Increased Cancer Mortality Following a History of Nonmelanoma Skin Cancer

Henry S. Kahn, MD; Lilith M. Tatham, DVM, MPH; Alpa V. Patel, MPH; Michael J. Thun, MD, MS; Clark W. Heath, Jr, MD

Context.—Cancer registries have reported an increased incidence of melanoma and certain noncutaneous cancers following nonmelanoma skin cancer (NMSC). Whether these findings were attributable to intensified surveillance, shared risk factors, or increased cancer susceptibility remains unclear.

Objective.—To determine whether a history of NMSC predicts cancer mortality.

Design.—Prospective cohort with 12-year mortality follow-up adjusted for multiple risk factors.

Setting.—Cancer Prevention Study II, United States and Puerto Rico.

Participants.—Nearly 1.1 million adult volunteers who completed a baseline questionnaire in 1982.

Main Outcome Measure.—Deaths due to all cancers and common cancers.

Results.—After adjusting for age, race, education, smoking, obesity, alcohol use, and other conventional risk factors, a baseline history of NMSC was associated with increased total cancer mortality (men's relative risk [RR], 1.30; 95% confidence interval [CI], 1.23-1.36; women's RR, 1.26; 95% CI, 1.17-1.35). Exclusion of deaths due to melanoma reduced these RRs only slightly. Mortality was increased for the following cancers: melanoma (RR, 3.36 in men, 3.52 in women); pharynx (RR, 2.77 in men, 2.81 in women); lung (RR, 1.37 in men, 1.46 in women); non-Hodgkin lymphoma (RR, 1.32 in men, 1.50 in women); men only, salivary glands (RR, 2.96), prostate (RR, 1.28), testis (RR, 1.27), urinary bladder (RR, 1.41), and leukemia (RR, 1.37); and in women only, breast (RR, 1.34). All-cause mortality was slightly increased (adjusted men's RR, 1.03 [95% CI, 1.00-1.06]; women's RR, 1.04 [95% CI, 1.00-1.09]).

Conclusions.—Persons with a history of NMSC are at increased risk of cancer mortality. Although the biological mechanisms are unknown, a history of NMSC should increase the clinician's alertness for certain noncutaneous cancers as well as melanoma.
RESULTS

After 12 years of follow-up, 26,622 men and 21,084 women in our analytic cohort had died of cancer. After adjusting for only age and race, a history of NMSC was associated with all-site (including melanoma) cancer mortality for men (relative risk [RR], 1.23; 95% confidence interval [CI], 1.17-1.30) and for women (RR, 1.23; 95% CI, 1.15-1.32). Additional multivariate adjustment (Table 1) did not attenuate the association between a history of NMSC and all-site cancer mortality (men’s RR, 1.30; women’s RR, 1.26). Excluding from the analyses 427 men and 221 women who died of melanoma produced minimal change in the association between NMSC and death from cancer (fully adjusted men’s RR, 1.27; women’s RR, 1.24; Table 2).

The increased RR for all-site cancer mortality paralleled the increased RRs that we identified for death from the following cancers: melanoma, pharynx, lung, non-Hodgkin lymphoma; in men only, salivary glands, prostate, testis, bladder, and leukemia; and in women only, breast, ovarian, and ovarian cancer.

for models predicting all-cancer mortality, mortality due to the major cancers, and all-cause mortality.

COMMENT

This large prospective study found death rates from all noncutaneous cancers to be 20% to 30% higher among participants who reported a history of NMSC than among participants who did not. Our finding is similar in direction and magnitude to the results of 3 previous studies based on incidence data from European cancer registries2,3,4 and the results of a fourth European incidence study when its analysis was restricted to persons whose initial squamous cell skin cancer was diagnosed at younger than 65 years.2 Our findings (Table 2) also resemble those from the European cancer registries with respect to the specific cancers associated with NMSC. For each of the cancers for which higher death rates were associated with NMSC in our study, at least 1 of the European studies reported increased cancer incidence. Our prospective study, like the European incidence studies, found no increase in cancers of the esophagus, stomach, pancreas, ovary, or colorectum.
Table 2.—Deaths, Adjusted Relative Risks, and 95% Confidence Intervals for Subsequent Cancers Associated With a History of Nonmelanoma Skin Cancer: Cancer Prevention Study II, 1982-1994*  

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Deaths With Previous NMSC</th>
<th>Deaths Without Previous NMSC</th>
<th>RR (95% CI)†</th>
<th>Deaths With Previous NMSC</th>
<th>Deaths Without Previous NMSC</th>
<th>RR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites, including melanoma</td>
<td>1611</td>
<td>25,011</td>
<td>1.30 (1.23-1.37)</td>
<td>801</td>
<td>20,283</td>
<td>1.26 (1.17-1.35)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>61</td>
<td>366</td>
<td>3.36 (2.55-4.42)</td>
<td>20</td>
<td>201</td>
<td>3.52 (2.21-5.61)</td>
</tr>
<tr>
<td>All sites, excluding melanoma</td>
<td>1550</td>
<td>24,645</td>
<td>1.27 (1.20-1.33)</td>
<td>781</td>
<td>20,082</td>
<td>1.24 (1.15-1.33)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>5</td>
<td>56</td>
<td>2.10 (0.83-5.29)</td>
<td>2</td>
<td>17</td>
<td>3.69 (0.84-16.3)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>3.69 (0.84-16.3)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2</td>
<td>33</td>
<td>1.18 (0.28-4.96)</td>
<td>1</td>
<td>36</td>
<td>0.85 (0.12-6.29)</td>
</tr>
<tr>
<td>Brain</td>
<td>46</td>
<td>703</td>
<td>1.33 (0.99-1.80)</td>
<td>21</td>
<td>643</td>
<td>1.00 (0.64-1.54)</td>
</tr>
<tr>
<td>Kidney</td>
<td>41</td>
<td>675</td>
<td>1.29 (0.94-1.77)</td>
<td>17</td>
<td>260</td>
<td>1.30 (0.72-2.38)</td>
</tr>
<tr>
<td>Male corpus</td>
<td>6</td>
<td>347</td>
<td>0.56 (0.25-1.26)</td>
<td>112</td>
<td>2958</td>
<td>1.34 (1.11-1.63)</td>
</tr>
<tr>
<td>Prostate</td>
<td>86</td>
<td>1549</td>
<td>1.12 (0.90-1.39)</td>
<td>45</td>
<td>1397</td>
<td>0.97 (0.72-1.31)</td>
</tr>
<tr>
<td>Liver</td>
<td>28</td>
<td>467</td>
<td>1.26 (0.86-1.84)</td>
<td>11</td>
<td>260</td>
<td>1.30 (0.72-2.38)</td>
</tr>
<tr>
<td>Rectum‡</td>
<td>18</td>
<td>404</td>
<td>0.90 (0.56-1.44)</td>
<td>10</td>
<td>308</td>
<td>1.09 (0.58-2.06)</td>
</tr>
<tr>
<td>Colon‡</td>
<td>133</td>
<td>2468</td>
<td>1.05 (0.88-1.25)</td>
<td>75</td>
<td>2319</td>
<td>1.01 (0.64-1.54)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>31</td>
<td>686</td>
<td>0.98 (0.68-1.41)</td>
<td>6</td>
<td>159</td>
<td>1.15 (0.51-2.61)</td>
</tr>
<tr>
<td>Stomach</td>
<td>40</td>
<td>846</td>
<td>1.01 (0.74-1.40)</td>
<td>16</td>
<td>435</td>
<td>1.21 (0.73-1.99)</td>
</tr>
<tr>
<td>Colon‡</td>
<td>18</td>
<td>404</td>
<td>0.90 (0.56-1.44)</td>
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*NMSC indicates nonmelanoma skin cancer; RR, relative risk; and CI, confidence interval. Ellipses indicate data not applicable.
†Data are adjusted for age, race, smoking, exercise, body mass index, education, vegetable and fat intake, aspirin use, alcohol consumption, marital status, diabetes, and (for women) menopausal status, parity, and use of oral contraceptives and estrogen replacement therapy. Colon, rectal, breast, ovarian, and prostate cancer are also adjusted for family history of site-specific cancer.
‡Data are also adjusted for family history of colon and rectal cancer.
§Data for women are also adjusted for family history of breast and ovarian cancer.

are not yet clear. However, a history of NMSC should increase the clinician’s alertness for selected neoplasms. 28

Since submission of our manuscript we have encountered 2 additional incidence studies reporting malignancies following basal cell skin cancer. One study 28 found an increased incidence of all-site, noncutaneous cancers and the other did not. 30

The authors thank the volunteers throughout the American Cancer Society who donated time and energy to CPS-II. Many staff members of the American Cancer Society’s National Home Office also contributed to this study.

References