Sex Differences in Melanoma Survival – a GEM Study

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Abstract

Sex differences in melanoma are prominent, with females having a significant survival advantage. However, it is unclear why we see this survival advantage. Here we investigate the relationship between sex, clinicopathologic variables, and melanoma specific survival in 1,753 single primary melanomas from patients in the GEM study. Using Cox proportional hazard models and formal mediation analysis, the effect of sex on survival is explained largely by differences in the clinicopathologic features of tumors at diagnosis. Specifically, we find evidence that 86.5% of the effect of sex on melanoma survival is mediated by differences in age at diagnosis, Breslow thickness, ulceration, mitoses and site (HR 1.85, *P* <0.001). This analysis indicates that the female survival advantage in melanoma is not due primarily to a direct effect of sex (HR 1.19, *P* = 0.42) but is largely a result of an indirect effect of sex mediated by clinicopathologic features.

Sex Differences in Melanoma Survival – a GEM Study

Sex differences in melanoma are prominent. In general, incidence is higher in females at young ages but males gradually predominate as age increases[1,2]. However, we consistently see females having a significant survival advantage compared to males [3-8] The current determinants of melanoma stage and prognostic factors include tumor characteristics such as Breslow thickness, ulceration, and nodal metastasis; however, several studies have also shown sex to be an independent prognostic factor after adjusting for these known tumor characteristics. [3-9] It is not yet fully understood why females have a survival advantage. Several mechanisms including behavioral differences, biological processes, and histopathologic variables have been speculated to explain the sex specific differences we see in melanoma survival.[10]

There are behavioral and biological differences between males and females that may contribute to the differences in survival. First, females are more likely to go to the doctor, which may result in earlier detection of melanoma.[11] Additionally, females are more likely to possess “skin awareness”, which is associated with a decreased risk of melanoma death. [12,13] Also, males have been shown to have higher UV exposure than females, another explanation for the differences in melanoma specific survival.[14] There are several biological factors such as hormone milieu, oxidative stress response, vitamin D levels, and differences in gene expression that have also been postulated to explain the difference. [15,16] Melanoma is an immunogenic disease, and there are innate immunological differences between males and females such that females may exhibit a stronger immune response compared to males.[17-20] Overall, there is no clear consensus

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on why females have improved melanoma specific survival compared to males. The goal of our study is to further examine the relationship between sex and melanoma specific survival and determine whether sex differences in survival are mediated by established prognostic factors.

The GEM (Genes, Environment, and Melanoma) study consists of 3579 patients with incident primary cutaneous melanoma from 1998-2003 (2373 single primary melanomas and 1206 multiple primary melanomas) at eight population-based cancer registries in Australia, Canada, United States, and Italy and one hospital-based institution in Michigan.[21] The Institutional Review Board at each center reviewed and approved the study protocol. In this analysis, we included 1753 patients. We excluded non-Caucasian patients, patients with multiple primary melanomas, and those with missing values in the analytic variables. These variables included sex, melanoma-specific survival, Breslow thickness, ulceration, mitoses, TIL grade, solar elastosis, histological subtype, anatomic site of melanoma, skin type, educational level, UVE dose, and age at diagnosis. All pathology was reviewed by expert dermatopathologists. Erythemally weighted UVE[22] and dose were calculated[23].

A descriptive analysis comparing males and females in our sample was performed. A bivariate Cox proportional hazards model was used to calculate a hazard ratio for association between sex and melanoma specific survival controlling for age and center. Then a multivariable Cox proportional hazards model was used to determine the association between survival and the selected variables associated with melanoma, adjusting for age and center (Table 1). Mediation analysis was then used to decompose

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the direct effect of sex from the indirect effects operating through clinicopathologic variables that were associated with survival.

The indirect effects were estimated from the coefficients of two regression models: a model regressing the survival outcome on the mediator, sex, and center, and a model regressing the mediator variable on sex and center. We conducted an initial mediation analysis examining one mediator variable at a time, and a multiple mediation analysis investigating the combined indirect effects of multiple clinicopathological variables. All analyses were performed using the *survival* package (for Cox models) and *CMAverse (for mediation analysis)* in *R Statistical Software*. A p-value <0.05 was considered significant for all analyses, and all tests of statistical significance are 2-sided.

Of the 1753 patients included in our sample, 836 (47.7%) were female and 917 (52.3%) were male. There were 34 females (4.1%) and 74 males (8.1%) who died within 7.4 years, the follow up time for this cohort. Controlling for only age and center, males are more likely to die of melanoma (HR 1.81, p=0.005). After adjusting for the clinicopathological variables, there is no longer a statistically significant association between sex and survival (HR 1.19, p=0.47). However, individuals with thicker tumors (HR 1.14, *P*<0.001), mitoses (HR 4.52, *P*<0.001), and ulceration (HR 3.11, *P*<0.001) had a higher risk of dying of melanoma. Older patients (HR 1.02, p=0.02), were also more likely to die of melanoma. Individuals with brisk TILs (HR 0.23, *P*=0.008), marked solar elastosis (HR 0.33, *P*=0.004), tumors on trunk/pelvis (HR 0.48, *P* =0.02) and extremities (HR 0.35, *P*<0.001) had a lower risk of dying of melanoma. College graduates were also less likely to die of melanoma (HR 0.50, *P*=0.01).

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In multivariable analyses, Breslow thickness, ulceration, mitoses, TIL grade, solar elastosis, and anatomic site were found to be statistically significantly associated with melanoma specific survival. An interaction analysis showed no interactions between age and sex. A mediation analysis conducted on these variables found that age, Breslow thickness, ulceration, and mitoses significantly mediated the effect of sex on melanoma specific survival (Table 2). Overall, 86.5% of the effect of sex on melanoma specific survival can be explained by age, Breslow thickness, ulceration, mitoses, and anatomic site (HR 1.85, P<0.001).

Several studies in the literature show sex to be an independent prognostic factor for melanoma.[3-9] However, the results of this study show that the effect of sex on melanoma-specific survival sex is largely mediated by clinicopathologic features of the tumors at time of diagnosis, with 86.5% of the effect of sex explained by age, Breslow, ulceration, mitoses, and anatomic site. It is unclear if the remaining 13.5%, although not statistically significant, represents an independent effect of sex, or if it captures the effect of other unmeasured variables. Regardless, an overwhelming majority of sex's effect on survival is explained through other variables, which suggests that the female survival advantage may be due to differences in tumor characteristics present at time of diagnosis.

There are several different hypotheses to explain the sex differences in melanoma survival which include both behavioral and biological differences. Many studies postulate that the differences in survival cannot fully be explained by behavioral differences as the female survival advantage persists even in advanced stages and metastatic melanoma.[6,7, 24,25] One study showed that mitotic rate is not an effect

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modifier or confounder of the relationship between sex and survival, indicating that biological or host-related factors may explain the survival advantage we see in females.[26]

In the present study we see the effect of sex on survival is significantly mediated through age, Breslow thickness, ulceration, mitoses, and anatomic site. The mediating effects of Breslow thickness and ulceration are suggestive that sex differences in melanoma progression and survival may be related to behavioral differences between males and females. Males tend to have deeper lesions at time of diagnosis, possibly because they are less likely to visit the doctor and to perform skin self-examinations, which may contribute to later stage at diagnosis in men. [11-13, 27,28]

Mitoses are also a significant mediator of the effect of sex on survival, which may be explained by both behavioral and biological differences between males and females. Given that females mount more robust immune responses than men, they may be better at slowing down melanoma progression. This may result in males having more aggressive tumors with higher mitotic rates at time of diagnosis.[20] Mitotic rate has also been shown to be associated with vitamin D levels and reactive oxygen species.[15, 29,30] In some studies, female have been shown to have higher vitamin D plasma levels. Vitamin D has been shown to have an anti-tumor effect, inhibiting DNA synthesis and melanoma cell doubling time, which may contribute to the higher mitotic rates we see in males.[15,31-34] Melanoma is characterized by high reactive oxygen species levels, which promote growth and metastasis, and males have been shown to have lower levels of anti-oxidant enzymes, possibly explaining why we mitoses are a mediator of the effect of sex on survival.[30, 35-37]

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Other researchers have argued that evolved differences in immunity for males and females may contribute to differences in immune responses in melanoma. Thus, we may have expected to see immunological variables such as TILs to differ significantly between males and females.[17-20] In our sample, only one female with brisk TILs died. This could show a protective effect of TILs that differ by sex, but our statistical ability to detect TILs as a mediating variable is limited, given that there is only one female with brisk TILs who died.

Another limitation of this study is that our sample is population-based and thus has substantially thinner tumors which may have influenced the significance of the relationship we see between sex and Breslow thickness.

In summary, this study shows that the effect of sex on melanoma specific survival is mediated through age, Breslow thickness, mitoses, and ulceration. Previous literature suggests that sex is an independent prognostic factor for melanoma.[3-9] However, our results indicate that the female survival advantage in melanoma is largely due to mediating effects of clinicopathologic features of male and female tumors at the time of diagnosis.

Data Availability: Data are available by contacting Dr. Marianne Berwick at mberwick@salud.unm.edu or Dr. Irene Orlow at orlowi@mskcc.org.

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Table 1. Multivariable analysis of melanoma-specific survival.*

Variable	n		Hazard Ratio	95% CI	*P*-value
	Female	Male			
Sex	836	917	1.19	(0.75, 1.89)	0.47
Median Breslow thickness (mm)**	0.70	0.83	1.14**	(1.09, 1.21)	<0.001
Ulceration					
Absent	786	825	Reference		
Present	50	92	3.11	(1.96, 4.95)	<0.001
Mitoses					
Absent	517	487	Reference		
Present	319	430	4.52	(2.50, 8.18)	<0.001
TIL grade					
Absent	184	180	Reference		
Non-brisk	536	593	0.65	(0.41, 1.02)	0.06
Brisk	116	144	0.23	(0.08, 0.68)	0.008
Solar Elastosis					
Absent	331	293	Reference		
Mild/moderate	387	470	0.69	(0.43,1.10)	0.12
Marked	118	154	0.33	(0.15, 0.70)	0.004
Histology					
Superfical Spreading Melanoma	642	638	Reference		
Nodular Melanoma	60	99	1.38	(0.83, 2.30)	0.22
Other	134	180	0.97	(0.52, 1.82)	0.93
Anatomic Site					
Head/neck	93	166	Reference		
Trunk/pelvis	250	539	0.48	(0.26, 0.87)	0.02
Extremities	493	212	0.35	(0.19,0.63)	<0.001
Skin type					
Freckle/Occasionally Tan	406	309	Reference		
Deeply/Moderately Tan	430	608	1.31	(0.86, 2.00)	0.21
Education Level					
≤ High school	597	618	Reference		
> High School	239	299	0.5	(0.29, 0.87)	0.01

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UVEdose (z-scaled)	1.02	(0.81, 1.28)	0.86

*Controlled for age and center

** Breslow thickness was log transformed for analyses

CI = Confidence interval

mm = millimeters

UVE = Erythemal ultraviolet radiation

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Table 2. Mediation analyses of age and clinicopathologic variables on the effect of sex on melanoma survival.

	Hazard Ratio	95% CI	*P*-value	Proportion Mediated
Indirect Effects				
Age	1.18	(1.07, 1.30)	**< 0.001**	29.0%
Breslow - mm	1.37	(1.17, 1.59)	**< 0.001**	52.0%
Ulceration	1.19	(1.05, 1.34)	**0.01**	28.6%
Mitoses	1.17	(1.07, 1.28)	**< 0.001**	27.8%
Solar Elastosis	1.00	(0.97, 1.04)	0.97	0.1%
TILs	0.98	(0.94, 1.02)	0.26	-4.5%
Site	1.12	(0.96, 1.29)	0.15	19.8%
Joint Effects*				
Indirect	1.85	(1.43, 2.58)	**< 0.001**	86.50%
Direct	1.15	(0.72, 1.92)	0.54	
Total	2.13	(1.39, 3.68)	**0.002**	

*Center is included as a covariate. Multiple mediators include age, ulceration,

Breslow thickness (log), presence of mitoses, and anatomic site.

CI = Confidence interval

mm = millimeters

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