The Age-Specific Effect Modification of Male Sex for Ulcerated Cutaneous Melanoma

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IMPORTANCE Tumor ulceration is an important prognostic factor for cutaneous melanoma (CM). Previous studies demonstrated that the proportion of ulcerated to nonulcerated CM rose with increasing tumor depth. These frequency-based studies, however, were not adjusted for the population at risk.

OBJECTIVE To determine the absolute incidence of ulcerated CM by tumor depth, stratified by sex and age at diagnosis.

DESIGN, SETTING, AND PARTICIPANTS We compared ulcerated CM by tumor thicknesses (<1.00, 1.01-2.00, 2.01-4.00, and ≥4.01 mm), stratified by sex among younger (10-39 years) and older (40-84 years) non-Hispanic whites in the National Cancer Institute’s Surveillance, Epidemiology, and End Results database from 2004 through 2008. Types of CM included superficial spreading, nodular, and unclassified in 5106 cases among 3206 men and 1900 women.

MAIN OUTCOMES AND MEASURES Incidence of ulcerated CM by tumor depth for younger and older men and women.

RESULTS The incidence of tumor ulceration was stable across all tumor depths among younger men and older women. Among younger women, it declined for the thickest lesions (0.08 per 100,000 for tumor depth ≥4.01 mm), although the trend was not statistically significant. In contrast, among older men, there was a statistically significant increase in ulceration for CM with a depth of approximately 1.4 per 100,000 for tumor depth of 2.00 mm or thicker.

CONCLUSIONS AND RELEVANCE Male sex is an age-specific effect modifier for ulcerated CM by tumor depth. Future studies and staging guidelines should consider the interaction among CM ulceration, thickness, sex, and age at diagnosis.


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Methods

The University Hospitals Case Medical Center Institutional Review Board approved this study. Melanoma case and population data were obtained from the National Cancer Institute’s SEER 17 program, which has a registries database that covers...
Table 1. Frequency Characteristics of Cutaneous Melanoma in Non-Hispanic Whites From the Surveillance, Epidemiology, and End Results 17 Program From 2004 Through 2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n = 23 068)</th>
<th>Women (n = 19 279)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-39</td>
<td>40-84</td>
<td>10-39</td>
</tr>
<tr>
<td>Total No. of cases</td>
<td>2627</td>
<td>4393</td>
</tr>
<tr>
<td>Histologic melanoma subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial spreading</td>
<td>1099</td>
<td>1927</td>
</tr>
<tr>
<td>Nodular</td>
<td>199</td>
<td>217</td>
</tr>
<tr>
<td>Unclassified</td>
<td>1329</td>
<td>2249</td>
</tr>
<tr>
<td>Ulceration status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>301</td>
<td>276</td>
</tr>
<tr>
<td>Absent</td>
<td>2326</td>
<td>4117</td>
</tr>
<tr>
<td>Unknowna</td>
<td>157</td>
<td>238</td>
</tr>
</tbody>
</table>

*Excluded from subsequent analyses.

approximately 26% of the US population, including tumor registries in Atlanta, Georgia; Connecticut; Detroit, Michigan; Hawaii; Iowa; New Mexico; San Francisco–Oakland, California; Seattle–Puget Sound, Washington; Utah; Los Angeles, California; San Jose–Monterey, California; rural Georgia; Alaska; greater California; Kentucky; Louisiana; and New Jersey.6 Demographic and melanoma tumor characteristics included sex, age at diagnosis, histologic subtype, tumor depth, and ulceration status. Because of a coding change for ulceration status in 2004 (Collaborative Stage Site-Specific Factor 2 ulceration),7 we incorporated data only from 2004 through 2008 to ensure consistency in coding. We included men and women between ages 10 and 84 years at diagnosis, where age at diagnosis was classified as “younger” for 10 to 39 years and “older” for 40 to 84 years based on the well-established changes in melanoma incidence that occur around age 40 in men and women.8-10 Non-Hispanic whites accounted for 93.2% of cases; therefore, we examined only non-Hispanic whites in the analysis. Using the International Classification of Diseases for Oncology, 3rd edition, we analyzed superficial spreading (code 8743) and nodular (code 8721) CM, the most common subtypes in younger and older individuals.11 We also added unclassified melanomas (code 8720), given the likelihood that they represent superficial spreading and nodular subtypes. We excluded cases of lentigo maligna melanoma and acral lentiginous melanoma since including these subtypes would bias our results, given their high incidence in older individuals and low incidence in younger people. Only the primary CM was used for analysis in those with multiple melanomas. Exclusion criteria were melanoma in situ, nonmicroscopically confirmed cases, diagnosis at autopsy or on the death certificate, and cases with unknown race, age, tumor depth, or ulceration status.

SEER*STAT 7.0.5 (produced by the Surveillance Research Program of the Division of Cancer Control and Population Sciences, National Cancer Institute, and includes software developed by the OpenSSL Project) was used to calculate incidence and incidence rate ratios (IRRs), both with 95% CIs, in 2 age and sex groups across 4 tumor depth categories (≤1.00, 1.01-2.00, 2.01-4.00, and ≥4.01 mm) by ulceration status. Incidence was calculated per 100 000 person-years and age-adjusted to the 2000 US standard population. Incidence and IRRs were plotted on a log-linear scale by category of tumor depth and stratified by sex among younger and older persons. All statistical tests were 2-sided, with P < .05 considered statistically significant.

Results

In total, 42 347 patients with CM fit our inclusion criteria (Table 1), with 23 068 men and 19 279 women. Cutaneous melanomas were more frequent in the older (40-84 years) than in the younger (10-39 years) age group among both men and women. The number of CMs was higher in younger women compared with men but higher in older men compared with women. Of the 5106 patients with ulcerated CM, 3206 and 1900 occurred in men and women, respectively. Ulcerated CM was more common among older than younger persons.

The incidence of ulcerated CM also was higher among older than younger persons (Table 2). In younger individuals, ulcerated CM rates were similar among men and women, but in older people, these rates were higher among men compared with women. Rates were stable across tumor depth for younger men and older women. In younger women, rates were stable across the first 3 tumor depth categories but then fell in the thickest category (0.08 per 100 000 for tumor depth ≥4.01 mm). In older men, rates rose with increasing tumor depth (approximately 1.4 per 100 000 for tumor depth >2.00 mm).

To further examine the rates for ulcerated CM by tumor depth (Figure), we assessed the linear trend in the logarithm of the IRR for each category of tumor depth among younger and older persons for men (Figure, A) and women (Figure, B). There was a significant linear trend in the logarithm of the IRR among men (P = .01) but not among women (P = .34).

We then investigated whether the increase in tumor ulceration for T2 to T4 melanomas is related to histologic subtype. We noted the same trend for each age and sex group when analyzing nodular, superficial spreading, and unclassified melanoma separately, but the trend was not statistically significant for the men until we combined the histologic subtypes; for women, the trends were not statistically significant when the 3 histologic subtypes were examined separately or combined.
Discussion

Similar to previous studies,\textsuperscript{2-14} we found that older men, aged 40 to 84 years, had the highest incidence rate of ulcerated CM. Furthermore, the incidence rate of ulcerated CM remained mostly stable for all age and sex groups across increasing tumor depth categories except in older men. These findings were unexpected since we hypothesized that the incidence of ulcerated CM would rise with increasing tumor depth for all age and sex groups. For comparison, we examined nonulcerated CM and did not observe significant differences in trends among different age and sex groups. Our results suggest that ulceration occurs at a fairly stable rate among older and younger women and younger men but at a higher rate for thicker tumors in older men. Furthermore, since we observed a significant linear trend in the logarithm of the IRR of ulcerated CM in older compared with younger men over increasing tumor depth, we conclude that age modifies the effect of tumor depth on ulceration in men. A significant trend was not observed in women, which could be a result of the loss of power in the thickest tumor depth category (≥4.01 mm) in younger women. Our findings support the hypothesis that CMs are heterogeneous tumors, given the age-specific interaction among men, and further suggest that the etiology of ulceration is likely due to complex tumor-host interactions that should be investigated in future studies.

Limitations of our study include the potential incorrect histologic diagnosis of CM and CM subtype by the pathologist; mis-coding of subtype, tumor depth, age, or sex; and delayed reporting by practitioners in SEER. Another limitation is that the mitotic rate, a component of the current staging system for CM as of 2009, is not reported in the SEER database during the period of our study, preventing us from including this important prognostic factor for melanoma survival in our analysis. According to the American Joint Committee on Cancer staging system, ulceration is defined as the absence of an intact epidermis overlying a portion of the primary melanoma based on microscopic examination of the epidermis; however, this does not distinguish between traumatic ulceration and tumor ulceration.\textsuperscript{3,15,16} A major limitation of SEER is the potential for either inaccurate coding of ulceration or variation in interpret-

\begin{table}
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Tumor Depth, mm} & \textbf{10-39 y} & \textbf{40-84 y} \\
\hline
\textbf{Men} & & \\
\hline
\textless{}1.00 & 81 & 0.13 (0.10-0.16) & 610 & 1.02 (0.94-1.11) \\
1.01-2.00 & 68 & 0.11 (0.08-0.14) & 619 & 1.05 (0.96-1.13) \\
2.01-4.00 & 81 & 0.13 (0.10-0.16) & 853 & 1.43 (1.34-1.54) \\
\textgreater{}4.01 & 71 & 0.11 (0.09-0.14) & 823 & 1.38 (1.28-1.47) \\
\hline
\textbf{Women} & & \\
\hline
\textless{}1.00 & 78 & 0.13 (0.10-0.16) & 410 & 0.61 (0.55-0.67) \\
1.01-2.00 & 76 & 0.13 (0.10-0.16) & 398 & 0.58 (0.53-0.64) \\
2.01-4.00 & 78 & 0.13 (0.11-0.17) & 406 & 0.60 (0.54-0.66) \\
\textgreater{}4.01 & 44 & 0.08 (0.05-0.10) & 410 & 0.60 (0.54-0.66) \\
\hline
\end{tabular}
\caption{Frequency and Incidence of Ulcerated Nodular, Superficial Spreading, and Unclassified Melanoma in Men and Women*}
\end{table}

* Rates are per 100,000 and age adjusted to the 2000 US standard population.

We assessed the linear trend for ulcerated cutaneous melanomas between older and younger men (A) and between older and younger women (B) by category of tumor depth. The null hypothesis of no trend was rejected at the $\alpha = .05$ level. A, $P = .01$ for IRR trend. B, $P = .34$ for IRR trend. IRR indicates incidence rate ratio.
ing ulceration among dermatopathologists and general pathologists with different experience levels.\textsuperscript{15,16} The consistent rate of ulceration, even in thin tumors, is interesting; however, we cannot exclude the possibility that these findings may be due to a consistent lack of experience in determining ulceration status among pathologists.

An additional limitation is the high frequency of cases with an unknown ulceration status. To address this limitation, we examined the annual percentage change of CM with unknown ulceration status in each age and sex group during the study period and found a similar decreasing trend in all groups; therefore, we may infer that the CMs with unknown ulceration status occur at random. Unfortunately, with unclassified data in SEER, it is not possible to further repartition the tumors with an unknown ulceration status. These tumors may be underestimated but are not biasing our data since the trend is in the same direction for all age and sex groups.

The SEER database has many strengths, including its high quality, large sample size, and the ability to limit the study population to those with microscopic confirmation, allowing for stratification by histologic type of melanoma. However, even with this large sample size, the numbers of younger men and women with ulcerated melanomas are relatively low. Additional studies with larger sample sizes and in other populations are needed to validate our findings.

**Conclusions**

Ulceration is an important independent prognostic factor for CM. We have demonstrated that the incidence of ulceration is actually stable across increasing tumor depth for all age and sex groups except older men (40–84 years), in whom the incidence of ulcerated CM increased in thicker tumors. Among younger women, the incidence of ulcerated CM declined for the thickest lesions ($\geq 4.01$ mm), although the trend was not statistically significant. In contrast, among older men, there was a statistically significant increase in the incidence of ulcerated CM with a depth of 2.01 mm or thicker. Therefore, for men, age at diagnosis modifies the effect of tumor depth on ulceration. Additional studies with greater sample sizes are needed to verify our findings and to further understand the biologic differences and the complex tumor-host interactions that give rise to ulcerated melanomas.

**REFERENCES**