Original Investigation

Distribution of Subsequent Primary Invasive Melanomas Following a First Primary Invasive or In Situ Melanoma Queensland, Australia, 1982-2010

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IMPORTANCE Melanoma survivors are known to have a highly elevated risk of subsequent primary melanomas.

OBJECTIVE To determine the relative risk of subsequent primary invasive melanomas following a first primary invasive or in situ melanoma, with a focus on body site.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study was conducted using population-based administrative data for melanoma diagnoses collected by the Queensland Cancer Registry, Queensland, Australia. Deidentified records of all cases of melanoma among Queensland residents during the period 1982-2005 were obtained and reviewed to December 31, 2010. There were 39 668 eligible cases of first primary invasive melanoma and 22 845 cases of first primary in situ melanoma.

MAIN OUTCOMES AND MEASURES Standardized incidence ratios (SIRs), a proxy measure for relative risk, were calculated by dividing the observed number of subsequent primary invasive melanomas by the product of the strata-specific incidence rates that occurred in the general population and the cumulative time at risk for the cohort. Synchronous subsequent melanomas (diagnosed within 60 days of the first primary melanoma) were excluded. Differences between SIRs were assessed using multivariate negative binomial regression adjusted for sex, age group, time to second diagnosis, and body site and expressed in terms of adjusted SIR ratios with corresponding 95% CIs.

RESULTS There were 5358 subsequent primary invasive melanomas diagnosed, resulting in SIRs of 5.42 (95% CI, 5.23-5.61) and 4.59 (4.37-4.82) for persons with a first primary invasive or in situ melanoma, respectively. The SIRs remained elevated throughout the follow-up period. In general, subsequent primary invasive melanomas were more likely to occur at the same body site as the initial invasive or in situ melanoma. The largest relative risk was for females with a first primary invasive melanoma on the head followed by a subsequent primary invasive melanoma also on the head (SIR, 13.32; 95% CI, 10.28-16.98).

CONCLUSIONS AND RELEVANCE Melanoma survivors require ongoing surveillance, with particular attention required for the body site of the initial lesion. Clinical practice guidelines have recognized the importance of monitoring for people with invasive melanoma; the results of the present study highlight the need for similar levels of supervision for those with a diagnosis of in situ melanoma.

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Melanoma is a major public health issue in Australia, particularly within the northeastern state of Queensland, which has the highest incidence rates of skin cancer in the world.[1,2] Incidence rates for invasive melanoma in Queensland[3] are more than 3 times those for the United States and almost 6 times higher than the average throughout Europe.[4] In addition, the incidence of in situ melanoma in Queensland has risen markedly since the 1980s, with rates now approaching levels similar to those of invasive melanoma.[2] Comparable data on in situ melanomas are not routinely reported for other countries, making benchmarking difficult.

Melanoma survivors are faced with an increased likelihood of developing subsequent melanomas. Australians with a first primary invasive melanoma are reported[5,6] to have a 6- to 7-fold higher risk of a second invasive melanoma compared with the general population. Although some authors[7,8] have found that the occurrence of subsequent primary invasive melanomas are correlated with the body site of the original invasive melanoma, to our knowledge, the relative risks by site have not been quantified. Furthermore, a small number of studies[9,10] have shown an elevated risk of subsequent primary invasive melanoma following an initial primary in situ melanoma; however, information is lacking on the relative risks for different combinations of body sites. We therefore conducted an examination of whether body site, sex, age group, and time since diagnosis influence the probability of developing subsequent invasive primary melanomas following a first invasive or in situ primary melanoma in a high-risk population.

Methods

Data Collection

A retrospective cohort study was conducted. Deidentified records for cases of invasive and in situ melanoma were obtained from the Queensland Cancer Registry. Notification of all cancers diagnosed for Queensland residents, apart from basal and squamous cell skin cancers, to the registry is required by law.[3] Ethics board approval was not required because this study was conducted using deidentified data.

Available variables included sex, age at diagnosis, tumor behavior, body site of the melanoma, date of diagnosis, and date of death (when applicable). Body site was categorized as head (including the face, ears, scalp, and neck), trunk, upper extremities (including the shoulders), and lower extremities (including the hips). Multiple primary melanomas for the same person were linked through the use of unique study numbers.

The cohort included all Queensland residents aged 15 years or older who received a diagnosis of a first primary invasive or in situ melanoma (*International Classification of Diseases* O-3 code C44 and morphology codes M872-M879) between January 1, 1982, and December 31, 2005. Those who died within 2 months of diagnosis were excluded.

Patients' records were reviewed until December 31, 2010, potentially allowing a minimum of 5 years and a maximum of 29 years to ascertain the occurrence of subsequent primary invasive melanomas. Synchronous primary tumors (defined as melanomas diagnosed within 2 months of the first primary tumor[11]) were excluded because they were more likely to have been diagnosed as a result of detection bias.[12] Additionally, we elected to exclude in situ second primary melanomas because of the risk of possible overdiagnosis.

If a person had more than 1 subsequent primary invasive melanoma that occurred at different body sites, these were included in the study separately. However, only the first occurrence of a subsequent melanoma at a given body site was retained for an individual person, and with evaluation of the body as a whole, only the next primary invasive melanoma (irrespective of body site) following the index melanoma was considered.

Statistical Analysis

Standardized incidence ratios (SIRs) were used to approximate the relative risk of a melanoma survivor receiving a subsequent primary invasive melanoma diagnosis compared with a person in the general population of Queensland. The SIR estimates were calculated using a 3-step process. First, the time at risk for each eligible member of the study was measured from 2 months after diagnosis until the end of 2010, date of death, or date of diagnosis of a subsequent invasive melanoma, whichever came first. Second, the expected number of subsequent primary invasive melanomas was calculated from the product of the person-years at risk and the incidence rate experienced by the Queensland population matched by sex, age group, year of diagnosis, and body site (when relevant). Finally, the observed number of cases was divided by the expected number, and corresponding 95% CIs were derived using a Poisson distribution.[13]

The degree and significance of differences between SIRs was then formally tested using negative binomial regression. Models were fitted with the observed number of subsequent primary invasive melanomas as the dependent variable, offset by the log of the expected value. Sex, age group, time to second diagnosis, and body site were included in each of the models as confounding variables. The resultant adjusted SIR ratios were considered statistically significant at $P < .05$ for the individual category compared with the reference category, as well as for the overall effect of that variable. The above analyses were stratified by the behavior of the first primary melanoma (invasive or in situ), as well as by sex, age at first diagnosis, time to second diagnosis, and site of the subsequent tumor.

Results

Between January 1, 1982, and December 31, 2005, a total of 39 668 eligible cases of first primary invasive melanoma and 22 845 first primary in situ melanomas were identified. The median follow-up times, excluding the first 2 months after the initial diagnosis, were 9.7 years (interquartile range, 5.7-15.5 years) and 9.4 years (interquartile range, 6.3-14.2 years), respectively. A total of 5358 subsequent primary invasive melanomas diagnosed in 4733 people were included in the study, of which 3520 melanomas (65.7%) occurred following a first pri-

Table 1. Characteristics of the Study Cohort

Characteristic	First Primary Invasive Melanoma, No. (%) of Patients (n = 39 668)	Subsequent Primary Invasive Melanomas, No. (%) of Melanomas (n = 3520)[a]	First Primary In Situ Melanoma, No. (%) of Patients (n = 22 845)	Subsequent Primary Invasive Melanomas, No. (%) of Melanomas (n = 1838)[a]
Sex				
Male	22 128 (55.8)	2374 (67.4)	12 426 (54.4)	1221 (66.4)
Female	17 540 (44.2)	1146 (32.6)	10 419 (45.6)	617 (33.6)
Age at diagnosis, y				
15-49	15 357 (38.7)	570 (16.2)	7061 (30.9)	196 (10.7)
50-64	11 152 (28.1)	912 (25.9)	7287 (31.9)	450 (24.5)
≥65	13 159 (33.2)	2038 (57.9)	8497 (37.2)	1192 (64.9)
Time to second diagnosis				
2 mo to <1 y	NA	325 (9.2)	NA	144 (7.8)
1 y to <5 y	NA	1081 (30.7)	NA	574 (31.2)
5 y to <10 y	NA	994 (28.2)	NA	589 (32.0)
≥10 y	NA	1120 (31.8)	NA	531 (28.9)
Site of melanoma				
Head	5997 (15.1)	690 (19.6)	6928 (30.3)	353 (19.2)
Trunk	13 367 (33.7)	1195 (33.9)	6417 (28.1)	604 (32.9)
Upper extremities	9218 (23.2)	933 (26.5)	5498 (24.1)	470 (25.6)
Lower extremities	8682 (21.9)	661 (18.8)	3476 (15.2)	312 (17.0)
Not specified	2404 (6.1)	41 (1.2)	526 (2.3)	99 (5.4)

Abbreviation: NA, not applicable.

[a] Numbers of subsequent primary invasive melanomas may represent more than 1 per person.

mary invasive melanoma and the remaining 1838 tumors (34.3%) following a first primary in situ melanoma. Of those with a subsequently diagnosed primary invasive melanoma, 4184 people (88.4%) had only 1 subsequent melanoma, 482 people (10.2%) had subsequent melanomas at 2 different body sites, 58 individuals (1.2%) had subsequent melanomas on 3 different sites, and 9 people (0.2%) had a subsequent melanoma on each of the 4 broad body sites. In regard to thickness, 25.0% and 28.6% of subsequent primary invasive melanomas following a first in situ or invasive melanoma, respectively, were more than 1 mm thick at diagnosis.

Other details of the study cohort are reported in **Table 1**. The most notable contrasts between first primary invasive and in situ melanomas were that a higher proportion of invasive tumors was diagnosed in patients younger than 50 years (38.7% vs 30.9%; $P < .001$) and that in situ melanomas were far more likely to occur on the head than were invasive melanomas (30.3% vs 15.1%; $P < .001$).

Although a significant difference was found in the distribution of the time to diagnosis of a subsequent primary invasive melanoma depending on whether the original melanoma was invasive or in situ ($P = .007$), there was no obvious pattern seen in the data (Table 1). Excluding cases in which the site was not reported, there was no evidence of a difference in body site of subsequent primary invasive melanomas by the behavior of the first melanoma ($P = .83$).

Relative Risk of Subsequent Primary Invasive Melanomas

People with a first primary invasive melanoma were 5.4 times more likely to develop a subsequently diagnosed primary invasive melanoma at any site compared with the general population (SIR, 5.42; 95% CI, 5.23-5.61). The risk was 4.6 times higher for those with an in situ first primary melanoma (SIR, 4.59; 95% CI, 4.37-4.82).

Site of First Primary Melanoma

The body site of the first primary invasive melanoma had no effect ($P = .27$) on the overall relative risk of a subsequent invasive primary melanoma (**Table 2**). There was, however, a significant difference ($P = .007$) by the body site of a first primary in situ melanoma; people who had an initial in situ melanoma on body sites other than their head had a higher relative risk of a subsequent primary invasive melanoma, particularly when the original lesion occurred on the lower extremities (adjusted SIR ratio, 1.34; 95% CI, 1.14-1.57).

Sex

Females with a first primary invasive melanoma on the head were relatively more likely (adjusted SIR ratio, 1.35; 95% CI, 1.08-1.69) to develop a subsequently diagnosed primary invasive melanoma compared with males (**Table 3**). In contrast, females had a less-elevated relative risk (adjusted SIR ratio, 0.84; 95% CI, 0.71-0.98) of a subsequent primary invasive melanoma than males if their initial invasive lesion was on the lower extremities. No significant differences by sex were found following a first primary in situ melanoma (**Table 4**).

Age at First Diagnosis

Variation by age in the relative risk of a subsequent invasive melanoma was found following a first primary invasive melanoma, but not for a first primary in situ melanoma (Table 2). Further analysis by body site showed that the effect of age was

Table 2. SIRs and Adj SIR Ratios for Subsequent Primary Invasive Melanomas Following a First Primary Invasive or In Situ Melanoma, Queensland, 1982-2010

	First Primary Melanoma					
	Invasive			In Situ		
Characteristic[a]	Obs	SIR	Adj SIR Ratio (95% CI)	Obs	SIR	Adj SIR Ratio (95% CI)
Site of first primary melanoma			*P* = .27			*P* = .007
Head	465	5.21	1 [Reference]	483	3.99	1 [Reference]
Trunk	1096	5.52	1.07 (0.95-1.22)	473	4.80	**1.22 (1.06-1.40)**
Upper extremities	739	5.38	1.04 (0.91-1.18)	392	4.83	**1.18 (1.02-1.36)**
Lower extremities	654	5.64	1.07 (0.94-1.22)	239	5.37	**1.34 (1.14-1.57)**
Not specified	143	4.68	0.90 (0.74-1.08)	49	4.44	1.21 (0.92-1.60)
Sex			*P* = .68			*P* = .11
Male	2057	5.43	1 [Reference]	1067	4.44	1 [Reference]
Female	1040	5.39	0.98 (0.90-1.07)	569	4.90	1.10 (0.98-1.23)
Age at first diagnosis, y			*P* = .007			*P* = .52
15-49	911	5.66	**1.18 (1.06-1.31)**	348	4.99	1.08 (0.94-1.25)
50-64	1024	5.44	1.10 (1.00-1.22)	563	4.57	1.02 (0.90-1.14)
≥65	1162	5.23	1 [Reference]	725	4.43	1 [Reference]
Time between diagnoses			*P* < .001			*P* = .39
2 mo to <1 y	315	7.71	**1.47 (1.28-1.69)**	142	5.53	1.14 (0.94-1.39)
1 y to <5 y	1008	5.63	1.10 (0.99-1.22)	545	4.50	0.96 (0.84-1.10)
5 y to <10 y	877	5.21	1.02 (0.92-1.13)	511	4.55	1.02 (0.90-1.17)
≥10 y	897	4.89	1 [Reference]	438	4.50	1 [Reference]
Site of subsequent primary invasive melanoma[b]			*P* < .001			*P* = .02
Head	690	5.48	1 [Reference]	353	4.31	1 [Reference]
Trunk	1195	6.01	1.03 (0.92-1.16)	604	4.99	1.16 (1.00-1.35)
Upper extremities	933	6.02	1.06 (0.94-1.19)	470	4.84	1.10 (0.95-1.29)
Lower extremities	661	5.43	0.94 (0.83-1.07)	312	4.21	0.94 (0.79-1.11)
Not specified	41	1.01	**0.18 (0.13-0.24)**	99	3.91	0.90 (0.71-1.14)

Abbreviations: Adj, adjusted; Obs, observed; SIR, standardized incidence ratio.

[a] *P* values represent the statistical significance of the overall effect for the variable. Adjusted SIR ratios shown in boldface type are statistically significant (*P* < .05).

[b] Numbers by site of subsequent primary invasive melanomas may represent more than 1 per person.

most prominent when the first primary invasive melanoma occurred on the trunk (Table 3). Within that subgroup, persons aged 15 to 49 years had an adjusted SIR ratio of 1.26 (95% CI, 1.08-1.46) compared with those 65 years or older.

Time Between Diagnosis

Despite the SIRs remaining elevated for all periods to the end of follow-up, the relative risk of a subsequent primary invasive melanoma was usually highest in the first year than it was 1 or more years after the initial diagnosis of a primary invasive melanoma (Tables 2 and 3). Compared with 10 or more years after diagnosis, the adjusted SIR ratios within 1 year of the original diagnosis were significant for first primary invasive melanomas that occurred on the head (1.61; 95% CI, 1.14-2.28), trunk (1.55; 95% CI, 1.26-1.92), or upper extremities (1.64; 95% CI, 1.27-2.12). Although the SIRs also tended to be higher in the first year after diagnosis among the in situ cohort, there was no clear pattern in the relative risks by time between diagnoses following a first primary in situ melanoma.

Site of Subsequent Primary Invasive Melanomas

The body site at greatest relative risk for a subsequent primary invasive melanoma was typically the same as the site of the first primary invasive or in situ melanoma (Tables 3 and 4 and **Figure**). This relationship was especially distinct following a first primary melanoma on the head. In particular, females with a first primary invasive melanoma on the head were 13 times more likely (SIR, 13.32; 95% CI, 10.28-16.98) to develop a subsequently diagnosed primary invasive melanoma on the head compared with the general population (Figure). A strong association was also found following a first primary invasive melanoma on the lower extremities, with the relative risk of a subsequent primary invasive melanoma occurring on the lower extremities being significantly higher (*P* < .001) than for any other body site. However, there was no significant difference (*P* = .41) observed in subsequent relative risk by body site for persons with a first primary in situ melanoma on the lower extremities.

Table 3. SIRs and Adj SIR Ratios for Subsequent Primary Invasive Melanomas by Site of First Primary Invasive Melanoma, Queensland, 1982-2010

Characteristic[a]	Site of First Primary Invasive Melanoma														
	Head			Trunk			Upper Extremities			Lower Extremities			Not Specified		
	Obs	SIR	Adj SIR Ratio (95% CI)	Obs	SIR	Adj SIR Ratio (95% CI)	Obs	SIR	Adj SIR Ratio (95% CI)	Obs	SIR	Adj SIR Ratio (95% CI)	Obs	SIR	Adj SIR Ratio (95% CI)
Sex			*P* = .009			*P* = .44			*P* = .20			*P* = .03			*P* = .27
Male	316	4.83	1 [Reference]	880	5.60	1 [Reference]	465	5.53	1 [Reference]	307	6.01	1 [Reference]	89	4.32	1 [Reference]
Female	149	6.28	**1.35 (1.08-1.69)**	216	5.21	0.94 (0.81-1.09)	274	5.15	0.91 (0.78-1.05)	347	5.36	**0.84 (0.71-0.98)**	54	5.45	1.21 (0.86-1.70)
Age at first diagnosis, y			*P* = .07			*P* = .009			*P* = .24			*P* = .84			*P* = .39
15-49	75	4.83	1.13 (0.85-1.51)	363	5.90	**1.26 (1.08-1.46)**	197	5.61	1.17 (0.97-1.41)	229	5.72	1.06 (0.87-1.28)	47	5.39	1.33 (0.88-2.01)
50-64	148	5.71	1.31 (1.04-1.65)	376	5.52	1.11 (0.97-1.28)	240	5.24	1.08 (0.92-1.27)	208	5.46	1.01 (0.83-1.22)	52	4.94	1.18 (0.80-1.74)
≥65	242	5.07	1 [Reference]	357	5.16	1 [Reference]	302	5.35	1 [Reference]	217	5.74	1 [Reference]	44	3.90	1 [Reference]
Time between diagnoses			*P* = .03			*P* < .001			*P* = .002			*P* = .06			*P* = .28
2 mo to <1 y	55	7.25	**1.61 (1.14-2.28)**	111	8.13	**1.55 (1.26-1.92)**	82	8.46	**1.64 (1.27-2.12)**	61	8.08	1.36 (1.02-1.82)	6	2.56	0.48 (0.21-1.11)
1 y to <5 y	172	5.53	1.21 (0.93-1.58)	360	5.83	1.13 (0.98-1.30)	230	5.27	1.10 (0.91-1.31)	210	6.14	1.05 (0.86-1.28)	36	4.27	0.80 (0.53-1.20)
5 y to <10 y	129	4.95	1.02 (0.78-1.34)	311	5.21	1.04 (0.90-1.20)	226	5.54	1.13 (0.95-1.35)	170	5.04	0.91 (0.74-1.11)	41	5.14	0.97 (0.66-1.41)
≥10 y	109	4.46	1 [Reference]	314	4.94	1 [Reference]	201	4.65	1 [Reference]	213	5.27	1 [Reference]	60	5.09	1 [Reference]
Site of subsequent primary invasive melanoma[b]			*P* < .001			*P* < .001			*P* < .001			*P* < .001			*P* = .15
Head	181	8.27	1 [Reference]	225	5.20	**0.79 (0.68-0.93)**	152	4.96	**0.74 (0.60-0.91)**	104	4.47	**0.59 (0.46-0.76)**	28	4.12	3.07 (0.93-10.1)
Trunk	149	4.84	**0.56 (0.43-0.73)**	520	6.83	1 [Reference]	254	5.55	**0.80 (0.67-0.95)**	212	5.98	**0.76 (0.62-0.94)**	60	5.64	4.08 (1.28-13.0)
Upper extremities	111	4.56	**0.52 (0.40-0.69)**	329	6.33	0.95 (0.82-1.09)	255	6.75	1 [Reference]	197	6.05	**0.81 (0.66-1.00)**	41	4.95	3.50 (1.08-11.3)
Lower extremities	63	3.61	**0.38 (0.28-0.52)**	188	4.96	**0.73 (0.62-0.87)**	164	5.40	**0.80 (0.66-0.98)**	215	7.27	1 [Reference]	31	4.85	3.25 (0.99-10.7)
Not specified	10	1.53	**0.17 (0.09-0.34)**	15	1.05	**0.16 (0.09-0.26)**	7	0.72	**0.11 (0.05-0.23)**	6	0.77	**0.10 (0.05-0.23)**	3	1.38	1 [Reference]

Abbreviations: Adj, adjusted; Obs, observed; SIR, standardized incidence ratio.

[a] *P* values represent the statistical significance of the overall effect for the variable. Adjusted SIR ratios shown in boldface type are statistically significant (*P* < .05).

[b] Numbers by site of subsequent primary invasive melanomas may include more than 1 per person.

The relative risk of subsequent primary invasive melanomas varied across the other secondary sites, depending on the person's sex and the site and behavior of the initial lesion, although all combinations resulted in a risk of melanoma that was significantly higher than that of the general population (ie, SIR >1; Figure). For example, males with a first primary invasive melanoma on the upper extremities had an equally high relative risk of a subsequently diagnosed primary invasive melanoma on the upper or lower extremities (Figure), but less so for the head (adjusted SIR ratio, 0.63; 95% CI, 0.49-0.81) or trunk (adjusted SIR ratio, 0.73; 0.59-0.90). In contrast, among females with an initial invasive melanoma on the upper extremities, there was an equally high relative risk of a subsequent primary invasive melanoma on the head, trunk, or upper extremities, but a less-elevated risk for the lower extremities (adjusted SIR ratio, 0.71; 95% CI, 0.53-0.96).

Discussion

The present investigation demonstrated that all people with melanoma, whether it be an invasive or in situ lesion, are at a significantly and substantially increased risk of a subsequent primary invasive melanoma compared with the age- and sex-matched general population. Although there was some variation in the size of the relative risk by key characteristics, such as sex, age at first diagnosis, time after initial diagnosis, the body site of both the first and subsequent melanomas, and whether the first primary melanoma was invasive or in situ, a highly increased risk was maintained across all of these subgroups.

We found that people with melanoma tended to have the greatest relative risk of subsequent primary invasive

Table 4. SIRs and Adj SIR Ratios for Subsequent Primary Invasive Melanomas by Site of First Primary In Situ Melanoma, Queensland, 1982-2010

	Site of First Primary In Situ Melanoma														
	Head			Trunk			Upper Extremities			Lower Extremities			Not Specified		
Characteristic[a]	Obs	SIR	Adj SIR Ratio (95% CI)	Obs	SIR	Adj SIR Ratio (95% CI)	Obs	SIR	Adj SIR Ratio (95% CI)	Obs	SIR	Adj SIR Ratio (95% CI)	Obs	SIR	Adj SIR Ratio (95% CI)
Sex			*P* = .19			*P* = .34			*P* = .22			*P* = .16			*P* = .40
Male	328	3.82	1 [Reference]	392	4.97	1 [Reference]	225	4.58	1 [Reference]	90	4.75	1 [Reference]	32	4.32	1 [Reference]
Female	155	4.41	1.14 (0.94-1.38)	81	4.09	0.89 (0.70-1.13)	167	5.21	1.14 (0.93-1.40)	149	5.83	1.21 (0.93-1.56)	17	4.68	1.29 (0.72-2.32)
Age at first diagnosis, y			*P* = .24			*P* = .67			*P* = .17			*P* = .56			*P* = .49
15-49	60	4.35	1.25 (0.95-1.65)	106	4.74	0.96 (0.76-1.22)	92	5.83	1.20 (0.93-1.56)	79	5.32	1.06 (0.77-1.45)	11	3.82	0.81 (0.37-1.77)
50-64	155	4.05	1.11 (0.91-1.34)	171	4.66	0.91 (0.75-1.11)	127	4.47	0.93 (0.75-1.17)	89	5.63	1.17 (0.87-1.57)	21	5.22	1.25 (0.67-2.31)
≥65	268	3.88	1 [Reference]	196	4.96	1 [Reference]	173	4.68	1 [Reference]	71	5.12	1 [Reference]	17	4.11	1 [Reference]
Time between diagnoses			*P* = .38			*P* = .20			*P* = .59			*P* = .33			*P* = .41
2 mo to <1 y	38	4.14	1.00 (0.70-1.43)	44	6.18	1.06 (0.76-1.49)	33	5.55	1.11 (0.75-1.64)	24	8.33	1.54 (0.97-2.43)	3	5.58	1.39 (0.40-4.82)
1 y to <5 y	158	3.74	0.90 (0.72-1.13)	169	4.95	0.89 (0.72-1.11)	127	4.51	0.90 (0.69-1.16)	77	5.53	1.05 (0.77-1.44)	14	5.44	1.51 (0.74-3.06)
5 y to <10 y	164	4.38	1.10 (0.88-1.36)	133	4.18	0.81 (0.65-1.01)	130	4.96	1.03 (0.80-1.32)	68	4.88	1.08 (0.79-1.47)	16	5.42	1.74 (0.90-3.36)
≥10 y	123	3.82	1 [Reference]	127	4.97	1 [Reference]	102	4.90	1 [Reference]	70	5.08	1 [Reference]	16	3.22	1 [Reference]
Site of subsequent primary invasive melanoma[b]			*P* = .001			*P* < .001			*P* = .005			*P* = .41			*P* = .71
Head	156	5.18	1 [Reference]	81	3.65	**0.60 (0.46-0.78)**	69	3.76	**0.67 (0.50-0.91)**	39	4.54	0.80 (0.54-1.20)	8	3.11	0.50 (0.16-1.58)
Trunk	142	3.52	**0.67 (0.53-0.85)**	223	6.02	1 [Reference]	140	5.31	0.95 (0.74-1.21)	79	5.83	1.03 (0.74-1.44)	20	5.36	0.83 (0.30-2.33)
Upper extremities	118	3.55	**0.67 (0.53-0.85)**	137	5.27	0.88 (0.71-1.09)	128	5.73	1 [Reference]	73	5.87	1.00 (0.72-1.40)	14	4.56	0.69 (0.24-2.00)
Lower extremities	82	3.43	**0.63 (0.48-0.82)**	71	3.84	**0.65 (0.50-0.86)**	76	4.26	**0.72 (0.54-0.96)**	69	6.02	1 [Reference]	14	6.02	0.88 (0.30-2.57)
Not specified	36	4.09	0.78 (0.54-1.12)	32	4.50	0.75 (0.52-1.08)	16	2.81	**0.50 (0.30-0.84)**	10	2.90	0.60 (0.31-1.17)	5	6.32	1 [Reference]

Abbreviations: Adj, adjusted; Obs, observed; SIR, standardized incidence ratio.

[a] *P* values represent the statistical significance of the overall effect for the variable. Adjusted SIR ratios shown in boldface type are statistically significant (*P* < .05).

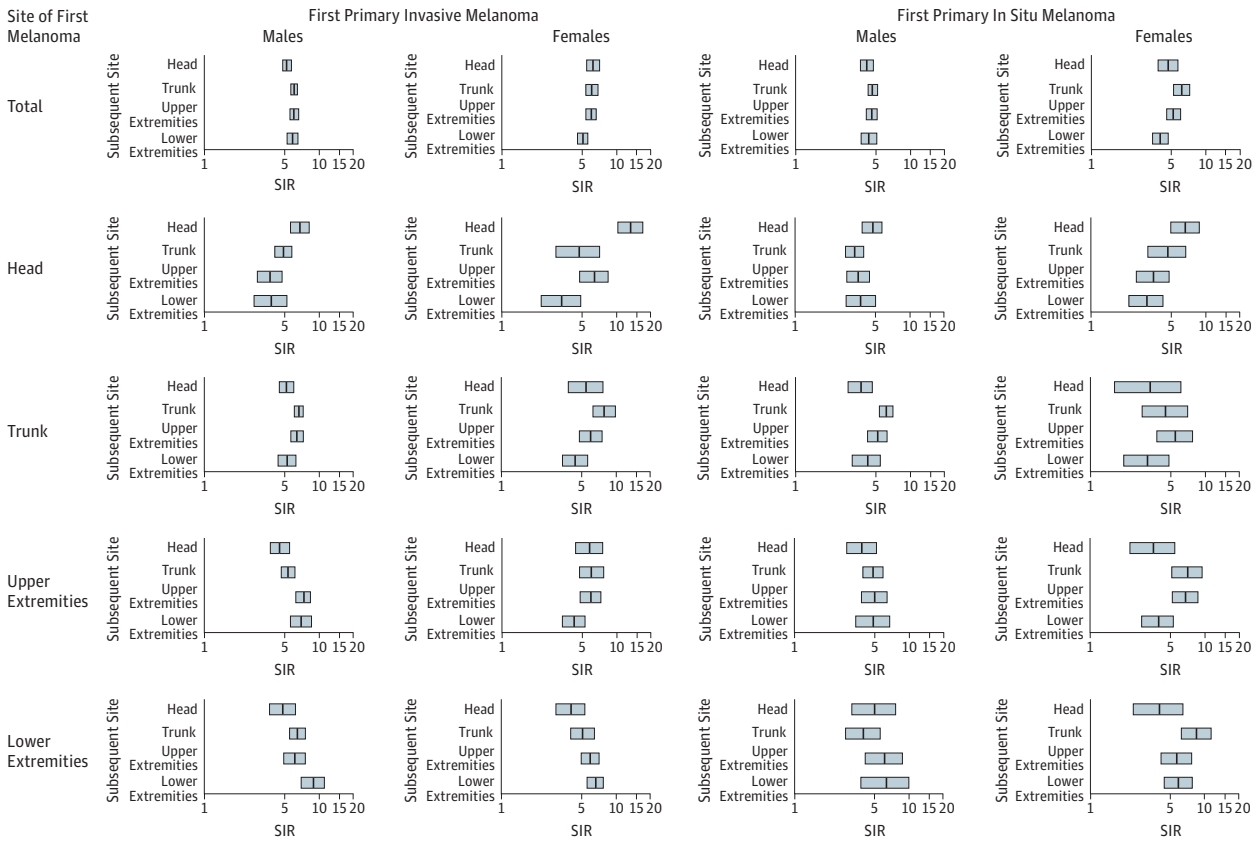
[b] Numbers by site of subsequent primary invasive melanomas may include more than 1 per person.

melanomas on the same part of the body, particularly the head. This is consistent with the findings of Giles et al,[7] who reported a significant site concordance. They postulated that this might signify a field effect because of the similar sun exposure history of neighboring skin. Given that the head is typically the most chronically sun-exposed part of the body, our findings add further weight to this theory and highlight the need for vigilant inspection around the site where the first primary melanoma appeared.

Recently, the issue of subsequent primary melanomas has become topical following improved survival for patients with late-stage melanomas who received treatment with vemurafenib.[14] High frequencies of newly detected primary melanomas within weeks of vemurafenib or other serine/threonine protein kinase inhibitors being administered have been described.[15,16] Dalle et al[17] and Haenssle et al[18] have stressed the importance of repeated skin examination, including sequential dermoscopy, for the early detection of subsequent primary melanomas in patients who receive these treatments.

Also of interest was our finding that the risk of a subsequent primary invasive melanoma following a first primary in situ melanoma was more than 4 times higher than that in the general population, and only slightly lower than the relative risk following a first primary invasive melanoma. Greater awareness and more widespread screening have contributed to an overdiagnosis of melanoma in recent years,[19-21] as evidenced by increases in the incidence of in situ and early-stage invasive tumors. Indeed, the higher incidence of subsequent melanomas within the first year of initial diagnosis may be explained, at least in part, by heightened attention among patients with melanoma and their physicians toward suspicious skin lesions. However, the continuing elevated risk during the entire period of

Figure. Standardized Incidence Ratios (SIRs) for Subsequent Primary Invasive Melanomas by Site, Behavior of First Primary Melanoma, and Sex—Queensland, 1982-2010



The SIR is presented on a log scale. The vertical black line indicates the SIR point estimate; gray shading, 95% CI.

follow-up clearly suggests that people with an in situ or invasive melanoma share an inherently higher melanoma risk than the general population.

Although the value of follow-up for patients with later-stage melanoma is unequivocal, the same level of consensus has not been evident for those with very thin or in situ melanoma.[22] The findings of the present study place patients with in situ melanoma in a high-risk category and provide strong grounds for continuing clinical follow-up and education within this group. To date, no randomized clinical trials have evaluated follow-up intervals or length of the follow-up period; nevertheless, most guidelines recommend more frequent follow-up for later-stage melanomas in the first 5 years and annually thereafter. However, there is little consistency in relation to follow-up for in situ melanoma.[23-25] The findings in the present study may indicate the need for patients with in situ or early-stage melanoma to be monitored more closely for a prolonged period. Furthermore, it is well recognized in Australia that patients are more likely than physicians to initially detect a primary melanoma[26] or a recurrence.[27] However, it seems that patients are less likely than physicians to detect a second primary melanoma.[28,29] Current Australian clinical practice guidelines[23] recommend that teaching skin self-examination should be a high priority in follow-up care for people with invasive melanoma; our results suggest that this should be extended to include those with an in situ melanoma.

It would seem reasonable to suggest that survival would decrease with a greater number of primary invasive melanomas, but studies[30,31] examining the effect of multiple primary melanomas on survival have not supported this view. A recent report from the Genes, Environment, and Melanoma Study[30] found no significant difference in prognosis between patients with single vs multiple primary invasive melanomas after adjusting for other factors. An earlier study[31] even reported a survival advantage for patients with 3 or more invasive melanomas compared with patients with a single melanoma; the authors speculated that this may be akin to an immunization effect. No literature is available on studies that assessed other possible consequences of the diagnosis of subsequent primary melanomas, such as the effect on quality of life for survivors.

One of the main strengths of the present study is the full population-based coverage of melanoma cases collected by the Queensland Cancer Registry. There was also a high level of histopathologic verification (99% in 2009 and 2010),[3] which enabled us to distinguish between new primary melanomas and metastases of an existing melanoma. Given the greatly increasing incidence of in situ melanoma during the study period,[2] we were unable to distinguish whether this is a real increase or the

result of unmeasured changes in clinical practice. It could be that there is some temporal heterogeneity in the composition of the in situ lesions; however, this would not explain the increased risk of subsequent invasive melanomas among this group.

The risks reported here are relative to those of the general population, and so do not represent the absolute risks of subsequent melanomas among the cohort. This is an important distinction and has implications for the comparison of subgroups. Similar to other investigations,[32-34] our study found that, compared with the general population, younger people had a higher relative risk of subsequent melanoma than did older people. However, it also has been shown[9] that the absolute risk is higher among older people, and this needs to be borne in mind when interpreting our results.

Although most patients in the present study with multiple lesions developed only 1 additional primary invasive melanoma, 11% developed 2 or more at different body sites. The possibility that this latter group may have a genetic predisposition cannot be excluded. It has been estimated[35] that approximately 10% of patients with melanoma have a family history of the disease.

The overall SIR presented for subsequent primary invasive melanomas was somewhat lower than the result reported in an earlier article[6] that considered all second primary cancers in Queensland. This was because of minor methodologic differences. In the first study, follow-up was truncated when any type of second primary cancer was diagnosed. Cancers other than melanoma were not considered in the present study; consequently, many melanoma survivors would have the potential for a longer follow-up time, which would in turn increase the expected number of melanomas and hence lower the SIR.

Conclusions

To our knowledge, we have quantified for the first time the relative risks by body site of a subsequent primary invasive melanoma being diagnosed in people with a first primary invasive or in situ melanoma. The relative risks were generally highest for the same body site, although the variation observed by key patient and tumor characteristics emphasizes that certain combinations of sites and demographic attributes require more vigilant follow-up. These findings have important implications for the dual spheres of public health and clinical practice and highlight that education and continued surveillance are paramount not only for persons with invasive melanoma but also for those with an in situ melanoma.

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Study concept and design: Youlden, Youl, Soyer, Baade.
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NOTABLE NOTES

Doctor, Your Next Patient Is the Rabbit in Room 7

Walter H. C. Burgdorf, MD

One of the US private practitioners who made inestimable research contributions was Vince Barranco (1937-2013) from Tulsa, Oklahoma. Vince was born in Granada, Mississippi, and trained in dermatology under Mark Allen Everett at the University of Oklahoma. In 1969 he joined Dwane Minor and Kendrick Doran at the Tulsa Dermatology Clinic.

Vince became fascinated by dapsone during his residency and decided to investigate its method of action. The clinic was in a new building that was designed with foresight to accommodate 4 physicians with 4 suites of examining rooms radiating out from a central nursing area. One wing was free; it became Vince's laboratory. He acquired 28 rabbits and injected them with large doses of vitamin A daily, inducing upregulation of lysosomal enzymes, damage to chondroitin sulfate, and floppy ears. Vince set up a classic study: 8 rabbits received vitamin A alone; 8, vitamin A plus methylprednisolone; and 8, vitamin A plus dapsone; and 4 served as controls. The distal ear tips collapsed in the rabbits treated with vitamin A alone by day 5; systemic signs of toxic effects and hair loss appeared by day 8. Both dapsone and methylprednisolone blocked the ear changes and reduced hair loss, although systemic toxic effects were not influenced.

The cartilage from the trachea and femoral head was studied histologically because previous studies had shown evaluating the ear cartilage was unreliable. The tracheal cartilage was thinned and stained poorly with toluidine blue in the rabbits treated only with vitamin A; in addition, the articular cartilage was reduced in thickness by two-thirds. Both dapsone and methylprednisolone prevented these changes.[1]

Vince was featured in one of Berton Roueché's[2] medical detective articles in *The New Yorker*. In *Antipathies*, published in March 1978, Roueché discussed a patient of Vince's, who developed a systemic allergic contact dermatitis triggered by an intrauterine contraception device containing copper. This article and Vince's work, which had been published 6 years earlier,[3] were almost the beginning of implant immunology studies, which acquired great relevance as physicians starting implanting all sorts of metals in many different body sites.

Vince was not only a creative, office-based researcher; he was also a consummate and caring clinician whose opinion was regularly sought on difficult cases anywhere within range of Tulsa. We should all remember him as a classic example of what can be accomplished in a private office by a curious clinician.

PS: When I shared this Notable Note with my frequent collaborator, David Bickers, he told me that his father, William M. Bickers, a gynecologist in Richmond, Virginia, had rabbits in his office in the 1950s, while he was looking for a drug to prevent or treat menstrual cramps.

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