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Gender differences in melanoma prognostic factors

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Abstract

Background: Although previous studies identify gender differences in melanoma, limited research on the phenomenon exists.

Methods: In this retrospective chart review, 1,156 adults diagnosed with melanoma, between 2006-2016, at the University of Colorado were included. Breslow depth, mitotic rate, ulceration status, and location were extracted from charts between March and August 2016. Cochran-Armitage trend tests and cumulative logistic regression were used to examine the association between gender and Breslow depth, univariately and after adjusting for potential confounders.

Results: In univariate analysis, males were significantly more likely to present with lesions with higher Breslow depths (p for trend=0.005). In models adjusted for age, melanoma subtype, and location, males were marginally more likely to present with lesions with higher Breslow depths (cumulative OR: 1.261, 95% CI: 0.988-1.611, p=0.060). Males were also marginally more likely to present with lesions with higher mitotic rates, after further adjustments for all other prognostic factors (cumulative OR: 1.244, 95% CI: 0.979-1.580, p=0.074).

Limitations: This was a retrospective single-institution study.

Conclusion Differences in mitotic rates among melanomas in males versus females, even after adjustments for all other prognostic factors, suggests that biological differences may contribute to the female prognosis advantage.

Keywords: malignant melanoma, gender, mitotic rate, Breslow depth, metastasis, ulceration, prognosis

Introduction

Over the last decade, the incidence of melanoma has steadily risen in the United States [1, 2]. Advancement in disease stage and older age at diagnosis contribute to decreased survival [3]. Previous studies have reported poor prognosis with several associated factors including melanoma subtype, anatomic location of primary lesion, presence of ulceration, and Breslow depth [4-7].

Gender differences in melanoma incidence and prognosis have been explored in recent years. One study reported significantly higher death rates in white adolescent males than in females [8]. Other studies have further supported an average delay in diagnosis of melanoma in males [9-11]. Najita et al. revealed that men with T1 melanoma presented up to one decade later than females [12]. Although past studies have revealed such differences, limited and inconclusive research on this topic exists. This study aims to identify gender differences in melanoma prognostic factors and secondarily investigates differences in behavior and biology as contributors to disease progression.

Methods

Data Collection

In this retrospective chart review, data from patient electronic medical records (EMRs) were extracted

from the University of Colorado Hospital. Medical Record Numbers of patients were obtained from: 1) "Dermatology Flow Sheets" from the Outpatient Dermatology Clinic EMRs (completed for all patients with an initial diagnosis or personal history of melanoma) and 2) the Melanoma Data Bank of the Cutaneous Oncology clinic (consisting of all melanoma patients seen in the clinic).

Adults (18 years or older) initially diagnosed with melanoma between January 2006 and March 2016 were included (n=1,463). Patients with melanomas in situ (n=164), ocular melanoma (n=40), or metastatic disease without identifiable primary lesions (n=103), were excluded. A total of 1,156 patients were thus retained in the analysis data set.

Demographic data included sex, age at diagnosis, relationship status, and up to second-degree relative family history of melanoma. Pathology report data included: Breslow depth with T categories defined per the 7th edition AJCC Melanoma Staging (T1: ≤1.00mm, T2: 1.01-2.00mm, T3: 2.01-4.00mm, T4: >4.00mm) [5], presence of metastases to at least one lymph node, melanoma subtype, anatomic location, anatomic body site, ulceration, and mitotic rate.

Statistical Analysis

Descriptive statistics such as the mean (standard deviation) and frequencies (%) were generated to describe patient characteristics and melanoma prognostic factors stratified by gender. The overall association between gender and each characteristic was evaluated via standard chi-square or Cochran-Armitage trend test. A multivariable model for Breslow depth category, adjusting for gender and a set of *a priori* predictors (age and primary melanoma subtype, location, and side) was assessed via cumulative logistic regression. The exponentiated gender effect from the cumulative logistic regression model for Breslow depth estimates the impact of being male with respect to the cumulative odds of having a higher Breslow depth category, adjusted for potential confounders. The assumption of proportional odds, meaning that the parameters are the same for all logits in the cumulative logit model, was examined via Score test [13]. Similarly, a cumulative logistic regression model for mitotic rate was examined, adjusting for the above *a priori* confounders along with other measures of tumor progression. Finally, a logistic regression model was estimated for the probability of presenting with metastatic disease using the same set of *a priori* predictors as the previous models. All analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC).

Results

A total of 1,156 melanoma patients, including 651 (56%) males and 505 (44%) females, were included. A significantly higher percentage of males were in the older age groups (60-69 years and 70-84 years), when compared to the percentage of females (28% vs. 19% and 21% vs. 14%, p=0.001). A significantly higher

Table 1. *Patient characteristics. N (%).*

		Male (n=651)	Female (n=505)	p-value
Age (years)		**Mean (SD)=58.4 (15.2)**	**Mean (SD): 53.4 (16.7)**	**<0.001[a]**
	18-29	20 (3)	36 (7)	<0.001[b]
	30-39	60 (9)	82 (16)	
	40-49	90 (14)	81 (16)	
	50-59	144 (22)	124 (25)	
	60-69	183 (28)	96 (19.)	
	70-84	134 (21)	70 (14)	
	85+	20 (3)	16 (3)	
Family History	No	113 (17)	93 (18)	0.640[c]
	Yes	538 (82)	412 (82)	
Relationship Status	Divorced	10 (2)	18 (4)	0.001[c]
	Married/Significant other	452 (73)	298 (62)	
	Single	152 (24)	154 (32)	
	Widowed	8 (1)	10 (2)	

Notes: [a]Wilcoxon Mann-Whitney test; [b]Cochran-Armitage test for trend; [c]Chi-square test for association.

percentage of females reported being single (32% vs. 24%) and a higher percentage of males reported being married or having a significant other (73% vs. 62%, p=0.001). No significant differences in family history of malignant melanoma existed between males and females (**Table 1**).

In the overall sample, males had a larger proportion of tumors with Breslow depths greater than 4.00 mm (16% vs. 11%), whereas females had a larger proportion of tumors with Breslow depths less than 1.00 mm (39% vs. 33%, p=0.005). A larger percentage of males also presented with initial lesions 1) on the head/neck (32% vs. 17%) and posterior trunk (23% vs. 15%, p<0.001), 2) with ulceration (28% vs. 22%, p=0.020), and 3) mitotic rates greater than 4.99 mm2 (p=0.001). A larger percentage of males also presented with metastatic disease (32% vs. 21%, p<0.001). Females, however, had a larger percentage presenting with lesions that were of the superficial spreading type (42% vs. 34%, p=0.010) and located on the lower extremities (35% vs. 16%, p<0.001), (**Table 2**).

A cumulative logistic regression model for Breslow depth revealed that males were more likely to present with lesions with higher Breslow depths after adjustments for age, melanoma subtype, and location (cumulative odd's ratio (OR): 1.261, 95% confidence interval (CI): 0.988-1.611, p=0.060, **Figure 3**). Breslow depth category and metastatic disease were strongly associated such that 69% of patients with depth <4.0 mm presented with metastatic disease, whereas less than 3% of patients with depth <1.0mm presented with metastatic disease (p< 0.001). Consistent with this, in adjusted logistic regression models for metastasis, males were also more likely to present with metastatic disease (OR=1.552, 95% CI: 1.145-2.104, p=0.005), along with patients presenting with nodular subtypes (OR=7.323, p < 0.001) and those with increasing age (OR=1.021, p < 0.001). The location of the melanoma

Table 2. *Univariate analyses of melanoma prognostic factors.*

		Male (n=651)	Female (n=505)	p-value
Breslow Depth (mm^2)	< 1.00 mm	218 (34)	199 (39)	0.005[b]
	1.01-4.00 mm	330 (51)	252 (50)	
	> 4.00 mm	103 (16)	54 (11)	
Metastatic Disease	No	445 (68)	399 (79)	<0.001
	Yes	206 (32)	106 (21)	
Melanoma Type±	Acral lentiginous	18 (2.8)	20 (4)	0.010
	Superficial spreading	219 (34)	213 (42)	
	Lentigo maligna melanoma	35 (5)	14 (3)	
	Nodular	111 (17)	84 (17)	
	Other	42 (7)	30 (6)	
Anatomic Location	Neither	91 (14)	65 (13)	0.810
	Left	314 (48)	242 (48)	
	Right	246 (38)	198 (39)	
Anatomic Body Site	Head/neck	209 (32)	88 (17)	<0.001
	Upper extremity	129 (20)	115 (23)	
	Anterior trunk	64 (10)	53 (11)	
	Posterior trunk	148 (23)	73 (15)	
	Lower extremity	101 (16)	176 (35)	
Mitotic Rate (mm^2)±	0-0.99	112 (17)	114 (23)	0.001[b]
	0.99-1.99	142 (22)	110 (22)	
	2.00-4.99	139 (21)	131 (26)	
	5.00-9.99	86 (13)	49 (10)	
	10.00-19.99	68 (11)	28 (6)	
	≥20.00	23 (4)	13 (3)	
Ulceration±	No	416 (64)	353 (70)	0.020
	Yes	181 (28)	110 (22)	

Notes: *Based on a Chi-square test for association with gender except where noted. Excludes missing category. ±Data on melanoma type, mitotic rate, and ulcerated was unreported in 141,444, and 96 cases, respectively; bCochran-Armitage test for trend.

Table 3. *Cumulative logistic regression model for increasing Breslow depth.*

Model Parameter	95% Confidence Limits			
	Odds Ratio	**Lower**	**Upper**	**p-value**
Male gender *(Ref: female)*	1.261	0.988	1.611	0.060
Age (continuous)	1.009	1.001	1.017	0.020
MELANOMA TYPE: Acral lentiginous	2.073	1.058	4.062	0.030
Lentigo maligna melanoma	0.304	0.151	0.612	0.001
Nodular	8.753	6.058	12.647	<0.001
Other	7.519	4.465	12.662	<0.001
Unspecified *(Ref: superficial spreading melanoma)*	2.901	2.185	3.853	<0.001
LOCATION: Head/neck	1.420	0.997	2.021	0.050
Anterior trunk	1.379	0.879	2.162	0.160
Posterior trunk	1.587	1.075	2.343	0.020
Lower extremity *(Ref: upper extremity)*	1.303	0.910	1.865	0.150
SIDE: neither	1.290	0.871	1.912	0.220
Left *(Ref: right side)*	1.047	0.815	1.346	0.540

was not observed to be associated with metastatic disease (**Figure 4**).

The strongest predictors of mitotic rate were Breslow depth, ulceration, and presentation with metastatic disease (p=0.002, p=0.090, and p<0.001, respectively). Gender differences in mitotic rates after adjustments for Breslow depths, ulceration, and metastatic disease in addition to age, location, and subtype were further conducted. Cumulative logistic regression revealed that males were more likely to present with lesions with higher mitotic rates, albeit with marginal significance (cumulative OR: 1.244, 95% CI: 0.979-1.580, p=0.074, **Figure 5**).

Table 4. *Logistic regression model for probability of presenting with metastatic disease.*

Model Parameter	95% Confidence Limits			
	Odds Ratio	**Lower**	**Upper**	**p-value**
Male gender *(Ref: female)*	1.552	1.145	2.104	0.005
Age (continuous)	1.021	1.011	1.030	<0.001
MELANOMA TYPE: Acral lentiginous	1.492	0.600	3.709	0.390
Lentigo maligna melanoma	0.840	0.365	1.931	0.680
Nodular	7.323	4.870	11.013	<0.001
Other	3.134	1.755	5.598	<0.001
Unspecified *(Ref: superficial spreading melanoma)*	2.255	1.562	3.255	<0.001
LOCATION: Head/neck	0.994	0.652	1.514	0.978
Anterior trunk	0.916	0.526	1.594	0.760
Posterior trunk	1.051	0.659	1.676	0.830
Lower extremity *(Ref: Upper extremity)*	0.826	0.521	1.309	0.420
SIDE: neither	1.569	0.991	2.484	0.080
Left *(Ref: right side)*	1.167	0.853	1.597	0.650

Table 5. *Cumulative logistic regression model for mitotic rate.*

Model Parameter	95% Confidence Limits			
	Odds Ratio	Lower	Upper	p-value
Male gender *(Ref: female)*	1.244	0.979	1.580	0.074
Age (continuous)	1.000	0.993	1.008	0.906
MELANOMA TYPE: Acral lentiginous	1.188	0.610	2.313	0.366
Lentigo maligna melanoma	0.600	0.322	1.120	0.111
Nodular	1.644	1.151	2.349	<0.001
Other *(Ref: superficial spreading melanoma)*	0.512	0.303	0.864	0.008
LOCATION: Head/neck	1.106	0.792	1.546	0.224
Anterior trunk	1.083	0.709	1.654	0.454
Posterior trunk	0.901	0.629	1.292	0.560
Lower extremity *(Ref: Upper extremity)*	0.786	0.554	1.115	0.082
BRESLOW DEPTH: 1.01-4.00mm	4.845	3.608	6.505	0.002
> 4.00 mm *(ref < 1.00mm)*	10.607	6.635	16.956	<0.001
Metastatic Disease	1.941	1.540	2.446	<0.001
Ulceration	1.293	0.959	1.745	.093

Discussion

This study identified important gender differences in melanoma prognosis. Previous studies have revealed that males are more likely to present with thicker and ulcerated tumors located on the head and trunk [1]. A recent study further reported differences in age of primary diagnosis of melanoma for T1, T2, and T3 tumors, with males presenting four to eight years later than females [12]. Our study confirms gender differences in Breslow depth, even after adjustments for anatomic location and age. Although the gender effect was observed to be only marginally statistically significant in our study (p-value=0.060), the 95% confidence interval for the cumulative odds ratio for the male gender (0.988, 1.611) does not support higher risk for females with respect to increasing Breslow depth, mitotic rate, or metastatic disease.

Our secondary models of mitotic rates further adjusted for several prognostic factors including Breslow depth, ulceration, and presence of metastatic disease, in addition to age and anatomic location. Delayed diagnosis as a function of individual behavior may lead to increased Breslow depth, presence of ulceration, and advancement to metastatic disease. Prior studies have therefore supported the use of mitotic rate as a marker of tumor aggression and an independent predictor of worse survival in melanoma patients [14].

The influence of biology versus behavior on the gender differences in melanoma is a topic of ongoing debate. In 2013, Joosse et al.'s randomized controlled trial of stage III and IV melanoma patients revealed a female advantage in 5-year disease specific survival that persisted after metastasis to lymph nodes and distant sites. The authors therefore suggested that a biologic sex trait, rather than behavioral differences, might explain the finding [15]. In 2015, they retrospectively investigated tumor aggressiveness, measured by mitotic rate, in Australian males versus females with melanoma. With adjustments for Breslow depth, ulceration, and primary tumor location, females had a 36% survival advantage compared to men, which disappeared when mitotic rate was added as a confounder. The authors argued that biological differences in host factors, and not in tumor characteristics, explain the female advantage in melanoma [16].

Although our study supports the role of biological traits in explaining the gender differences in melanoma prognosis, unlike the 2015 Joosse study, it further identifies gender differences in the mitotic rates of presenting tumors. Our findings cannot

confirm the previous conclusions that behavioral factors do not account for gender differences or that host factors alone account for biological differences between males and females. Consistent with Nosrati and Wei, we believe that biology (e.g., hormonal influences and gene expression) and behavior (e.g., ultraviolet light exposure and health care services utilization) work together to increase rates of melanoma in men [17].

Also consistent with previous literature, our study identifies gender differences in anatomic locations of presenting lesions [18]. A greater percentage of melanomas presented on the head/necks and posterior trunks in males (32% and 23%, respectively) versus the lower and upper extremities in females (35% and 23%, respectively, $p<0.001$). Although the reasons for this remain unclear, we highlight a need for thorough examination of these sites in patients at risk for melanoma.

Strengths of our study include a large sample, which included patients with varied stages of disease. We further collected information on numerous variables associated with prognosis of disease including metastasis to lymph nodes or distant sites, mitotic rate, specific anatomic location, and melanoma subtype that are not readily available in larger population-based studies. Limitations of our study include the retrospective nature of the chart review, which limited prospective analyses on patient survival. We further acknowledge the limitations of generalizability inherent in a single-institution study.

Conclusion

Our study identifies gender differences in melanoma prognostic factors that clinicians may consider when screening their patients. We support the role of both biology and behavior in explaining this finding. Special attention to more common areas of involvement such as the head and neck and posterior trunk is needed in males, versus the upper and lower extremities in females. Increased efforts to educate men on the importance of early detection of melanoma may reduce the risk of advanced stage disease.

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