STUDY

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.

Design: Population-based registry study.

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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In 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 survivors[1] and that more than 20% of the new malignant tumors were also melanomas. Studies of multiple primary cancers are useful to etiological 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 monograph[1] 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

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

Characteristic	Total	Men	Women
No. of patients with melanoma	**89 515 (100.0)**	47 804 (53.4)	41 711 (46.6)
Median age at cancer diagnosis, y	54	56	52
Median year of cancer diagnosis	1997	1997	1997
Median person-years at risk	9.2	8.5	10.0
Age at cancer diagnosis, y			
<30	**7448** (8.3)	2746 (5.7)	4702 (11.3)
30-49	**30 534** (34.1)	14 514 (30.4)	16 020 (38.4)
≥50	**51 533** (57.6)	30 544 (63.9)	20 989 (50.3)
Site of melanoma			
Head and neck	**16 316** (18.2)	10 834 (22.7)	5482 (13.1)
Trunk	**30 402** (34.0)	19 857 (41.5)	10 545 (25.3)
Upper limbs	**20 944** (23.4)	10 216 (21.4)	10 728 (25.7)
Lower limbs	**18 138** (20.3)	4515 (9.4)	13 623 (32.7)
Multisite/NOS	**3715** (4.2)	2382 (5.0)	1333 (3.2)
Histological analysis of melanoma			
SSM	**35 506** (39.7)	17 731 (37.1)	17 775 (42.6)
LMM	**7416** (8.3)	4359 (9.1)	3057 (7.3)
NM	**5630** (6.3)	3526 (7.4)	2104 (5.0)
ALM	**643** (0.7)	287 (0.6)	356 (0.9)
NOS	**37 278** (41.6)	20 169 (42.2)	17 109 (41.0)
Other[b]	**2207** (2.5)	1269 (2.7)	938 (2.2)
Unknown[c]	**835** (0.9)	463 (1.0)	372 (0.9)
Initial treatment			
Any radiation	**1886** (2.1)	1296 (2.7)	590 (1.4)
With surgical treatment	**929** (1.0)	626 (1.3)	303 (0.7)
Without surgical treatment	**957** (1.1)	670 (1.4)	287 (0.7)
No radiation	**87 629** (97.9)	46 508 (97.3)	41 121 (98.6)
With surgical treatment	**83 543** (93.3)	44 219 (92.5)	39 324 (94.3)
Without surgical treatment	**4086** (4.6)	2289 (4.8)	1797 (4.3)
No. of patients with multiple cancers[d]			
2 Cancers only	**9348** (10.4)	5701 (11.9)	3647 (8.7)
3 Cancers only	**1290** (1.4)	842 (1.8)	448 (1.1)
≥4 Cancers	**219** (0.2)	148 (0.3)	71 (0.2)
Histologically confirmed, %[d]			
First and second cancers	96.8	96.5	97.2
All subsequent cancers	96.4	96.1	96.9
Initial melanoma only	2.8	3.0	2.4

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.

[a] Data are given as number (percentage) of participants 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 subsequent new primary cancer diagnosis. New primary cancers include cancers of the lip, tongue, tonsil, salivary gland, gums, floor of mouth, pharynx, esophagus, stomach, small intestine, colon, rectum, anus, liver, gallbladder, pancreas, nose, middle ear, larynx, lung, trachea, mediastinum, breast, cervix, ovary, vagina, vulva, uterus, prostate, testis, penis, bladder, kidney, ureter, brain, thyroid, thymus, adrenal gland, bones, soft tissue, mesothelioma, non-Hodgkin lymphoma, Hodgkin lymphoma, leukemia, and melanoma.

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).[1] 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 Census Bureau rankings.[4] The study was limited to whites because of the small numbers of patients with melanoma in other racial groups. The participants were reported to 1 of 9 population-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, Detroit, 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 Classification of Diseases in Oncology, 3rd revision* (*ICD-O-3*),[5] as follows: superficial spreading melanoma (category 8743), lentigo maligna melanoma (8742), acral lentiginous melanoma (8744), and nodular melanoma (8721). Information on histological subtype is limited because there is no centralized pathological review, and 42.5% 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 editing, case-finding audits, reabstracting of cases, and various educational programs. Standards have established a case ascertainment rate of 98%, a follow-up rate of 95%, and an overall microscopic diagnostic confirmation rate of more than 98%.[6]

Person-years at risk (PYR) were accumulated for each participant beginning 2 months after initial melanoma diagnosis and ending 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 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 excess absolute risk (EAR) per 10 000 person-years as $([O - E] / PYR) \times 10\,000$.[1] Relative risk measures the fold difference (eg, 2-fold) between 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 available SEER data.[8]

RESULTS

A total of 89 515 patients survived 2 months or longer following a diagnosis of a primary melanoma. The patients were followed up for a maximum of 34 years (median, 9.2 years); 53.4% of the patients were men and 46.6% were women (**Table 1**). The median age at first melanoma 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

Table 2. Risk of Selected Subsequent Primary Cancers After Melanoma in the 9 SEER Registries From 1973-2006[a]

Subsequent Primary Cancer	Time Since First Primary Cutaneous Melanoma Diagnosis													
	2 mo-1 y (N=89 515)		1-5 y (n=81 921)		5-10 y (n=54 958)		10-20 y (n=33 935)		>20 y (n=11 044)		Total (N=89 515)			
	Observed[b]	O:E	Observed[b]	O:E	Observed[b]	O:E	Observed[b]	O:E	Observed[b]	O:E	Observed[b,c]	Expected	O:E	EAR
Person-years at risk for melanoma survivors	71 088	...	268 018	...	217 890	...	209 675	...	55 571	...	822 241	...	...	...
All sites	1312	1.78[d]	3959	1.38[d]	3233	1.27[d]	3122	1.12[d]	933	1.07	**12 559**	9796	1.28[d] (1.26-1.30)	33.60
Melanoma of the skin	450	16.94[d]	1024	9.80[d]	758	8.15[d]	676	6.62[d]	186	5.58[d]	**3094**	359	8.61[d] (8.31-8.92)	33.26
Salivary gland	6	3.22[d]	13	1.81	7	1.11	14	2.04[d]	6	2.75[d]	**46**	24	1.89[d] (1.38-2.52)	0.26
Small intestine	3	1.21	22	2.26[d]	11	1.26	10	1.01	4	1.18	**50**	34	1.46[d] (1.08-1.92)	0.19
Female breast	86	1.12	355	1.14[d]	334	1.14[d]	347	0.99	134	1.15	**1256**	1146	1.10[d] (1.04-1.16)	1.34
Prostate	195	1.32[d]	711	1.24[d]	599	1.19[d]	547	1.02	148	0.96	**2200**	1913	1.15[d] (1.10-1.20)	3.49
Kidney	36	2.18[d]	88	1.36[d]	71	1.24	67	1.06	23	1.10	**285**	223	1.28[d] (1.13-1.44)	0.76
Ocular melanoma	0	0.00	7	1.72	5	1.42	11	2.91[d]	1	0.84	**24**	14	1.77[d] (1.13-2.63)	0.13
Thyroid	38	5.19[d]	50	1.73[d]	35	1.39	40	1.48[d]	7	0.82	**170**	97	1.75[d] (1.50-2.04)	0.89
Soft-tissue sarcoma	6	1.75	28	2.10[d]	20	1.71[d]	28	2.19[d]	9	2.15	**91**	45	2.00[d] (1.61-2.46)	0.55
Non-Hodgkin lymphoma	65	2.32[d]	134	1.22[d]	126	1.28[d]	111	1.00	45	1.21	**481**	384	1.25[d] (1.14-1.37)	1.18
Chronic lymphocytic leukemia	15	1.81[d]	39	1.22	34	1.20	31	1.00	13	1.26	**132**	110	1.20[d] (1.00-1.42)	0.27

Abbreviations: 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.

[a] Only subsequent cancers that were significantly elevated after cutaneous multiple melanoma are presented in the table.

[b] Data are given as the observed number of melanoma survivors developing subsequent primary cancer unless otherwise indicated.

[c] There are 4730 subsequent primary cancers that are not shown in the table. Only those sites where the relative risk (O:E) was significantly elevated are shown. Those not shown include cancers of the lip, tongue, tonsil, gums, floor of mouth, pharynx, esophagus, stomach, colon, rectum, anus, liver, gallbladder, pancreas, nose, middle ear, larynx, lung, trachea, mediastinum, cervix, ovary, vagina, vulva, uterus, testis, penis, bladder, ureter, brain, thymus, adrenal gland, bones, mesothelioma, Hodgkin lymphoma, and leukemia (other than chronic lymphocytic leukemia).

[d] $P < .05$.

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 9348 patients (10.4%) with 2 primary cancers, 1290 (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 25% 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 [95% CI, 4.80-6.44]). The relative risk of subsequent primary melanoma was similar for men and women (O:E, 8.40 [95% CI, 8.04-8.78]; EAR, 43/10 000 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 (1.10; 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

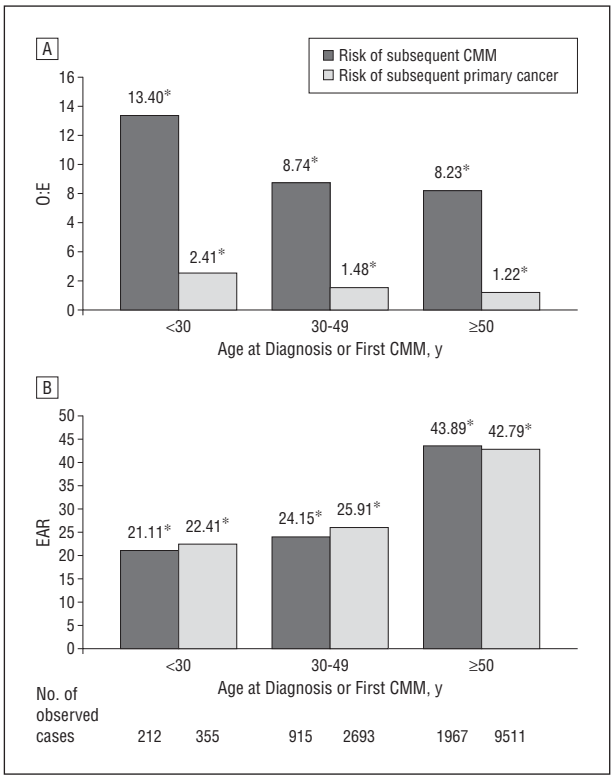

Figure. Risk of subsequent primary cancers after cutaneous malignant melanoma (CMM) diagnosis by age groups in the 9 SEER (Surveillance, Epidemiology, and End Results) Registries, 1973-2006. A, Relative risk (observed to expected ratio [O:E]). B, Excess absolute risk (EAR) is defined as the excess number of subsequent cancers per 10 000 person-years. *$P<.05$.

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).

The lack of central review of histological characteristics limited our ability to fully evaluate the risk of subsequent melanomas according to histological type, but there did not appear to be large differences. Based on limited data, risks of subsequent melanomas appeared lower for first acral lentiginous melanoma (data not shown). Risks by thickness were also difficult to interpret. Overall, patients whose first melanoma was more than 2.01 mm thick (based on fewer observations) had higher risks for developing subsequent melanomas (Table 3). This group, however, is the group that is most likely to have misclassification of second melanomas owing to misdiagnosis of local recurrence as a new primary melanoma.

Table 4 compares thickness of multiple primary melanomas. Second melanomas were significantly more likely to be thin compared with the first of multiple primary melanomas (77.9% vs 70.3% diagnosed at <1.00 mm, respectively; $P<.001$). Also, women had a higher percentage of thin melanomas than did men. However, we could not discount a calendar effect for these trends. When we stratified the thickness of subsequent melanomas by calendar periods, there was a higher percentage of 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).

COMMENT

With the expansion to 89 515 cutaneous malignant melanoma survivors and an additional 308 529 person-years of observation, we enhanced the previous[1] 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)[1] and are consistent with several other studies of multiple cancers after melanoma.[9-27] 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 multiple primary melanomas.

We found that the risk of subsequent primary melanomas decreased somewhat with increasing latency but remained quite elevated more than 20 years after diagnosis of a first primary melanoma. The higher risk within the first year could well be owing to surveillance[28] and detection of changing pigmented lesions that have been influenced by the same etiological factors as the initial melanoma. Within the setting of families at high risk of developing melanoma, several pigmented lesions can change during a limited period.[29,30] Initial staging of these individuals for metastatic disease could also contribute to the increased risk within the first year for cancers of the thyroid, salivary gland, and kidney, as well as NHL and chronic lymphocytic leukemia. The decline in risk of melanoma over time could also reflect decreasing risk of melanoma owing to changed

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

Characteristic of Initial Melanoma	Total (N=89 515)				Men (n=47 804)				Women (n=41 711)			
	Observed[a]	Mean Age at Diagnosis, y	O:E (95% CI)	EAR	Observed[a]	Mean Age at Diagnosis, y	O:E (95% CI)	EAR	Observed[a]	Mean Age at Diagnosis, y	O:E (95% CI)	EAR
Person-years at risk for melanoma survivors	**822 240**	. . .	. . .	. . .	405 693	. . .	. . .	. . .	. . .	416 547	. . .	. . .
Age of patient, y												
<30	**212**	26	13.40 (11.66-15.33)	21.11	76	25	15.53 (12.24-19.44)	21.41	136	26	12.45 (10.44-14.73)	20.95
30-49	**915**	41	8.74 (8.18-9.32)	24.15	519	42	9.36 (8.57-10.20)	30.19	396	40	8.03 (7.26-8.86)	19.05
≥50	**1967**	65	8.23 (7.87-8.60)	43.89	1395	65	7.91 (7.50-8.33)	55.66	572	66	9.16 (8.42-9.94)	29.14
Anatomic site												
Head and neck	**671**	62	9.69 (8.97-10.45)	46.72	475	62	8.72 (7.96-9.54)	51.59	196	61	13.22 (11.43-15.20)	38.32
Trunk	**1151**	53	8.79 (8.29-9.31)	35.31	866	55	8.55 (7.99-9.14)	41.86	285	46	9.60 (8.52-10.78)	24.03
Upper limbs	**707**	55	8.03 (7.45-8.65)	30.79	442	58	8.10 (7.36-8.89)	43.19	265	51	7.92 (7.00-8.94)	20.80
Lower limbs and hip	**532**	51	8.57 (7.85-9.33)	25.65	182	52	9.18 (7.89-10.61)	40.65	350	51	8.28 (7.44-9.19)	21.48
Multisite/NOS	**33**	54	3.63 (2.50-5.10)	11.76	25	56	3.78 (2.44-5.58)	15.46	8	45	3.25 (1.40-6.40)	6.55
Tumor thickness, mm[b]												
0.01-1.00	**1183**	56	9.26 (8.74-9.81)	39.72	739	59	8.62 (8.01-9.26)	48.99	444	52	10.58 (9.62-11.61)	30.38
1.01-2.00	**296**	59	10.03 (8.92-11.24)	45.68	202	60	9.62 (8.34-11.04)	55.62	94	57	11.04 (8.92-13.51)	33.15
2.01-4.00	**190**	62	13.28 (11.46-15.31)	66.11	131	63	12.64 (10.57-15.00)	80.28	59	61	14.96 (11.39-19.30)	47.67
>4.00	**65**	66	11.64 (8.98-14.83)	61.12	52	66	12.31 (9.20-16.15)	81.15	13	67	9.54 (5.07-16.31)	30.36

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.

[a] Data are given as the observed number of melanoma survivors developing subsequent melanoma unless otherwise indicated.

[b] SEER tumor thickness data are available only for tumors diagnosed after 1988.

behavior, such as decreased sun exposure and enhanced sun-protective behaviors after an initial diagnosis of melanoma. In US population registry studies, migration of individuals out of the area covered by the cancer registry is always a concern and could account for some decrease in observed subsequent primary melanomas many years after the initial melanoma diagnosis. Currently, there is no international consensus for follow-up guidelines for patients with melanoma. Most investigators who assessed follow-up surveillance and the development of subsequent primary melanomas advocate lifelong follow-up.[14,16,31-35] Given that the substantially elevated risk of a subsequent primary melanoma remains more than 20 years after the initial melanoma diagnosis, these results support continued long-term surveillance in melanoma survivors with complete skin examination.

Young age of onset of the initial cancer and multiple primary cancers may be an indication of genetic predisposition.[36] We found a markedly increased risk of subsequent malignancy in those with a first melanoma before age 30, which was almost entirely owing to subsequent melanomas. Host susceptibility factors, such as pigmentary characteristics[37] and nevi,[38] 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*.[39] 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.[40] These findings identify common susceptibility alleles related to known risk factors for melanoma.

Table 4. Thickness of Multiple Primary Melanomas by Sex in the 9 SEER Registries, 1988-2006[a]

Tumor Thickness, mm	Multiple Cutaneous Malignant Melanomas		
	First	Second	Third
All Participants (N=64 047)			
≤1.0	5133 (70.3)	1619 (77.9)	210 (82.4)
>1.0-2.0	1245 (17.1)	234 (11.3)	28 (11.0)
>2.0-4.0	643 (8.8)	147 (7.1)	12 (4.7)
>4.0	280 (3.8)	78 (3.8)	5 (2.0)
Men (n=34 808)			
≤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.

[a] Data are presented as number (percentage) of participants. SEER tumor thickness data are available only for tumors diagnosed after 1988.

Although the relative risk for developing subsequent melanoma is not as high for older individuals as for those

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.[41] There also may be some effect of an age-related diminished immune response.[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.[2] Head and neck melanomas also have been reported to have a worse prognosis than melanomas at other anatomic sites.[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.[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.[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,[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.[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 (≥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 *BRCA2* mutations in breast cancer.[53,54] Although epidemiological evidence of a hormonal role in melanoma is inconsistent,[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.[55,56] Immunological defects, which have been linked to soft tissue sarcoma,[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 underascertained,[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 50 years, particularly men. Although subsequent melanomas are more likely to be thin 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 melanomas and other cancers.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Bradford, Freedman, Goldstein, and Tucker. *Acquisition of data*: Bradford and Freedman. *Analysis and interpretation of the data*: Bradford, Freedman, Goldstein, and Tucker. *Drafting of the manuscript*: Bradford and Freedman. *Critical revision of the manuscript for important intellectual content*: Bradford, Freedman, Goldstein, and Tucker. *Statistical analysis*: Bradford. *Obtained funding*: Tucker. *Administrative, technical, and material support*: Bradford, Freedman, and Tucker. *Study supervision*: Freedman and Tucker.
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Archives *Web Quiz Winner*

Congratulations to the winner of our December quiz, Denis Malvy, MD, PhD, Department of Internal Medicine and Tropical Diseases, Hôpital Saint-André, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France. The correct answer to our December challenge was *primary cutaneous nocardiosis*. For a complete discussion of this case, see the Off-Center Fold section in the January *Archives* (Hartford OA, Pothiawala GA, Goldman GD. Ulcerated facial nodules in a renal transplant recipient. *Arch Dermatol*. 2010;146[1]: 81-86).

Be sure to visit the *Archives of Dermatology* Web site (http://www.archdermatol.com) to try your hand at the interactive quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month's print edition of the *Archives*. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of *The Art of JAMA II*.