Melanoma Survival Disadvantage in Young, Non-Hispanic White Males Compared With Females

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IMPORTANCE Worse survival among patients with melanoma has been demonstrated in middle-aged and older men compared with women, but few studies have explored survival differences by sex in adolescents and young adults, in whom melanoma is the third most common cancer. Focusing on sex disparities in survival among younger individuals may provide further evidence of biological rather than behavioral factors that affect melanoma outcome.

OBJECTIVE To determine whether long-term survival varies between white male and female adolescents and young adults with melanoma (15 to 39 years of age at diagnosis) in the United States.

DESIGN, SETTING, AND PARTICIPANTS Population-based cohort with a mean follow-up of 7.5 years of 26,107 non-Hispanic white adolescents and young adults with primary invasive melanoma of the skin diagnosed from January 1, 1989, through December 31, 2009, and reported to the Surveillance, Epidemiology, and End Results network of cancer registries.

MAIN OUTCOME AND MEASURE Melanoma-specific survival.

RESULTS There were 1561 melanoma-specific deaths in the study population. Although adolescent and young adult males accounted for fewer overall melanoma cases (39.8%) than females, they comprised 63.6% of melanoma-specific deaths. Adolescent and young adult males were 55% more likely to die of melanoma than age-matched females after adjustment for tumor thickness, histologic subtype, presence and extent of metastasis, and anatomical location (hazard ratio, 1.55; 95% CI, 1.39-1.73). Males were also more likely to die within each age range assessed (eg, 15-24, 25-29, 30-34, and 35-39 years), and even those with thin melanomas (<1.00 mm) were twice as likely to die as age-matched females (hazard ratio, 1.95; 95% CI, 1.57-2.42). Adjustment for health insurance and socioeconomic status in a subanalysis did not significantly alter these results.

CONCLUSIONS AND RELEVANCE Male sex is associated with worse survival among white adolescents and young adults with melanoma after controlling for thickness and other prognostic factors. Continued public health efforts are necessary to raise awareness of the outcome of melanoma in young men. Further investigation of possible biological mechanisms that account for these sex differences is merited.
Understanding melanoma mortality in adolescents and young adults (AYAs) is critical because melanoma is the third most common cancer in AYAs and accounts for the most years of potential life lost compared with all malignant tumors. Prior research in the United States and worldwide has found that women with melanoma have a consistent 17% to 47% survival advantage compared with men, but the study populations were predominantly composed of middle-aged and older individuals. Few studies have addressed differences in melanoma mortality between AYA men and women.

Proposed explanations for the sex disparity in melanoma mortality observed in older populations include behavioral and biological differences. A recent pooled analysis of melanoma outcomes among patients with comparable follow-up and treatment in randomized trials revealed that women were 30% less likely to die compared with men, suggesting that behavior differences alone are unlikely to account for the sex disparity. A biologic basis, either a protective factor in females or a stimulating factor in males, has been proposed to account for these sex differences.

The aim of this analysis is to describe survival in AYAs with melanoma and to evaluate prognostic factors that may contribute to sex disparities in survival. Using the national Surveillance, Epidemiology, and End Results (SEER) Program, we analyzed survival in AYAs with invasive cutaneous melanoma with up to 20 years of follow-up according to age, anatomical site, tumor thickness, histologic subtype, and presence and extent of metastasis. For this analysis, we defined AYAs as individuals 15 to 39 years of age at cancer diagnosis, as recommended by the Adolescent and Young Adult Oncology Progress Review Group.

Methods

Population

Information about mortality from melanoma was obtained from the National Center for Health Statistics. At the time of this analysis, vital status follow-up was complete through December 31, 2009.

Because approximately 95% of cutaneous melanoma cases occur in whites, the analysis was limited to non-Hispanic white patients. Race/ethnicity in cancer registries was abstracted from the medical record. Analyses were restricted to the period of 1989 to 2009 to evaluate up to 20 years of follow-up. Because of the expansion of SEER Program registries in 2000 to include additional geographical locations, there were twice as many patients diagnosed as having invasive cutaneous melanoma in 2000 to 2009 as in 1989 to 1999. Results are presented overall and by decade to confirm that patterns were similar. Furthermore, trends from the 1989 to 1999 group were of particular interest because T1 melanomas (≤1.00 mm) have been associated with late recurrence (eg, ≥10 years after diagnosis).

Tumor thickness was classified according to 2009 American Joint Committee on Cancer (AJCC) tumor categories: 1.00 mm or less, 1.01 to 2.00 mm, 2.01 to 4.00 mm, or 4.01 mm or greater. Histologic subtype was classified by the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) histology codes (8720-8780): superficial spreading melanoma (SSM), nodular melanoma (NM), and melanoma not otherwise specified. Other specified histologic types (eg, acral lentiginous, lentigo maligna, spindle cell, and desmoplastic) were classified as rare subtypes. Anatomical site was classified by ICD-O-3 site codes (C44.0-C44.9): head and neck, trunk, upper extremity, lower extremity, and unknown sites. Cutaneous disease was classified as no lymph node or distant metastasis, regional disease as 1 or more lymph nodes involved but no evidence of distant metastasis, and metastatic disease as distant metastasis regardless of lymph node involvement.

Statistical Analysis
The χ2 test was used to compare the distribution of demographic and clinical characteristics between men and women. Kaplan-Meier method and log-rank test were used to compare univariate survival between male and female patients. Stratified multivariate Cox proportional hazards regression model was used to estimate hazard ratios (HRs) and associated 95% CIs to evaluate the sex disparity on melanoma-specific survival by each demographic and clinical characteristic. For deceased patients, survival time was measured in months from the date of diagnosis to the date of death from melanoma for melanoma-specific survival. Patients who died of other causes were censored at the time of death for analyses of melanoma-specific survival. Patients alive at the study end date (December 31, 2009) were censored at this time or at date of last follow-up (ie, last known contact): 91% of censored patients had a follow-up date within 2 years of the study end date. The Cox proportional hazards regression model assumption was checked graphically with the correlation between weighted Schoenfeld residuals and logarithmically transformed survival time. No violations of the assumption were observed. Stratified multivariate regression models included variables significant at $P < .05$ in univariate models. Effect modification between sex and age at diagnosis, anatomical site, other primary cancer, tumor thickness, presence of metastasis, and histologic subtype was considered present if the interaction term in the multivariable model was significant ($P < .05$). The association between neighborhood socioeco-
conomic status (SES) and primary payer source on melanoma-specific survival was examined in 7503 AYA patients listed as having a diagnosis of melanoma in the California Cancer Registry (2000-2008). Neighborhood SES was determined based on patients’ residential census-block group at diagnosis using a previously described index.17,18

All statistical tests were performed using SAS statistical software, version 9.3 (SAS Institute Inc). All P values reported were 2-sided, and P<.05 was considered statistically significant.

Results

From 1989 through 2009, there were 26 107 invasive cutaneous melanoma cases among non-Hispanic whites aged 15 to 39 years (Table 1) and 1561 melanoma-specific deaths (Table 2). Overall mean (SD) follow-up was 7.5 (5.5) years, with a mean (SD) follow-up of 13.1 (5.0) years for 1989-1999 cases and 4.7 (2.9) years for 2000-2009 cases. Although males accounted for fewer melanoma cases (39.8%) compared with females, they comprised 63.6% of melanoma-specific deaths.

The mean (SD) age at melanoma diagnosis was 31.9 (6) years in males and 31.2 (6) years in females (Table 1). Most melanomas were in individuals 30 to 39 years old, although 34.2% of melanomas were diagnosed in individuals 15 to 29 years old. A history of other primary cancer was present in 6.2% of men and 7.4% of women. Patients diagnosed as having melanoma in 1989-1999 had a higher frequency of other primary cancer compared with individuals in 2000-2009 (9.3% vs 5.6%; Table 1). The trunk was the predominant site of melanoma in males (46.2%) and females (36.1%), although females also commonly developed melanoma on the lower extremity (32.0%).

The most common histologic subtype in males and females was SSM, but males were more likely to be diagnosed as having NM (6.8% vs 4.1%). A greater discrepancy in the frequency of NM was seen in the 1989-1999 diagnostic period (8.1% in males vs 4.5% in females). Although most melanomas were 1.00 mm or less for both males and females (55.4% vs 62.7%), males were slightly more likely to present with thicker melanomas, generally demonstrating a 2% higher frequency in the thicker categories compared with females (Table 1). Most melanoma cases were cutaneous only (88.6%), but males presented with a higher frequency of both regional disease (9.2% vs 4.7%) and distant metastasis (3.0% vs 0.9%) compared with females. For both males and females, thicker melanomas and regional disease were more common in the 2000-2009 diagnostic period (Table 1). Of note, all baseline characteristics were significantly different between males and females (P<.01; Table 1).

Kaplan-Meier Curves

The unadjusted, overall survival at 10 years was 88.3% (95% CI, 87.6%-89.0%) in males and 95.2% (95% CI, 94.7%-95.6%) in females (log-rank P < .001; Figure 1). Survival at 10 years in males and females also differed by the presence and extent of metastasis (log-rank P < .001; Figure 2). For cutaneous-only disease, the survival at 10 years was 94.3% (95% CI, 93.7%-94.9%) in males and 97.0% (95% CI, 96.6%-97.4%) in females.

The 10-year survival for regional and distant metastatic disease was 56.6% (95% CI, 52.3%-60.7%) and 14.5% (95% CI, 9.7%-20.2%) in males and 77.1% (95% CI, 73.0%-80.7%) and 25.2% (95% CI, 17.7%-33.5%) in females, respectively.

Multivariate Analysis

Risk of melanoma-specific death during the entire time frame was 55% higher among AYA males compared with females, independent of age at diagnosis, year of diagnosis, history of other primary cancer, anatomical site, histologic subtype, tumor thickness, and presence and extent of metastasis (HR, 1.55; 95% CI, 1.39-1.73; Table 2). The male survival disadvantage was demonstrated in both diagnostic periods (1989-1999: HR, 1.45; 95% CI, 1.25-1.67; 2000-2009: HR, 1.60; 95% CI, 1.36-1.89).

Males were 35% to 80% more likely to die than females in each age group (eg, 15-24, 25-29, 30-34, and 35-39 years) (Table 2), but the interaction between sex and age was not significant (data not shown). For individuals 15 to 29 years old, the higher risk of death among males was driven primarily by the 2000-2009 diagnostic period, in which males were 2.2 to 2.5 times more likely to die compared with females (Table 2).

Similar to the overall cohort, males were 54% more likely to die than females among patients without a history of another primary cancer (HR, 1.54; 95% CI, 1.38-1.72; Table 2). However, in those with a history of another primary cancer, males diagnosed as having melanoma in the period 1989-1999 but not 2000-2009 (HR, 0.88; 95% CI, 0.39-1.97) were twice as likely to die (HR, 2.01; 95% CI, 1.10-3.68).

Males with upper extremity melanomas were twice as likely to die compared with females (HR, 2.08; 95% CI, 1.59-2.72). A higher risk of death in males compared with females was also seen with lower extremity (HR, 1.67; 95% CI, 1.24-2.24) and trunk melanomas (HR, 1.48; 95% CI, 1.24-1.77). Although a significant interaction was found between anatomical site and sex (PInteraction = .02; data not shown), there was no interaction between sex and histologic subtype (PInteraction = .28; data not shown), although males with SSMs and NMs were significantly more likely to die of melanoma than females (SSM: HR, 1.73; 95% CI, 1.39-2.16; NM: HR, 1.89; 95% CI, 1.44-2.49).

Further analysis revealed that males were significantly more likely to die than females in each thickness category (PInteraction = .001; data not shown) except for 1.01 to 2.00 mm, which ranged from a 95% higher risk among those with the thinnest melanomas (<1.00 mm: HR, 1.95; 95% CI, 1.57-2.42; Table 2) to a 36% higher risk in those with the thickest melanomas (>4.01 mm: HR, 1.36; 95% CI, 1.01-1.83). Among those with T2 melanomas (1.01-2.00 mm), the higher risk among young men was borderline significant (HR, 1.22; 95% CI, 0.94-1.59), driven primarily by individuals in the 1989-1999 diagnostic period. Because recent data have suggested that survival may differ according to more precise thickness cutoff points in T1 melanomas,19,20 an analysis of T1 and T2 tumors by 0.5-mm gradations (eg, 0.0-0.50, 0.51-1.00, 1.01-1.50, and 1.51-2.00 mm) was performed and demonstrated similar results to those for the entire T1 and T2 categories (data not shown).

In terms of extent of disease, males with cutaneous-only disease were 52% more likely to die of melanoma than females
Table 1. Demographic and Clinical Characteristics of Non-Hispanic Whites Aged 15 to 39 Years Diagnosed as Having Invasive Melanoma, Surveillance, Epidemiology, and End Results, 1989-2009*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 26,107)</th>
<th>Period of Diagnosis</th>
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<tr>
<td></td>
<td>No. (%) of Patients</td>
<td>1989-1999 (N = 8,853)</td>
<td>2000-2009 (N = 17,254)</td>
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<tr>
<td></td>
<td>Total (n = 10,378)</td>
<td>Male (n = 5,146)</td>
<td>Female (n = 5,146)</td>
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<td>Age at diagnosis, y</td>
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<td></td>
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<td>15-24</td>
<td>3909 (15.0)</td>
<td>728 (14.1)</td>
<td>2774 (16.1)</td>
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<td>25-29</td>
<td>5010 (19.2)</td>
<td>1013 (19.7)</td>
<td>3151 (19.4)</td>
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<td>30-34</td>
<td>7074 (27.1)</td>
<td>2459 (42.4)</td>
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<td>35-39</td>
<td>10,114 (38.7)</td>
<td>6100 (40.8)</td>
<td>3984 (25.8)</td>
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<td>Age, mean (SD)</td>
<td>31.44 (5.95)</td>
<td>31.89 (5.92)</td>
<td>31.15 (5.95)</td>
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<td>Other primary cancer</td>
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<td>No</td>
<td>24,310 (93.1)</td>
<td>9,978 (93.8)</td>
<td>14,332 (92.6)</td>
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<td>Yes</td>
<td>1797 (6.9)</td>
<td>1,392 (6.2)</td>
<td>4,051 (7.4)</td>
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<td>Anatomical siteb</td>
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<td></td>
<td></td>
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<tr>
<td>Head and neck</td>
<td>3010 (11.5)</td>
<td>1,733 (16.7)</td>
<td>1,277 (8.1)</td>
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<tr>
<td>Trunk</td>
<td>10,480 (40.1)</td>
<td>4,799 (46.2)</td>
<td>5,681 (36.1)</td>
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<td>Upper extremity</td>
<td>5271 (20.2)</td>
<td>1,914 (18.4)</td>
<td>3,357 (21.3)</td>
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<td>Lower extremity</td>
<td>6,518 (25.0)</td>
<td>1,477 (14.2)</td>
<td>5,041 (32.0)</td>
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<td>Acral</td>
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<td>77 (0.5)</td>
<td>41 (0.4)</td>
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<td>Unknown</td>
<td>710 (2.7)</td>
<td>296 (1.9)</td>
<td>299 (3.4)</td>
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<tr>
<td>Histologic subtypec</td>
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<tr>
<td>SSM</td>
<td>11,291 (43.2)</td>
<td>4,307 (41.5)</td>
<td>6,984 (44.4)</td>
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<td>NM</td>
<td>1,341 (5.1)</td>
<td>701 (6.8)</td>
<td>640 (4.1)</td>
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<td>Rare subtypes</td>
<td>1,183 (4.5)</td>
<td>513 (4.9)</td>
<td>670 (4.3)</td>
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<tr>
<td>NOS</td>
<td>12,292 (47.1)</td>
<td>4,857 (46.8)</td>
<td>7,435 (47.3)</td>
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<td>Tumor thickness, mm</td>
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<tr>
<td>≤1.00</td>
<td>15,613 (59.8)</td>
<td>5,746 (55.4)</td>
<td>9,867 (62.7)</td>
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<tr>
<td>1.01-2.00</td>
<td>2888 (11.1)</td>
<td>1,298 (12.5)</td>
<td>1,590 (10.1)</td>
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</tr>
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<td>2.01-4.00</td>
<td>1,580 (6.1)</td>
<td>728 (7.0)</td>
<td>852 (5.4)</td>
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<tr>
<td>≥4.01</td>
<td>3,120 (12.0)</td>
<td>1,391 (13.4)</td>
<td>1,729 (11.0)</td>
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<td>Unknown</td>
<td>2,906 (11.1)</td>
<td>1,215 (11.7)</td>
<td>1,691 (10.8)</td>
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<tr>
<td>Presence of metastasis</td>
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<tr>
<td>Cutaneous only</td>
<td>23,122 (88.6)</td>
<td>8,774 (84.5)</td>
<td>14,348 (91.2)</td>
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<tr>
<td>Regional metastasis</td>
<td>1689 (6.5)</td>
<td>951 (9.2)</td>
<td>738 (4.7)</td>
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<tr>
<td>Distant metastasis</td>
<td>455 (1.7)</td>
<td>308 (1.0)</td>
<td>147 (0.9)</td>
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<tr>
<td>Unknown</td>
<td>841 (3.2)</td>
<td>345 (3.3)</td>
<td>496 (3.2)</td>
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</tr>
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Abbreviations: NM, nodular melanoma; NOS, not otherwise specified; SSM, superficial spreading melanoma.

*Data are presented as number (percentage) of patients unless otherwise indicated. All P values for differences in proportions of demographic and clinical characteristics between males and females were <.01.

Anatomical site was classified by International Classification of Diseases for Oncology, Third Edition (ICD-O-3) site codes: head and neck (C44.0-C44.9), trunk (C44.5), upper extremity (C44.6), lower extremity (C44.7), and unknown sites (C44.8-C44.9). Acral anatomical site was classified by ICD-O-3 in conjunction with acral histologic subtype (8744).

Histologic subtype was classified by ICD-O-3 histology codes: SSM (8743), nodular (8721), rare subtypes (8722-8742, 8744-8780), and NOS (8720).
In addition to melanoma-specific survival, an analysis of all-cause survival found similar results to those presented above (data not shown). In a subset of patients diagnosed as having melanoma in California, survival results were similar after adjustment for a composite measure of neighborhood SES that incorporates 7 US Census tract variables (including education and income)\(^17,18\) and primary source of payment (health insurance)\(^21\) (data not shown).
ies and a pooled analysis of randomized trials in melanoma patients, although most patients in these studies were diagnosed as having melanoma at 50 years or older.

Although the male melanoma survival disadvantage has been demonstrated in older populations, few studies have evaluated survival disparities in AYAs, in whom biology may have a more prominent role than behavioral factors. Prior studies of melanoma-specific survival in younger populations generally explored sex differences through subgroup analyses but most included middle-aged individuals between 40 and 54 years of age. Three of these registry-based studies found a similar association between male sex and poor melanoma survival, but the survival analyses were limited to 5 years of follow-up after diagnosis, and factors associated with the higher mortality in young men were not examined. A US study of patients in the National Cancer Database between 1985 and 1988 found an 88% higher risk of death among men younger than 45 years compared with women. Likewise, a Dutch study found a 74% higher risk of death among men younger than 45 years compared with women. Another study of several European cancer registries did not adjust for tumor characteristics but found a survival advantage among women younger than 54 years. In contrast, a South Swedish cancer registry cohort of 711 melanoma patients found no association between male sex and melanoma mortality in individuals younger than 50 years, but this may have been due to the small number of patients.

The survival advantage we observed among females may be due to better health maintenance behaviors, which could promote detection of thinner, more curable tumors or biological differences between men and women. Overall, young individuals are less knowledgeable about skin cancer and less likely to perform skin self-examinations than older individuals. Although report of skin self-examinations in a 12-month period was not significantly different by sex among students (18-26 years old) at one Midwestern university, women at a Northeastern university were more likely to have “ever” completed a skin self-examination. Women 18 to 44 years old are 3 times more likely to contact or visit a physician than men, but melanomas in individuals younger than 50 years are generally discovered by patients (55%-70%), and only 5% to 9% are found by physicians. This low rate of physician detection may not be surprising given that only 8% to 14% of AYAs report ever having had a skin examination by a clinician. Although we cannot exclude the possibility that increased physician visits by AYA females during their reproductive years may contribute to improved survival, physician discovery and skin self-examination practices are less likely to play a role in thinner melanoma detection in AYAs compared with older individuals.

Instead, the results of our study support a biologic explanation for a male survival disadvantage because males with more favorable tumor characteristics still fared worse than females. Males with the thinnest melanomas (≤1.00 mm) were nearly twice as likely to die than their female counterparts. Anatomical site is an independent predictor of melanoma-specific survival, with lower extremity tumors associated with better outcomes, whereas head and neck and trunk tumors are associated with poorer outcomes. However, AYA males in this study were 67% more likely to die of lower extremity melanomas than females, even after adjusting for tumor thickness. Although males presented with more NMs, which have been associated with rapid growth, the male survival disadvantage was not limited to this subtype. In fact, AYA males with SSM, the most common melanoma subtype, had a 73% higher risk of melanoma death compared with females. This study provides evidence that the AYA male survival disadvantage is not explained simply by health screening differences because one would then expect the sex disparity to be limited to thicker primary melanomas or to tumors located on the head and neck or trunk.

Several biologic mechanisms for the higher male melanoma mortality have been proposed, including differences in sex hormones, immune homeostasis, vitamin D metabolism, and oxidative stress. Evidence of a role of estrogen in melanoma development and progression has been...
Some findings have suggested that the balance of estrogen receptor α to estrogen receptor β may correlate with melanoma progression, but a case series found no sex difference in estrogen receptor β expression in melanocytic nevi or melanomas. In addition, a meta-analysis found no sex difference in the incidence of BRAF and NRAS mutations, which have been associated with cutaneous melanoma development.

Another proposed hypothesis is that the antitumor immune response may vary by sex. This hypothesis is supported by evidence that melanomas in women are less likely to relapse and/or progress. In a registry-based study by Joosse et al, women were 42% less likely to develop lymph node metastasis and 36% less likely to develop distant metastasis compared with men. Furthermore, women who developed lymph node metastasis during follow-up were 20% less likely to die compared with men. Another population-based study found that men with advanced melanoma (nodal and/or systemic involvement) had a higher risk of death compared with women (relative excess risk, 1.70; 95% CI, 1.30-2.23). This evidence of a survival disparity among individuals with advanced disease is consistent with our finding that males with lymph node metastasis were 74% more likely to die compared with females. Greater immune surveillance in females may explain the lower rates of metastasis and improved survival after development thereof. In general, females are more likely to develop certain autoimmune diseases, and escape of various X-linked genes from X-inactivation or a functional deficiency of regulatory T cells may have a key role. In one study of murine melanoma, reduced regulatory T-cell function accounted for the superior antitumor immunity in female compared with male mice. A similar differential immune response has not been confirmed in humans.

Skin cancer prevention recommendations by federal and national organizations in the United States vary widely. Currently, the US Preventive Services Task Force only advises counseling fair-skinned individuals 10 to 24 years on minimizing UV radiation exposure. Some have commented that there has been “little national investment to support frequent, sustained, and coordinated sun protection programs” in the United States, calling for increased efforts to create consistent preventive messaging. Targeting young women who indoor tan and older white men (>50 years), who have the highest melanoma mortality rates, has been emphasized, but our study suggests that future efforts should also focus on increasing melanoma awareness and early detection strategies among AYA males.

Although randomized data demonstrating decreased melanoma mortality as a result of skin screening are lacking, several studies have suggested that prevention efforts are effective at decreasing diagnosis of the thickest melanomas, a proxy for mortality. Recently, a pilot study of physician skin examinations among citizens older than 20 years in a northern German state found that mortality rates 5 years after completion of the screening intervention decreased by nearly 50% in both men and women, whereas no decreases were noted in neighboring, unscreened populations. In addition, a greater percentage of thin melanomas were diagnosed during the screening period compared with the earlier years, leading to the German Federal Joint Committee to add skin cancer screenings to nationwide health services in 2008. In the United States, both physician and self skin examinations have been associated with thinner melanomas as well. Thus, future efforts should focus on increasing skin examination and melanoma awareness in AYAs.

This study provides an analysis of melanoma survival among AYAs with long-term follow-up using detailed population-based SEER data but has several important limitations. First, the most recent AJCC staging highlights the importance of ulceration and mitosis for melanoma prognostication, factors that were variably reported to SEER and could not be included as confounders in this analysis. However, some studies have not found a sex disparity in survival despite adjustment for these factors. SEER does not collect variables that evaluate patients’ behavior, such as skin self-examination, or physician detection, which limits our ability to consider detection patterns in young patients and may contribute to residual confounding in this study. Of note, our analysis of a subset of patients diagnosed as having melanoma in California demonstrated that the higher risk of melanoma death in AYA males persisted after adjustment for health insurance and SES, factors that have been correlated with skin examination. Second, these results may be affected by incomplete or underreporting of melanoma, although reporting differences by patient sex are unlikely. Third, the SEER database collects limited data on first-course treatment data; thus, we could not incorporate treatment timing or type into these analyses. Despite this limitation, a recent analysis found a persistent 30% female survival advantage regardless of similar treatments in the European Organisation for Research and Treatment of Cancer randomized clinical trials. Fourth, misclassification of the cause of death may have occurred, but results for all-cause survival were similar to our results for melanoma-specific survival.

Our analysis was designed to explore survival differences between AYA males and females with cutaneous melanoma, and it demonstrates that AYA males (similar to predominantly middle-aged and older men in prior publications) fare worse than females when matched for tumor thickness, anatomical location, histologic subtype, and extent of disease. Despite lower melanoma mortality rates in younger men and women compared with older individuals, the risk of death in young men is 55% higher than that in young women. This alarming difference in outcome highlights the urgent need for both behavioral interventions to promote early detection strategies in young men and further investigation of the biological basis for the sex disparity in melanoma survival.
take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.
Acquisition of data: Clarke, Keegan, Tao. Analysis and interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Tao. Administrative, technical, or material support: Clarke.

Study supervision: Swetter.

Conflict of Interest Disclosures: None reported.

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REFERENCES

1. Adolescent and Young Adult Oncology Progress Review Group. Closing the Gap: Research and Care Imperatives for Adolescents and Young Adults With Cancer. Bethesda, MD: National Institutes of Health; 2006.
The first reported remedy for baldness was prepared for Ses, the mother of the Egyptian King Teta, and comprised “Toes-of-a-dog, refuse-of-dates [and] hoof-of-an-an.” Topical application of blended fats from a lion, hippopotamus, crocodile, cat, serpent, and an Egyptian goat were purported to prevent further hair shedding on a balding head. A third concoction for baldness comprised a mixture of writing fluid, hippopotamus fat, and gazelle dung.

Several medicaments for gray hair are proposed, including the bile of crabs and dried tadpoles from the canal, crushed in oil. While perhaps unconventional by our standards, we should consider that crab bile and tadpoles may be less likely to evoke contact allergies than our contemporary array of hair products. Another seemingly esoteric suggestion to banish graying, the application of “blood from the neck of the gagbu bird” to the scalp placing it alongside a living falcon and a swallow, is also unlikely to expose the user to p-phenylenediamine.

More enduring treatments to encourage hair growth are also listed, including use of castor oil and perhaps one of the earliest descriptions of a hairbrush, comprising “hair-of-the-hunta-animal, warm[ed] in oil.”

The Ebers Papyrus is reportedly the oldest medical reference in existence. Discovered in an Egyptian tomb in 1867 and named after the Egyptologist, Georg Ebers, who purchased the manuscript, extracts have been translated from the original hieroglyphics into German and rendered into English. The papyrus is a compilation of tales, incantations, and remedies for ailments of all bodily systems, from the alimentary and cardiovascular systems to the skin and hair. While written in approximately 1500 BC, some of the remedies are dated as much as 2000 years earlier, perhaps unconventional by our standards, we should consider that crab bile and tadpoles may be less likely to evoke contact allergies than our contemporary array of hair products. Another seemingly esoteric suggestion to banish graying, the application of “blood from the neck of the gagbu bird” to the scalp placing it alongside a living falcon and a swallow, is also unlikely to expose the user to p-phenylenediamine.

More enduring treatments to encourage hair growth are also listed, including use of castor oil and perhaps one of the earliest descriptions of a hairbrush, comprising “hair-of-the-hunta-animal, warm[ed] in oil.” Further contemporary resonance is garnered from an ode to the sun to charm away alopecia with concomitant application of an iron-containing medicament.

When reading renditions of the Ebers Papyrus, dermatologists should be reminded of the intrigue, skepticism, and incredulity with which current practice may be regarded by our progeny in 4000 years.

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