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Sex Differences in Age at Primary Melanoma Diagnosis in a Population-Based Analysis (US Surveillance, Epidemiology, and End Results, 2005–2011)

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TO THE EDITOR

Melanoma represents 5% of skin cancers, yet accounts for the majority of skin cancer deaths. Males are more likely to present with tumors that are thicker, ulcerated, and located on the head and trunk. Although males are generally older at initial diagnosis of invasive cutaneous melanoma (Jemal et al., 2011), it is unclear whether sex differences in age at diagnosis persist when controlling for thickness, ulceration status, and anatomic site. The recent availability of ulceration status and improved completeness on tumor thickness in Surveillance, Epidemiology, and End Results (SEER) registry data provide an opportunity to investigate sex differences in age, stratified by tumor thickness, ulceration status, and anatomic site.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2016.03.044.

We included Caucasian patients whose initial primary diagnosis of invasive cutaneous melanoma was reported to one of the 18 SEER cancer registries between 1 January 2005 and 31 December 2011 (Surveillance Research Program, National Cancer Institute). Patients without evidence of distant metastasis at presentation (i.e., localized or regional SEER stage) were included. Data on sex, age at first primary diagnosis (age), anatomic site (site), tumor thickness, and ulceration status (available for patients diagnosed 2004 and later) were obtained. Tumor thickness was categorized according to American Joint Committee on Cancer 7th edition T-category criteria (Balch et al., 2009). Site was classified according to ICD-O-3 codes.

Because patients who had more than one primary melanoma could potentially contribute more than one record, we considered the earliest diagnosis of invasive melanoma to avoid counting the same individual more than once. Anatomic site was categorized as lower extremity, trunk, upper extremity, scalp/neck, and other. Median age and 95% confidence intervals were determined within 40 categories combining sex, T category, ulceration status, and site using nonparametric methods. Sex differences in age were considered statistically significant if 95% confidence intervals were nonoverlapping. The hypothesis that sex differences in age do not vary by site among T1 tumors, which constitute the majority of primary melanomas, was tested using a four-degree-of-freedom likelihood ratio test in a quantile regression model (test for sex-site interaction). Trends in sex differences in age with increasing tumor thickness were described using a second quantile regression model that included T1–T4 tumors, treating tumor thickness as a continuous variable. To model median age as a function of thickness by sex and site, three-way interactions (sex-site-thickness) were included assuming a linear relationship between median age and tumor thickness within a sex-site combination. Because the models included interaction terms, individual coefficient estimates were not directly interpretable in terms of sex difference in age within a site. Trends were summarized graphically by plotting predicted median age as a function of thickness by sex and site. Ulcerated and nonulcerated tumors were evaluated separately.

There were 102,095 patients diagnosed with invasive primary cutaneous melanoma for whom age was known, including 43,631 (42.7%) females (Table 1). Overall, median age at diagnosis ranged from 54 to 70 years for females and 63–69 years for males for patients with T1–T4 tumors, respectively (Supplementary Table S1 online).

Among patients with nonulcerated tumors (n = 84,856), males were significantly older than females by 8, 6, and 4 years for T1–T3 tumors, respectively. Stratifying by site, males were older by 10, 10, 7, and 5 years and by 9, 8.5, 4, and 2 years among T1–T4 trunk and scalp/neck tumors, respectively. Among upper extremity tumors, males were older by 6, 4, and 3 years for T1–T3 tumors, but 2 years younger for T4 tumors. Among patients with lower extremity tumors, males were 4 and 1 years older for T1–T2 tumors and 0.5 and 3 years younger for T3–T4 tumors. Statistical differences occurred in T1–T2 trunk, scalp/neck, upper extremity, T1 lower extremity, and T3 trunk tumors but not in other strata. The test for sex-site interaction was highly significant ($P < 0.0001$). Plots of predicted median age showed that sex differences in age declined with increasing thickness, with larger differences for trunk melanomas and smaller differences among lower extremity melanomas (Supplementary Figure S1 online).

Among patients with ulcerated tumors (n = 12,227), males were 2–6 years older than females for T1–T3 tumors, respectively, and 3 years younger for T4 tumors. Patterns similar to those of nonulcerated tumors were noted (Supplementary Table S1). A significant sex-site interaction was not observed ($P = 0.23$). Plots of predicted median age also showed declining differences with thickness. Compared with patients with nonulcerated tumors, differences were attenuated among patients with ulcerated tumors (Supplementary Figure S2 online).

In this analysis of the most recent cohort of patients with invasive cutaneous melanoma from the SEER registry quantifying sex differences in age at diagnosis of invasive cutaneous melanoma that accounts for ulceration status, site, and tumor thickness, males were significantly older than females in nearly all tumor thickness groups (i.e., T1–T3, but not T4).

Two prior studies showed significant age differences for truncal melanomas. An earlier SEER analysis (2000–2004) found that males, at 55 years, were 10 years older at diagnosis (Lachiewicz et al., 2008). Similarly, an earlier Australian study of melanomas diagnosed 1982–1990 found that males were older by 9.2, 4.5, and 1.5 years for trunk, upper extremity, and lower extremity tumors, respectively (Siskind et al., 2005). In contrast to our study, neither of these studies controlled for tumor thickness and ulceration status, both of which, importantly, increase with age.

The current study significantly adds to these studies revealing a striking sex difference in age, yet the underlying cause for this difference remains largely unknown. Males could be older if they delayed seeking medical attention after first noticing a suspicious lesion. However, gender differences in delay do not appear to explain the observed differences herein. A South African study of 250 patients with stage I melanoma found an overall mean delay of 9.8 months: 6.6 months for males and 12.2 months for females (Krige et al., 1991). A Connecticut study involving 222 patients with melanoma found that 36 (16%) experienced a delay of more than 3 months. Although males represented approximately 50% of the cohort, they accounted for only 39% of those with diagnostic delay of more than 3 months, suggesting that longer delay occurred more frequently among females (Oliveria et al., 1999). A French study of 590 patients also found that diagnosis was delayed longer in females than males (5.5 vs. 4.6 months) (Richard et al., 2000). Together, these studies suggest that diagnostic delay among males is unlikely to be greater than 1 year, making it less likely to account for our observed sex differences of atleast 4 years in age at diagnosis. If males delay longer, they could be older and have thicker tumors at diagnosis even within a given T category. Exploratory analysis of the joint distributions of age and tumor thickness suggests that later onset of melanoma as well as longer delay among males could contribute to our observed differences assuming little sex difference in time to first noticing a suspicious lesion (Supplementary Figures S3 and S4 online).

Less frequent use of health services among males may contribute to the observed differences; however, utilization rates among males and females (aged 45–64 years) have not been shown to differ (Hsiao et al., 2010).

Additional factors may explain the observed sex differences in age at diagnosis. Males could be older if they were less likely to notice changes in their skin (Koh et al., 1992) or noticed a lesion but took longer to recognize it as suspicious (Richard et al., 2000) even if they did not subsequently experience much longer delay. Males have a greater predilection for melanoma on the back than do females, which may also contribute to delay in diagnosis and more advanced melanoma at presentation (Geller et al., 2009). The SEER registry does not distinguish between back, chest, or abdomen melanomas, so we cannot eliminate location on the trunk as a possible confounder. However, Temoshok et al. (1984) found that the mean delay was 3.3 months for the chest and 6.0 months for the upper and lower back. Based on these estimates, even if nearly all trunk melanomas located on the back are among males and those on the chest are among females, delay alone may not be sufficient to explain a 10-year sex difference among trunk melanomas, which represent one-third of all melanomas in our data set.

A potential limitation of our study is that we cannot completely eliminate regional nodal metastasis as a confounder because of limited information on sentinel node biopsy and microscopic nodal metastasis in the SEER registry during the time frame studied. Although confounding by American Joint Committee on Cancer stage could occur if nodal metastasis is more frequent among males and older patients, when controlling for other factors, sentinel node positivity is more frequent in younger patients (Balch et al., 2014) and not consistently more frequent among men (Joosse et al., 2011; Scoggins et al., 2006). Further, nodal metastasis is uncommon among T1 melanoma and represents only 10–15% of T2 melanoma, so seems unlikely to explain the largest sex differences in age. We also could not control for potential confounding by tumor mitotic rate, which is higher in men (Shen et al., 2014) and ultraviolet radiation exposure.

We observed site differences in age that could be explained by the divergent pathway model proposed by Green and colleagues wherein melanomas occur in individuals with lower nevus counts at chronically sun-exposed sites, such as the face, whereas in those with higher nevus counts, intense, intermittent ultraviolet radiation is required to initiate carcinogenesis at less exposed sites such as the trunk (Green, 1992; Whiteman et al., 2003). The significant sex-site interaction we observed suggests that differences in age at melanoma onset exist by sex, in addition to site.

Our overall observed sex difference in age reflects a persistent older male age among T1 melanoma by up to one decade and older male age in most T2 strata. Older age among males was not consistently seen in other strata. Further studies are needed to explain sex differences in age among patients with T1 tumors and the apparent pattern of smaller differences in age with increasing melanoma thickness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation

SEER Surveillance, Epidemiology, and End Results

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Table 1

Clinicopathological factors of patients diagnosed with invasive cutaneous melanoma between 2005 and 2011

Characteristic	Female N = 43,631		Male N = 58,464	
Age at diagnosis (y)				
Mean (SD)	56.5 (17.2)		62.6 (15.1)	
Median (Min–Max)	56 (0–85)		64 (2–85)	
SEER stage	N	(%)	N	(%)
Localized	40,091	91.9	52,307	89.5
Regional	3,540	8.1	6,157	10.5
T category (mm)				
≤1.00, T1	30,207	69.2	37,178	63.6
1.01–2.00, T2	5,983	13.7	8,900	15.2
2.01–4.00, T3	3,102	7.1	5,494	9.4
4.01+, T4	2,006	4.6	3,726	6.4
No tumor found	141	0.3	299	0.5
Unknown	2,192	5.0	2,867	4.9
Ulceration status				
No	37,046	84.9	47,810	81.8
Yes	4,466	10.2	7,761	13.3
Unknown	2,119	4.9	2,893	4.9
Site				
Lower extremity	13,150	30.1	5,244	9.0
Scalp/neck	1,801	4.1	6,400	10.9
Trunk	11,396	26.1	22,690	38.8
Upper extremity	12,811	29.4	14,161	24.2
Other	4,473	10.3	9,969	17.1

Excludes 10 female patients and 12 male patients with missing data on age at first invasive melanoma diagnosis.

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.