Tumor Ulceration Does Not Fully Explain Sex Disparities in Melanoma Survival among Adolescents and Young Adults

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TO THE EDITOR

Melanoma is one of the most common cancers diagnosed in adolescent and young adults (AYAs) aged 15–39 years, an age-group defined by the Adolescent and Young Adult Oncology Progress Review Group (Adolescent and Young Adult Oncology Progress Review Group, 2006), and has the potential to result in the greatest years of life lost of any cancer (Ekwueme *et al.*, 2011). We previously reported that non-Hispanic white AYA males were 55% more likely to die from melanoma compared with females of the same age, even after adjusting for tumor thickness, anatomical site, histologic subtype, and presence/extent of metastasis (Gamba *et al.*, 2013). Over 20 years (1989–2009), males had significantly poorer survival across all ages <40, tumor thicknesses (except T2 melanoma, 1.01–2 mm), and subtypes, in cases of cutaneous only disease and regional metastasis (Gamba *et al.*, 2013). However, our analyses did not take into account primary tumor ulceration, a well-known negative prognostic factor (Balch *et al.*, 2001), because this information was not routinely collected by cancer registries until 2004, following its incorporation into AJCC staging in 2002.

A recent cancer registry analysis of 10–39-year-old melanoma patients (2004–2008) showed that ulceration rates were lower than older patients (40–84 years), but similar by sex and tumor thickness, except for young females with T4 melanoma ⩾4.00 mm who had lower ulceration rates than young males (Richardson *et al.*, 2014). The few studies that considered the impact of ulceration on sex survival disparities were conducted in selected populations of patients from clinical trials (Joosse *et al.*, 2012, 2013) or a single institution (Joosse *et al.*, 2015) or limited by missing inform-

Table 1. Demographic and clinical characteristics of non-Hispanic white adolescents and young adults 15–39 years of age when diagnosed with a first primary, invasive melanoma, 2004–2011

	Total ($n=13,348$)		Male ($n=5,083$)		Female ($n=8,265$)		P^1
	n	%	*n*	%	*n*	%	
Primary tumor ulceration status							
Absent	11,340	85.0	4,134	81.3	7,206	87.2	<0.001
Present	970	7.3	514	10.1	456	5.5	
Unknown	1,038	7.8	435	8.6	603	7.3	
Age at diagnosis							
15–24 years	2,113	15.8	710	14.0	1,403	17.0	<0.001
25–29 years	2,689	20.1	918	18.1	1,771	21.4	
30–34 years	3,529	26.4	1,371	27.0	2,158	26.1	
35–39 years	5,017	37.6	2,084	41.0	2,933	35.5	
Anatomic site							
Head and neck	1,702	12.8	984	19.4	718	8.7	<0.001
Trunk	5,243	39.3	2,229	43.9	3,014	36.5	
Upper extremity	2,713	20.3	935	18.4	1,778	21.5	
Lower extremity	3,286	24.6	724	14.2	2,562	31.0	
Acral	70	0.5	22	0.4	48	0.6	
Unknown	334	2.5	189	3.7	145	1.8	
Histologic subtype							
Superficial spreading	5,160	38.7	1,880	37.0	3,280	39.7	<0.001
Nodular	644	4.8	323	6.4	321	3.9	
Rare subtypes	646	4.8	270	5.3	376	4.5	
NOS	6,898	51.7	2,610	51.3	4,288	51.9	
Breslow depth (in mm)							
0.00–1.00	9,596	71.9	3,369	66.3	6,227	75.3	<0.001
1.01–2.00	1,748	13.1	764	15.0	984	11.9	
2.01–4.00	7,51	5.6	367	7.2	384	4.6	
⩾4.01	368	2.8	219	4.3	149	1.8	
Unknown	885	6.6	364	7.2	521	6.3	
Presence/extent of metastasis							
Cutaneous	11,507	86.2	4,159	81.8	7,348	88.9	<0.001
Regional	953	7.1	514	10.1	439	5.3	
Metastatic	260	1.9	170	3.3	90	1.1	
Unknown	628	4.7	240	4.7	388	4.7	
Subsequent primary cancer							
No	12,632	94.6	4,840	95.2	7,792	94.3	0.019
Yes	716	5.4	243	4.8	473	5.7	

[1]chi-squared *P*-value for differences in proportions of demographic and clinical characteristics between males and females.

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Table 2. Melanoma-specific survival among non-Hispanic white adolescent and young adults 15–39 years of age when diagnosed with first primary melanoma, 2004–2011

Primary tumor ulceration status	No. of deaths			Stratified analysis HR[1] (95% CI)	
	Male	Female	Males only	Females only	Male vs. Female[2]
Absent	111	64	Reference	Reference	1.59 (1.15–2.19)
Present	107	54	2.45 (1.74–3.44)	3.22 (2.03–5.12)	1.10 (0.77–1.57)
Unknown	89	44	1.72 (1.18–2.52)	2.33 (1.44–3.75)	1.24 (0.85–1.81)

Abbreviations: CI, confidence intervals; HR, hazard ratio.
[1]HR and 95% CI adjusted for age at diagnosis, marital status at diagnosis, subsequent primary cancer, anatomic site, histologic subtype, Breslow depth, and presence/extent of metastasis.
[2]*P* for interaction between ulceration status and sex = 0.004.

ation on tumor ulceration (>62%) in population-based data (Joosse *et al.*, 2011). In addition, no population-based study has examined whether ulceration explains the strong disparity in survival we reported among male AYAs with melanoma. Therefore, to address this question, we used the National Cancer Institute's SEER18 database, a population-based cancer registry database covering ~28% of the United States population, to examine survival for all non-Hispanic white patients 15–39 years of age when diagnosed with their first primary melanoma during 2004–2011 Surveillance, Epidemiology and End Results (SEER).

Stratified multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) to evaluate the association of ulceration status and sex with melanoma-specific survival. Multivariable models were adjusted for age at diagnosis, marital status at diagnosis, subsequent primary cancer, anatomic site, histologic subtype, Breslow depth (thickness), and presence/extent of metastasis (cutaneous, regional nodal, and distant metastatic disease), as done previously (Reyes Ortiz *et al.*, 2007; Aizer *et al.*, 2013; Gamba *et al.*, 2013). For deceased patients, survival time was measured from the date of diagnosis to death from melanoma. Patients who died of other causes were censored at the time of death. AYAs diagnosed by death certificate/autopsy only were excluded ($n = 4$). Patients alive at the study end date (31 December 2012) were censored at this time or last follow-up. This analysis was approved by the Cancer Prevention Institute of California Institutional Review Board.

In 13,348 non-Hispanic white AYA melanoma patients with a mean follow-up of 3.8 years (±2.4), we found that males were almost twice as likely to have ulcerated tumors (10.1% vs. 5.5%, $P < 0.001$) than females (Table 1). Among AYAs with ulcerated tumors, 24.1% of males and 14.7% of females had T4 melanoma (data not shown in tables). Primary tumor ulceration was associated with over a 2-fold increased risk of death in males and an over 3-fold increased risk of death in females after consideration for socio-demographic and clinical factors (Table 2). However, the addition of ulceration status to the multivariable model did not substantially attenuate the sex disparity on melanoma-specific survival (multivariate-adjusted HR without ulceration: 1.46, 95% CI: 1.19–1.78; HR with ulceration: 1.39, 95% CI: 1.14–1.71), suggesting that the male/female survival disparity cannot be explained by ulceration status alone. Further, we found that the sex survival disparity was greatly influenced by ulceration status ($P_{interaction} = 0.004$). Specifically, among AYAs without ulcerated tumors, AYA males were 59% more likely to die than AYA females, whereas among AYAs with ulcerated tumors, there were no significant sex survival differences (Table 2).

Our findings suggest that both primary tumor ulceration and sex are important prognostic factors in AYAs with melanoma, but that ulceration does not fully explain the worse survival in young males. AYA males with ulcerated tumors were more likely than females to have T4 melanoma in our study, as found previously (Richardson *et al.*, 2014), but we did not observe a significant sex survival disparity among AYAs with ulcerated primary melanoma. However, among AYAs without primary tumor ulceration, comprising >81% of AYAs, markedly increased mortality among AYA males was observed, even after adjusting for other prognostic factors.

Both behavioral and biological factors have been proposed to account for the survival disparity by sex across melanoma patients of all ages (Nosrati and Wei, 2014), with this study adding to the growing literature specific to AYAs, in whom biology may have a more prominent role than behavioral factors (Fisher and Geller, 2013; Gamba *et al.*, 2013). Although the biological basis is unknown, biological factors proposed to influence these sex survival differences include sex hormones, immune homeostasis and regulation, response to ultraviolet radiation, vitamin D metabolism, and oxidative stress response (Fisher and Geller, 2013; Nosrati and Wei, 2014). There is also growing evidence for the tumor suppressive role of the long non-coding RNA, Xist, which is required for X-chromosome inactivation (Yildirim *et al.*, 2013; Chu *et al.*, 2015). Our population-based study had a large, representative series of melanoma patients, but also the potential for variation in interpretation of primary tumor ulceration by pathologists or coding by registrars (Richardson *et al.*, 2014); strengths include the low (7.8%) rate of missing ulceration status in the cancer registry data. Future studies with longer follow-up should continue to investigate the possible biological mechanisms that account for sex differences in melanoma survival, as they may

inform novel prevention and treatment strategies.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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Mutations in the Kinetochore Gene KNSTRN in Basal Cell Carcinoma

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TO THE EDITOR

Basal cell carcinomas (BCCs) are the most common cancers in the United States, with an annual national incidence of ~2 million (Lomas *et al.*, 2012). Although the majority are localized to the skin and cured by surgery, in rare cases, they can progress to advanced and metastatic tumors that result in severe morbidity and death. BCCs are typically caused by activating mutations in the sonic hedgehog (HH) pathway, most commonly through loss of the receptor Patched1 (PTCH1) or activation of the G-protein-coupled receptor Smoothened (SMO; Epstein, 2008). Here, we report the presence of Kinastrin (kinetochore-localized astrin/SPAG5 binding protein (KNSTRN)) mutations in BCC. KNSTRN encodes a kinetochore-associated protein that is an essential component of the mitotic spindle and is required for faithful chromosomal segregation during mitosis (Fang *et al.*, 2009). It is expressed in a broad range of tissues, including skin, and its mutations have been detected in both squamous-cell carcinoma (SCC) and melanoma, leading to its recent classification as an oncogene (Lee *et al.*, 2014).

In order to elucidate the role of KNSTRN in BCC, we interrogated 18

Abbreviations: BCC, basal cell carcinoma; CNV, copy-number variation; COSMIC, Catalogue of Somatic Mutations in Cancer; HH, sonic hedgehog pathway; KNSTRN, kinetochore-localized astrin/SPAG5 binding protein; PTCH1, patched 1; SCC, squamous-cell carcinoma; SMO, smoothened; TP53, tumor protein 53

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