Increased Risk of Second Primary Cancers After a Diagnosis of Melanoma

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Objective: To quantify the risk of subsequent primary cancers among patients with primary cutaneous malignant melanoma.


Setting: We evaluated data from 9 cancer registries of the Surveillance, Epidemiology, and End Results program from 1973-2006.

Participants: We included 89,515 patients who survived at least 2 months after their initial melanoma diagnosis.

Results: Of the patients with melanoma, 10,857 (12.1%) developed 1 or more subsequent primary cancers. The overall risk of a subsequent primary cancer increased by 28% (observed to expected [O:E] ratio = 1.28). One quarter of the cancers were subsequent primary melanomas (O:E = 8.61). Women with head and neck melanoma and patients younger than 30 had markedly increased risks (O:E = 13.22 and 13.40, respectively) of developing a subsequent melanoma. Second melanomas were more likely to be thin than were the first of multiple primary melanomas (thickness at diagnosis <1.00 mm, 77.9% vs 70.3%, respectively; P < .001). Melanoma survivors had increased risk of developing several cancers; the most common cancers with elevated risks were breast, prostate, and non-Hodgkin lymphoma (O:E = 1.10, 1.15, and 1.25, respectively).

Conclusions: Melanoma survivors have an approximately 9-fold increased risk of developing subsequent melanoma compared with the general population. The risk remains elevated more than 20 years after the initial melanoma diagnosis. This increased risk may be owing to behavioral factors, genetic susceptibility, or medical surveillance. Although the percentage of subsequent primary melanomas thicker than 1 mm is lower than for the first of multiple primary melanomas, it is still substantial. Melanoma survivors should remain under surveillance not only for recurrence but also for future primary melanomas and other cancers.

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I n 2006, the National Cancer Institute published the Surveillance, Epidemiology, and End Results (SEER) monograph New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000,1 which evaluated the risk of new malignant tumors after cutaneous malignant melanoma and other first primary cancers. The monograph found that the overall risk of subsequent primary cancers, excluding nonmelanoma skin cancers, increased by 24% among melanoma survivors1 and that more than 20% of the new malignant tumors were also melanomas. Studies of multiple primary cancers are useful to etiologic research and physicians because they provide clues to shared environmental and genetic risk factors for the first and later cancers and help to identify individuals at higher risk for subsequent cancers. Although melanoma is a potentially lethal form of skin cancer, survival rates are high, with a 5-year survival rate of 92.3% and 86.9% for white women and men, respectively.2 Hence, the risk of subsequent cancer is an important issue for melanoma survivors. This report updates the 2006 SEER monograph1 and analyzes risks of new invasive melanomas and other cancers diagnosed among white melanoma survivors between 1973 and 2006, with an additional 23,456 survivors and 6 more years of follow-up. We also examine the risks for subsequent melanomas according to characteristics of the initial melanoma, such as anatomic site and thickness, and we examine the thickness of subsequent melanomas.

METHODS

We evaluated the risk for subsequent invasive primary cancers among patients diagnosed with an initial primary cutaneous malignant melanoma using data collected from the SEER program.2 We included patients diagnosed with melanoma between 1973-2006 who survived at least 2 months after their initial diagnosis and were followed up through December 31, 2006. Only subsequent (second, third, fourth, etc) primary invasive cancers that were diagnosed within 2 months of the initial melanoma diagnosis were included in the analysis. Melanoma recurrences were not analyzed in this article. Because heightened screening of patients with cancer during the initial medical
work-up may identify simultaneous cancers, we excluded from
the calculations the first 2 months of follow-up and the new
malignant tumors diagnosed during this period (n = 1005).5 The
SEER coders classified race for individuals using all resources
in the medical facility, including medical records, face sheets,
physician and nursing notes, photographs, and electronic data.3
Options for race were classified according to the 2000 US Cen-
sus Bureau rankings.4 The study was limited to whites be-
cause of the small numbers of patients with melanoma in other
racial groups. The participants were reported to 1 of 9 popu-
lation-based registries encompassing approximately 10% of the
US population and including 5 states (Connecticut, Hawaii, Iowa,
New Mexico, and Utah) and 4 metropolitan areas (Atlanta, De-
troit, San Francisco/Oakland, and Seattle/Puget Sound).2

The SEER data include age at diagnosis, date of diagnosis,
date of death (until December 31, 2006), sex, initial treatment
modality, and, for melanoma, tumor histological characteristics,
anatomic site of tumor, and tumor thickness (available since
1988). The major histological subtypes of cutaneous malignant
melanoma were defined based on the International Classifi-
cation of Diseases in Oncology, 3rd revision (ICD-O-3).1 As
follows: superficial spreading melanoma (category 8743), lentigo
dermal melanoma (8742), acral lentiginous melanoma (8744),
and nodular melanoma (8721). Information on histological sub-
type is limited because there is no centralized pathological re-
view, and 42.3% were reported as melanoma, not otherwise
specified (ICD-O-3 category 8720). Quality assurance in the
SEER program is maintained through on-site monitoring, data
documenting, case-finding audits, reabstracting of cases, and vari-
ious educational programs. Standards have established a case
ascertainment rate of 98%, a follow-up rate of 95%, and an over-
all microscopic diagnostic confirmation rate of more than 98%.6

Person-years at risk (PYR) were accumulated for each partici-
ent beginning 2 months after initial melanoma diagnosis and end-
ing at the date of death, the date last known alive, or December
31, 2006. The expected numbers of new cancers of specific types
were estimated by assuming that incidence rates for new primary
malignant tumors corresponded to sex, age, and calendar time-specific SEER rates for similar invasive primary cancers and applying those rates to the accumulated person-years of observation. We then calculated the standardized incidence ratio, as an estimate of the relative risk, using the observed number of patients (O) divided by the expected number of patients (E). We estimated the absolute
risk (EAR) per 10 000 person-years as (O – E) / PYR.

Relative risk measures the fold difference (eg, 2-fold) be-
tween the observed and expected number of events, whereas EAR
measures the actual number of excess events normalized to the
number of person-years observed. The relative risk (O/E) provides
a useful tool to test etiological hypotheses.7 In contrast, the EAR
is often the most useful measure of risk to assess the impact of the
subsequent public health cancer burden in a specific population
of patients with cancer or when interest centers on the potential
effectiveness of screening or prevention programs.1 We assumed
a Poisson distribution of the observed tumors, and all statistical
tests and 95% confidence intervals (CIs) were 2-sided and based
on an α level of .05.

This population-based study is exempt from institutional
review board approval because it is based on publicly avail-
able SEER data.6

Table 1. Characteristics of Patients With Cutaneous Malignant Melanoma in the 9 SEER Registries
From 1973-2006

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with melanoma</td>
<td>89 515 (100.0)</td>
<td>47 804 (53.4)</td>
<td>41 711 (46.6)</td>
</tr>
<tr>
<td>Median age at cancer diagnosis, y</td>
<td>54</td>
<td>56</td>
<td>52</td>
</tr>
<tr>
<td>Median year of cancer diagnosis</td>
<td>1997</td>
<td>1997</td>
<td>1997</td>
</tr>
<tr>
<td>Median person-years at risk</td>
<td>9.2</td>
<td>8.5</td>
<td>10.0</td>
</tr>
<tr>
<td>Age at cancer diagnosis, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>7448 (8.3)</td>
<td>3763 (5.7)</td>
<td>3685 (8.7)</td>
</tr>
<tr>
<td>30-49</td>
<td>30 534 (34.1)</td>
<td>14 514 (20.4)</td>
<td>16 020 (23.4)</td>
</tr>
<tr>
<td>≥50</td>
<td>51 557 (57.6)</td>
<td>26 544 (36.9)</td>
<td>25 013 (35.3)</td>
</tr>
<tr>
<td>Site of melanoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>16 316 (18.2)</td>
<td>8 153 (13.7)</td>
<td>8 163 (14.4)</td>
</tr>
<tr>
<td>Trunk</td>
<td>30 402 (34.0)</td>
<td>15 247 (21.4)</td>
<td>15 155 (22.6)</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>20 944 (23.4)</td>
<td>10 216 (14.4)</td>
<td>10 728 (17.7)</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>18 138 (20.3)</td>
<td>9 051 (13.4)</td>
<td>9 087 (15.9)</td>
</tr>
<tr>
<td>Multisite/NOS</td>
<td>3718 (4.2)</td>
<td>1822 (2.7)</td>
<td>1896 (3.4)</td>
</tr>
<tr>
<td>Histological analysis of melanoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSM</td>
<td>35 506 (39.7)</td>
<td>17 731 (27.1)</td>
<td>17 775 (31.6)</td>
</tr>
<tr>
<td>LMM</td>
<td>7418 (8.3)</td>
<td>3659 (0.1)</td>
<td>3637 (5.3)</td>
</tr>
<tr>
<td>NM</td>
<td>5630 (6.3)</td>
<td>2956 (2.4)</td>
<td>2674 (4.9)</td>
</tr>
<tr>
<td>ALM</td>
<td>643 (0.7)</td>
<td>287 (0.6)</td>
<td>356 (0.9)</td>
</tr>
<tr>
<td>NOS</td>
<td>37 278 (41.6)</td>
<td>19 306 (25.9)</td>
<td>18 972 (31.7)</td>
</tr>
<tr>
<td>Otherb</td>
<td>2207 (2.5)</td>
<td>1269 (2.7)</td>
<td>938 (2.2)</td>
</tr>
<tr>
<td>Unknownc</td>
<td>835 (0.9)</td>
<td>463 (1.0)</td>
<td>372 (0.9)</td>
</tr>
<tr>
<td>Initial treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any radiation</td>
<td>1886 (2.1)</td>
<td>1296 (2.7)</td>
<td>590 (1.4)</td>
</tr>
<tr>
<td>With surgical treatment</td>
<td>929 (1.0)</td>
<td>626 (1.3)</td>
<td>303 (0.7)</td>
</tr>
<tr>
<td>Without surgical treatment</td>
<td>957 (1.1)</td>
<td>670 (1.4)</td>
<td>287 (0.7)</td>
</tr>
<tr>
<td>No radiation</td>
<td>87 629 (97.9)</td>
<td>46 508 (73.7)</td>
<td>41 121 (76.3)</td>
</tr>
<tr>
<td>With surgical treatment</td>
<td>83 543 (93.3)</td>
<td>44 219 (63.4)</td>
<td>39 324 (66.9)</td>
</tr>
<tr>
<td>Without surgical treatment</td>
<td>4086 (4.6)</td>
<td>2289 (4.8)</td>
<td>1797 (3.4)</td>
</tr>
<tr>
<td>No. of patients with multiple cancersd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Cancers only</td>
<td>9348 (10.4)</td>
<td>5701 (11.9)</td>
<td>3647 (8.7)</td>
</tr>
<tr>
<td>3 Cancers only</td>
<td>1290 (1.4)</td>
<td>842 (1.8)</td>
<td>448 (1.1)</td>
</tr>
<tr>
<td>≥4 Cancers</td>
<td>219 (0.2)</td>
<td>148 (0.3)</td>
<td>71 (0.2)</td>
</tr>
<tr>
<td>Histologically confirmed, %d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First and second cancers</td>
<td>96.8</td>
<td>96.5</td>
<td>97.2</td>
</tr>
<tr>
<td>All subsequent cancers</td>
<td>96.4</td>
<td>96.1</td>
<td>96.9</td>
</tr>
<tr>
<td>Initial melanoma only</td>
<td>2.8</td>
<td>3.0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Abbreviations: ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results; SSM, superficial spreading melanoma.

Data are given as number (percentage) of patients unless otherwise indicated.

b Other includes balloon cell, amelanotic, desmoplastic, mucosal lentiginous, mixed epitheloid/spindle cell, epitheloid, and spindle cell melanomas.

c Histological analysis results labeled “unknown” in the SEER registries.

d Refers to patients with an initial diagnosis of melanoma and a

RESULTS

A total of 89 515 patients survived 2 months or longer following a diagnosis of a primary melanoma. The pa-
tients were followed up for a maximum of 34 years (mean,
9.2 years); 53.4% of the patients were men and 46.6% were
women (Table 1). The median age at first melano-
oma diagnosis was 54 years, with men having a higher
median age at diagnosis than women (56 vs 52 years,
respectively). The proportion diagnosed at ages 50 years

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and older was also substantially greater among men than women (63.9% vs 50.3%, respectively). Among men, the most common site of the first melanoma was the trunk (41.5%), whereas in women, it was the lower limbs (32.7%). In men (37.1%) and women (42.6%), the most frequent histological diagnosis of the first primary melanoma was superficial spreading melanoma. The large majority of patients were surgically treated (94.3%), and few patients received radiation treatment (2.1%).

Of the 89,515 patients diagnosed with an initial melanoma, 12.1% developed 1 or more subsequent primary tumors (Table 1), including 9,348 patients (10.4%) with 2 primary cancers, 1,290 (1.4%) with 3 primary cancers, and 219 (0.2%) with 4 or more primary cancers. A total of 96.4% of patients had their first and all subsequent cancers confirmed via histological analysis.

In survivors of a first primary melanoma, the overall risk of developing a subsequent primary cancer increased by 28% among men and women who survived for 2 months or longer (O:E, 1.28; O, 12,559 [95% CI, 1.26-1.30]; EAR, 34/10,000 person-years) (Table 2). This excess was primarily owing to subsequent primary melanoma (O:E, 8.61), with 23% of the subsequent cancers being primary melanomas. The risk of subsequent primary melanoma was highest 2 months to 1 year after the initial melanoma diagnosis (O:E, 16.94), with the risk decreasing as the latency period increased. At 20 years or longer after the initial melanoma diagnosis, however, the risk was still elevated (O:E, 5.58; EAR, 24/10,000 person-years; and 9.00 [8.47-9.54]; EAR, 24/10,000 person-years, respectively).

There were, however, significantly elevated risks for specific subsequent primary cancers other than melanoma. For each of the cancer types listed in Table 2, increased risks among melanoma survivors were noted in comparison to what would be expected in the general population. The most common cancers with elevated risks after an initial melanoma were prostate cancer (O:E, 1.15; EAR, 3.49), female breast cancer (O:E, 1.10; EAR, 1.34), and non-Hodgkin lymphoma (NHL) (1.25; 1.18) (Table 2). Risks were also significantly increased for cancers of the salivary gland, small intestine, kidney, ocular melanoma, and thyroid as well as soft tissue sarcomas and chronic lymphocytic leukemia.

We evaluated the risks for subsequent primary cancers among melanoma survivors in 3 age groups: younger...
than 30 years, 30 through 49 years, and 50 years and older. Patients younger than 30 had the greatest relative risk for developing subsequent cancers after a melanoma diagnosis (O:E, 2.41 [95% CI, 2.17-2.68]) (Figure, A). This was owing to the markedly higher relative risks of developing subsequent melanoma in those initially diagnosed at ages younger than 30 (O:E, 13.40 [95% CI, 11.66-15.33]) (Table 3 and Figure, A). Among those aged 30 through 49 years, the relative risk of second primary melanoma was 8.74; among those aged 50 years and older, it was 8.23. Figure, B, shows that the EAR for developing melanoma increased as patients aged. The EAR for developing subsequent melanomas was highest among those aged 50 years and older at the first melanoma diagnosis (43.89) (Figure, B).

Overall, individuals with their initial melanoma on the head or neck had the highest risk of developing subsequent primary melanomas (O:E, 9.69 [95% CI, 8.97-10.45]; EAR, 46.72) compared with those with initial melanomas on other anatomic sites (Table 3). Individuals with melanoma of the head and neck were also older (mean age at diagnosis, 61.6 years) compared with those diagnosed with melanoma at other sites (mean age range, 50.9-55.4 years). Women with initial head and neck melanoma had a higher relative risk (O:E, 13.22 [95% CI, 11.43-15.20]) of developing a subsequent melanoma than did men (8.72 [7.96-9.54]). Men who had their first melanoma on the head and neck, however, had higher EARs of developing subsequent melanomas than did women (51.59 and 38.32, respectively). The most frequent result of histological analysis of the melanomas of the head and neck in both sexes was lentigo maligna melanoma (data not shown).

With the expansion to 89,515 cutaneous malignant melanoma survivors and an additional 308,529 person-years of observation, we enhanced the previous population-based evaluation of multiple primary cancers after melanoma in the United States. We found an overall 28% increased risk of subsequent primary cancers, primarily owing to the nearly 9-fold risk of subsequent primary melanomas. These findings are based on a larger number of observed subsequent primary melanomas (3094 vs 1579) and are consistent with several other studies of multiple cancers after melanoma. In addition, we examined risks of subsequent primary melanomas according to characteristics of the initial primary melanoma, such as site and thickness, and we compared tumor thickness between first, second, and third melanomas with a thickness at diagnosis of less than 1.00 mm during the period 1997-2006 in comparison to 1988-1996 (data not shown).
We found a markedly increased risk of subsequent primary cancers may be an indication of genetic predisposition. Young age of onset of the initial cancer and multiple characteristics and nevi, are major determinants of melanoma risk but are not available in registry studies. In a recent genome-wide association study of melanoma in a group enhanced for genetic susceptibility, including individuals with multiple primary melanomas, GenoMEL (the Melanoma Genetics Consortium) identified several areas of association with melanoma. The strongest signals were in pigmentation genes MC1R and TYR, both plausible candidate genes for melanoma. The third locus was near MTAP and CDKN2A. Two of the markers of interest in this region were also significantly related to the number of nevi in a separate genome-wide association study of nevi. These findings identify common susceptibility alleles related to known risk factors for melanoma.

Although the relative risk for developing subsequent melanoma is not as high for older individuals as for those age 30, which was almost entirely owing to subsequent malignancy in those with a first melanoma before age 30. Given the substantially elevated risk of a subsequent primary melanoma in a group enhanced for genetic susceptibility, in addition to individuals with multiple primary melanomas, these results support continued long-term surveillance in melanoma survivors with complete skin examination.

Table 3. Risk of Subsequent Melanoma by Sex, Age, and Tumor Characteristics of Initial Melanoma Based on Data From the 9 SEER Registries, 1973-2006

<table>
<thead>
<tr>
<th>Characteristic of Initial Melanoma</th>
<th>Total (N=89,515)</th>
<th>Mean Age at Diagnosis, y</th>
<th>O:E (95% CI) EAR</th>
<th>Observed</th>
<th>Women (n=41,711)</th>
<th>Mean Age at Diagnosis, y</th>
<th>O:E (95% CI) EAR</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patient, y</td>
<td>30-49</td>
<td>915</td>
<td>41</td>
<td>8.74 (8.18-9.32)</td>
<td>24.15</td>
<td>519</td>
<td>42</td>
<td>9.36 (8.57-10.20)</td>
</tr>
<tr>
<td>≥50</td>
<td>1,967</td>
<td>65</td>
<td>8.23 (7.87-8.58)</td>
<td>43.89</td>
<td>1,395</td>
<td>65</td>
<td>7.91 (7.50-8.33)</td>
<td>55.66</td>
</tr>
<tr>
<td>Anatomic site</td>
<td>Head and neck</td>
<td>671</td>
<td>62</td>
<td>9.69 (9.07-10.45)</td>
<td>46.72</td>
<td>475</td>
<td>62</td>
<td>8.72 (7.96-9.54)</td>
</tr>
<tr>
<td>Trunk</td>
<td>1,151</td>
<td>53</td>
<td>8.79 (8.29-9.31)</td>
<td>35.31</td>
<td>866</td>
<td>55</td>
<td>8.55 (7.99-9.14)</td>
<td>41.86</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>707</td>
<td>55</td>
<td>8.03 (7.45-8.65)</td>
<td>30.79</td>
<td>442</td>
<td>58</td>
<td>8.10 (7.36-8.89)</td>
<td>43.19</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>532</td>
<td>51</td>
<td>8.57 (7.85-9.33)</td>
<td>25.65</td>
<td>182</td>
<td>52</td>
<td>9.18 (7.89-10.61)</td>
<td>40.65</td>
</tr>
<tr>
<td>Multisite/NOS</td>
<td>33</td>
<td>54</td>
<td>6.34 (5.20-8.10)</td>
<td>11.72</td>
<td>25</td>
<td>56</td>
<td>3.78 (2.44-5.58)</td>
<td>15.46</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; EAR, excess number of subsequent cancers per 10,000 person-years; ellipses, not applicable; O:E, observed to expected ratio (relative risk) of developing a subsequent melanoma; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results.

Table 4. Thickness of Multiple Primary Melanomas by Sex in the 9 SEER Registries, 1988-2008

<table>
<thead>
<tr>
<th>Tumor Thickness, mm</th>
<th>Multiple Cutaneous Malignant Melanomas</th>
<th>All Participants (N=64,047)</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.0</td>
<td>5133 (70.3)</td>
<td>1619 (77.9)</td>
<td>210 (82.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.0-2.0</td>
<td>1245 (17.1)</td>
<td>234 (11.3)</td>
<td>28 (11.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2.0-4.0</td>
<td>643 (8.8)</td>
<td>147 (7.1)</td>
<td>12 (4.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>280 (3.8)</td>
<td>78 (3.8)</td>
<td>5 (2.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Men (n=34,688) | | |
|----------------|-----------------------------|-----------------------------|-----|-----|-----|
| ≤1.0           | 3117 (68.9)               | 1017 (78.7)                 | 141 (81.5) |
| >1.0-2.0       | 805 (17.8)                | 157 (12.2)                  | 21 (12.1) |
| >2.0-4.0       | 411 (9.1)                 | 96 (7.4)                    | 9 (5.2) |
| >4.0           | 192 (4.2)                 | 22 (1.7)                    | 2 (1.2) |

| Women (n=29,239) | | |
|-----------------|-----------------------------|-----------------------------|-----|-----|-----|
| ≤1.0           | 2016 (72.6)               | 602 (80.7)                  | 69 (84.2) |
| >1.0-2.0       | 440 (15.9)                | 77 (10.3)                   | 7 (8.5) |
| >2.0-4.0       | 232 (8.4)                 | 51 (6.8)                    | 3 (3.7) |
| >4.0           | 88 (3.2)                  | 16 (2.1)                    | 3 (3.7) |

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

Data are presented as number (percentage) of participants. SEER tumor thickness data are available only for tumors diagnosed after 1988.
younger than 30, the EAR is much higher. Clinically, this translates into a larger number of subsequent primary melanomas, particularly among older men. Part of the risk for older individuals may result from increased outdoor activities after retirement. In a case-control study, older individuals spent more time outdoors than those who were still working.\textsuperscript{31} There also may be some effect of an age-related diminished immune response.\textsuperscript{14,42,43}

Of interest, patients with melanomas diagnosed on the head and neck region had higher risks of developing subsequent melanomas. These patients were also older compared with patients with melanoma diagnosed at other anatomic sites, and most of the head and neck melanomas were lentigo maligna melanomas, which are known to affect fair-skinned, older individuals with chronic sun exposure. The incidence of cutaneous head and neck melanoma has been increasing in the United States.\textsuperscript{2} Head and neck melanomas also have been reported to have a worse prognosis than melanomas at other anatomic sites.\textsuperscript{44,45} Some of the increased risk of second primary melanomas may be related to misclassification of local recurrence, similar to the thicker lesions, or it may be related to cumulative sun exposure. Given the poorer prognosis of these head and neck melanomas, along with an increased risk of developing subsequent melanomas, patients with melanomas on the head and neck should be monitored closely.

We found that second and third multiple primary melanomas were more likely to be thin at diagnosis than were the first of multiple primary melanomas. Thicknesses of lesions decreased with each subsequent melanoma diagnosis. These findings suggest that many patients diagnosed with melanoma are either being followed up closely or are learning the signs of melanoma and seeking subsequent medical care more quickly. However, we could not discount the calendar effect for these trends, which has been previously described. In the past few decades, an overall decrease of tumor thickness to prognostically more favorable levels has been observed in several countries.\textsuperscript{46} Despite the decreasing thickness of the subsequent primary melanomas, the percentage of lesions measuring 1 mm or thicker seems relatively high for individuals under close surveillance, which suggests that many of these patients are not being monitored closely.

The pattern of elevated risks for nonmelanoma subsequent cancers was generally consistent with that of the 2006 SEER monograph.\textsuperscript{1} As noted earlier, the highest risk within the first year for a second melanoma, NHL, chronic lymphocytic leukemia, and cancers of the salivary gland, kidney, and thyroid are likely owing to detection in the process of staging the initial melanoma. The diagnosis of NHL remained elevated in subsequent periods. Because reciprocal increases in subsequent primary cutaneous melanoma are seen after NHL,\textsuperscript{47-49} there may be shared risk factors, especially immunological defects, as suggested by the excess risks of both tumors in a variety of immunosuppressed populations.\textsuperscript{50,52}

As in the SEER monograph, subsequent breast and prostate cancers were the most frequent nonmelanoma cancers after a primary melanoma diagnosis. Although the risk of these tumors was fairly constant across most latency periods, there was some decline in prostate cancer risk among long-term survivors (\geq 20 years), suggesting that early medical surveillance may have contributed to the increased short-term risks. As noted earlier, the decrease in cancers with increasing latency could also be partially owing to individuals moving out of the registry areas. There is also some suggestion of shared hormonal or genetic mechanisms, such as \textit{BRCA2} mutations in breast cancer.\textsuperscript{53,54} Although epidemiological evidence of a hormonal role in melanoma is inconsistent,\textsuperscript{53} the changing ratio of female to male incidence after menopause suggests that hormonal variations and changing exposure patterns may contribute to these differences. It is also possible that the relationships with breast and prostate cancer may partly reflect correlates of higher socioeconomic status, including increased diagnostic surveillance.

The risk of soft tissue sarcoma was also increased more than 1 year after a diagnosis of melanoma. Although differentiating melanoma from soft tissue sarcoma may pose diagnostic difficulties, previous reports suggest that the association remains after careful histological review.\textsuperscript{55,56} Immunological defects, which have been linked to soft tissue sarcoma,\textsuperscript{55,56} such as iatrogenic immune suppression, may also contribute to the association with melanoma.

With 89,515 melanoma survivors and 12,559 subsequent cancers, of which 3094 were melanomas, the case numbers in this cohort are sufficiently large to allow review of a greater range of second cancer sites than is usually possible, as well as permitting analysis according to characteristics of the first melanoma. In addition, the data are of high quality, and 96% of the first and subsequent cancers were histologically confirmed by local pathologists. Our study also had certain limitations. Despite this high confirmation rate, there was no central specialist pathology review, and the possibility of confusing cutaneous recurrences and new primary tumors remains, particularly for thicker initial tumors. Also, second cancers that occurred among patients who moved outside of SEER areas may have been underscertained,\textsuperscript{57} which would lead to artificially reduced second cancer risks.

**CONCLUSIONS**

In the SEER program, patients with melanoma have approximately a 9-fold risk of developing a subsequent melanoma compared with the general population. Melanoma survivors are at an increased risk long after initial diagnosis for subsequent primary cancers, most likely owing to genetic susceptibility, behavioral risk factors, and increased medical surveillance. Although individuals with melanoma of the head and neck and patients younger than 30 years have higher relative risks of a subsequent melanoma, larger numbers of subsequent melanoma occur among those older than 30 years, particularly men. Although subsequent melanomas are more likely to be thinner than the initial melanomas, the percentage of thin melanomas could likely be increased. In addition to melanoma, survivors of melanoma are at increased risk of several other types of cancer, the most frequent of which are female breast cancer, prostate cancer, and NHL. Patients who have been diagnosed with melanoma, there-
fore, should remain under continued surveillance not only for melanoma recurrence but also for new primary malignancies and other cancers.

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