diameter, BCCs with a high-risk histologic subtype and tumors requiring extensive MMS (defined as 5 or more stages). Patient gender, age range and smoking, immunosuppression, and hormone status did not correlate with an increased risk of these tumor characteristics.

However, patient gender did correlate with repair technique (Table 4). Women were more than twice as likely as men to be referred to plastic surgery for repair and comprised 75% of all referrals, despite a smaller mean defect diameter. Defects referred to plastic surgery were more likely to be on the head and neck (97.59% vs 67.33%, P<0.001), however, referrals accounted for less than 9% of defects occurring in this area. Defect diameter was not predictive of referral to plastic surgery. Men were more than twice as likely to have repair with xenografting, constituting 64% of all xenografts.

Patients Undergoing Multiple MMS

Patients who underwent 10 or more MMS during the study period were significantly more likely to be immunosuppressed (75% of those with 10 or more MMS vs 5.35% with 2 to 9 MMS vs 3.51% with a single MMS, P<0.001). There was no significant difference in gender, age range, smoking, or hormonal status in those patients with multiple MMS treated during the study period. Young patients who had multiple (2 to 9) MMS during

FIGURE 1. Percentage of BCC and SCC by age range.
BCC = basal cell carcinoma, SCC = squamous cell carcinoma

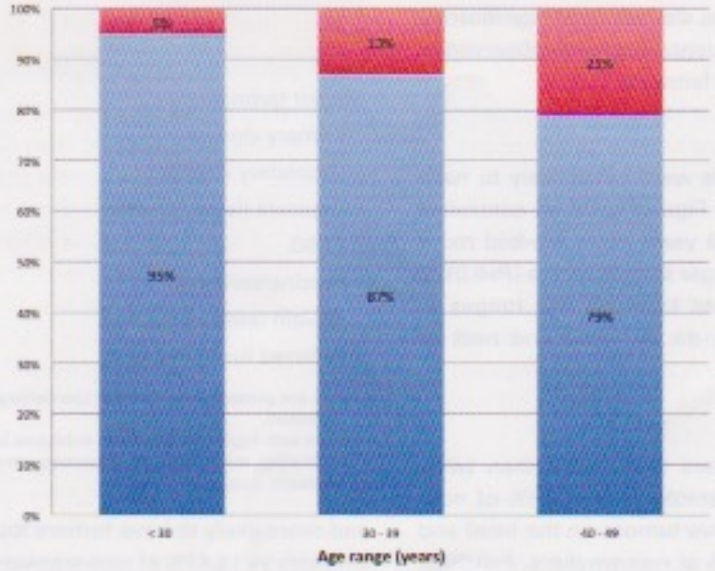

TABLE 1. *Continued*

Demographic Characteristics of Patients Younger Than 50 Years With NMSC Referred for MMS, Laser and Skin Surgery Center, 2009-2013[a]

Characteristic	Finding (N=1,018)[b]
Hormonal influence[e]	
No	922 (90.6)
Yes	96 (9.4)
Total MMS during study period	
1	827 (81.2)
2-9	187 (18.4)
≥10	4 (0.4)

[a]Reflects characteristics at initial presentation for MMS during the study period
[b]Data are presented as number (percentage) of patients unless otherwise indicated
[c]Family history defined as mother or father
[d]Immunosuppression considered positive in patients taking immunosuppressive medications or with an immunosuppressive condition, including conditions that inherently predispose to cutaneous malignancies
[e]Hormonal influence was considered positive in patients who were pregnant or taking hormonal medications.

of tumor location or laterality on the head and neck. Women had smaller mean tumor and defect diameters than men (6.3 vs 7.7 mm, $P<0.001$ and 12.9 vs 14.9 mm, $P<0.001$, respectively).

Patients younger than 30 years at the time of initial MMS were more than twice as likely to be female, while patients aged 40 to 49 years were more likely to be male (Table 3). At the time of tumor removal, women were slightly younger when compared with men (41.3 +/- 6.2 years vs 42.2 +/- 5.8 years, $P=0.007$). There was no difference in personal history of NMSC or MM between genders, however females were more likely to have a family history of NMSC (45.41% of women vs 35.40% of men, $P=0.001$) and MM (15.19% of women vs 7.08% of men, $P<0.001$). Smoking and immunosuppression status did not vary significantly between genders. A hormonal influence was only observed in women and represented 16.96% of females.

Age

When stratified by decade, patients were more likely to have SCC with increasing age ($P<0.001$; Figure 1). When controlled for gender, patients aged 40 to 49 years were 4.5-fold more likely to have SCC than those younger than 30 years ($P=0.012$). There was no significant difference between age ranges in terms of tumor location, laterality on the head and neck or mean tumor and defect diameters.

Smoking

Compared to non-smokers, smokers were more than twice as likely to have SCC (37.25% of smokers vs 16.25% of non-smokers, $P<0.001$), less likely to have tumors on the head and neck (50.98% of smokers vs 66.33% of non-smokers, $P=0.005$), and more likely to have tumors located on the trunk (35.29% of smokers vs 18.41% of non-smokers, $P=0.005$). Mean tumor and

TABLE 2.

Tumor Characteristics of NMSC Treated With MMS in Patients Younger Than 50 Years, Laser and Skin Surgery Center, 2009-2013

Characteristic	Finding (N=1,332)[a]
Tumor type	
BCC	1088 (81.7)
HR histology[b]	60 (5.5)
SCC	244 (18.3)
Recurrent	
No	1,284 (96.4)
Yes	48 (3.6)
Location	
Head and neck	922 (69.2)
R	391 (42.4)
L	389 (42.2)
M	142 (15.4)
Trunk	229 (17.2)
Upper extremity	119 (8.9)
Lower extremity	62 (4.7)
Pre-op tumor diameter, cm	
Mean (SD)	0.7 (0.5)
Median (range)	0.6 (0.1 – 5.0)
≥ 2 cm	36 (2.7)
Post-op defect diameter, cm	
Mean (SD)	1.4 (0.7)
Median (range)	1.3 (0.2 – 8.0)
Stages	
1	524 (39.3)
2	538 (40.4)
3	199 (14.9)
4	54 (4.1)
≥ 5	17 (1.3)
Repair technique	
Primary closure	905 (67.9)
Secondary intention	225 (16.9)
Adjacent tissue transfer	66 (5)
FTSG	33 (2.5)
Porcine/xenograft	11 (0.8)
Erbium laser	9 (0.7)
Referred for PS repair	83 (6.2)

[a]Data are presented as number (percentage) of patients unless otherwise indicated.
[b]BCCs with high-risk histologic subtypes included morpheaform, sclerosing, infiltrative, micronodular, or basosquamous.
PS=plastic surgery

TABLE 4.

Repair Technique by Gender		
Repair technique	**Female, n (%)**	**Male, n (%)**
Primary closure	490 (66.49)	415 (69.75)
Secondary intention	122 (16.55)	103 (17.31)
Adjacent tissue transfer	37 (5.02)	29 (4.87)
FTSG	17 (2.31)	16 (2.69)
Porcine/xenograft	4 (0.54)	7 (1.18)
Erbium laser	5 (0.68)	4 (0.67)
Referred for PS repair	62 (8.41)	21 (3.53)
Total	737	595

*P=0.020
PS=Plastic surgery

our study period, were more likely to have had personal history of NMSC (14.97% vs 3.87% with a history of SCC, P<0.001; 71% vs 16.81% with a history of BCC, P<0.001) and family history of NMSC (50.8% vs 38.69%, P< 0.009) at time of initial presentation than those who only had one MMS during the study period.

DISCUSSION

Patient Demographics and Tumor Characteristics

Most patients younger than 50 years undergoing MMS for BCC or SCC during our 5-year study period were women (55.3%), and women were slightly younger at the time of tumor removal when compared with men. Within our cohort, we appreciated a reversal of gender predominance with increase in age, with patients under 30 being twice as likely to be female. These findings are consistent with those of Evans et al who found women comprised a statistically significant majority of patients with BCC in younger age groups (10 to 49 years) compared to those aged 50 to 99 years, as well as a statistically significant increase in the female representation between the two groups with respect to SCC.[7]

BCCs were the most common tumor in both men and women younger than 50 years. However, women had a higher proportion of BCCs and a 1.4 higher odds ratio of developing BCC compared to men. Additionally, patients younger than 30 years had a higher proportion of BCCs compared with those patients aged 40 to 49 years. Although our study was unable to report on the incidence or prevalence of NMSC, both the higher representation of women and BCCs occurring in women within this young cohort are consistent with previous studies showing an increase in NMSC diagnosed in patients younger than 40 years, particularly in women diagnosed with BCC.[2-4]

The role of factors such as ultraviolet (UV) exposure or hormonal influence in the development of NMSC in younger women is incompletely understood. Although our study did not include data on UV exposure, it is recognized that female gender is associated with more frequent sunbathing and tanning bed use.[8] Indoor tanning has been reported as a strong risk factor for early-onset BCC in patients younger than 40, especially among females.[9] Additionally, women younger than 40 years with BCC have been found to be more likely to have a past or current history of cigarette smoking and blistering sunburns compared to age-matched controls.[10] Smoking among our patients demonstrated an increased likelihood of developing SCC rather than BCC. In our study, differences in tumor type between women with hormonal influences, including oral contraceptive pills or active pregnancy, and women without hormonal influences, was not statistically significant after adjusting for age. Therefore, just as data showing an increased incidence of melanoma in young woman over recent decades has suggested,[11] increases in NMSC in young woman may represent behavioral changes related to UV exposure rather than hormonal factors, which are expected to be more constant over time.

Although our cohort did not demonstrate gender differences in tumor location, other studies have shown the lower legs to be a common location for SCC in women and attribute this, in part, to gender-specific differences in clothing coverage and, therefore, UV exposure.[12-14] Additionally, increased awareness of skin cancer among the general population[15] along with better adherence to self-skin examinations by women[16] may contribute to earlier detection among females. These factors may contribute, at least in part, to the smaller mean tumor diameter observed in woman in our study.

Our study showed a higher prevalence of SCC in men younger than 50 years, with a 1.4 higher odds ratio of developing SCC compared to women. This male predominance is consistent with studies comparing gender differences in patients of all ages with NMSC.[7,13,17-19] Previous theories have attributed this gender discrepancy to increased risk factors for SCC in men including smoking and cumulative lifetime UV exposure.[13] In our patients younger than 50 years, smoking status did not differ significantly between genders but smokers were more than twice as likely to have SCC than non-smokers. Unlike previous studies[13,20] that found the scalp and ears to be more commonly affected in men relative to women across all ages, our cohort did not demonstrate gender differences in tumor location. Interestingly, smokers were less likely to develop tumors on the head and neck, suggesting the higher prevalence of this distribution seen in men of older age may be largely attributed to the effects of cumulative lifetime UV exposure not yet to fully manifested in our younger population.

Regardless of gender, patients aged 40 to 49 years were 4.5-fold more likely to have SCC than those younger than 30 years, which supports an early effect of cumulative UV exposure in SCC development in patients younger than 50 years. Other

known risk factors for SCC include organ transplantation and fair skin type.[21-23] We found an increased proportion of SCC in our immunocompromised patients, which included transplant patients and those on immunosuppressive therapy. Yet, there were no significant gender differences in immunosuppression or Fitzpatrick skin type in our cohort of younger patients. Therefore, it is unlikely that these factors alone could account for the significantly higher proportion of men younger than 50 years presenting with SCC.

High-Risk Tumor Features and Surgical Implications

Recurrence, high-risk histologic subtypes and large tumor diameter (≥ 2 cm) are well recognized as high-risk tumor features in NMSC that are predictive of a more aggressive tumor biology.[5] Whether NMSC, particularly BCC, occurring in younger patients represents a more aggressive tumor has been previously debated and remains controversial. Some studies have reported an increased frequency of BCCs with aggressive histologic subtypes and recurrent BCCs in younger patients[24,25] while others have disputed this.[26-28] Of all NMSCs treated with MMS in our cohort of younger patients, only 3.6% were recurrent and 2.7% had large diameters. Only 5.5% of all BCCs were reported to have a high-risk histologic subtype while no SCCs were reported to have high-risk histologic features. The host factors examined were not associated with an increased risk of these high-risk tumor characteristics, nor with MMS requiring 5 or more stages, however the relatively small percentage of NMSC with these aggressive features in our cohort may have prevented differences from meeting statistical significance.

Gender differences were observed with respect to repair technique, with women being more than twice as likely as men to be referred for reconstruction by a plastics subspecialty, despite having a smaller mean defect diameter. This is consistent with findings by Lee et al among women of all ages undergoing MMS.[13] Interestingly, defect location on the head and neck correlated with referral to plastic surgery, accounting for 98% of referred defects, however defect diameter did not, suggesting a greater concern for aesthetic outcomes on the face in young females and successful branding of plastic surgery.

Strengths and Limitations

The strengths of this study include a large cohort size allowing for detection of small differences in the variables examined. This was a retrospective chart review conducted at a single, referral-based practice based in New York City, limiting the generalizability of our findings and our ability to estimate tumor prevalence or incidence within our young cohort of patients. However, our data are supported by other studies, including population-based ones, which lessens this concern. Furthermore, this was a descriptive study comparing differences in patient and tumor characteristics based on gender, age range, and smoking, immunosuppression, and hormone status and would be strengthened by an age-matched control group or an older comparison group to further elucidate the risk factors for NMSC in this younger population.

CONCLUSION

Patients younger than 50 years with NMSC may represent a growing population being referred for treatment with MMS. The association of both female gender and younger age with increased likelihood of BCC observed in our study supports recent population-based studies showing an increase in incidence of BCC among young females. Contributory factors for NMSC in this population, such as smoking and hormonal influence, remain unclear. High-risk tumor features were rare among younger patients referred for MMS. Female gender was associated with an increased rate of referral for repair by a plastics subspecialty.

DISCLOSURES

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