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Number of Nevi and Survival with Melanoma

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Abstract

Possession of a higher than average number of nevi has long been substantiated as one of several factors that predispose patients to malignant melanoma. Despite the relative certainty of this relationship, little is known about the relationship between the number of nevi a person possesses and risk of death from melanoma. A cohort of melanoma patients was followed prospectively to determine if a significant relationship exists between number of nevi and increased mortality from melanoma. Age at diagnosis, melanoma of the head and neck, increasing Breslow thickness and presence of mitoses all were associated with poorer survival in our multivariate analysis. Existence of a dermal nevus at the site of melanoma was also associated with poorer survival, while solar elastosis and skin awareness were associated with improved survival. Our study also suggests that having a large number of nevi increases the risk of death from melanoma more than two-fold. Further research elucidating the prognostic indications of a high number of nevi possessed by melanoma patients could potentially lead to considerable advances in the classification, diagnosis, and therapy for cutaneous melanoma.

Introduction

Individuals who have many nevi are at higher risk for developing melanoma. In fact, a large number of nevi has been shown to be the strongest known risk factor for developing melanoma among Caucasians (Armstrong, 2004). Even in the absence of clinically atypical nevi, a very high number of nevi (e.g., more than 100) have been shown to significantly increase risk for melanoma (Huynh et al., 2003). Risk is based on the total number of nevi, not those at a particular anatomic site (Weinstock et al., 1989).

Survival among melanoma patients has been shown to be influenced by pathologic characteristics such as tumor thickness (Breslow depth), histogenetic subtype, Clark level, microscopic satellites, ulceration, vascular invasion, mitotic rate and growth phase (Barnhill et al., 1996). Regression and solar elastosis have been shown to be protective (Barnhill et al., 1996; Berwick et al., 2005). Tumor thickness is probably the most important pathologic prognostic factor in localized, cutaneous melanoma (Lemish et al., 1983; Heenan et al., 1991; Barnhill et al., 1996; Berwick et al., 2005). In an analysis of prognostic factors for 17,600 melanoma patients, increasing tumor thickness was highly correlated with 10-year melanoma specific mortality ($p<0.00001$) (Balch et al., 2001). In one study, level of awareness of skin alterations is associated with improved survival and is probably another important prognostic factor (Berwick et al., 1996). It is not clear that early detection of melanoma through skin self-examination reduces mortality, but one study indicated that it may decrease risk by up to 63% (Berwick et al., 1996). Melanoma has been associated with a worse prognosis when the site of origin is

the head or neck as opposed to the extremities (Lemish et al., 1983) and females have been shown to have a higher survival rate than males (Clark et al., 1989). These prognostic factors are potential confounders of survival studies. Despite the existence of extensive research that documents the risk for developing malignant melanoma with increasing numbers of nevi, a relationship between number of nevi and survival with melanoma has yet to be identified.

Although the number of nevi has been shown to be determined by genetic factors, (Zhu et al., 1999; Bataille et al., 2000) environmental factors are also important for nevus development (Kefford et al., 2004). Epidemiological studies in several countries have shown that exposure to excessive sunlight in childhood is associated with total number of nevi. Habitual sun exposure, (Darlington et al., 2002) severe sunburns, (Green et al., 1986; Dennis et al., 1996; Valiukeviciene et al., 2005) recent chronic sun exposure (Armstrong et al., 1986) and total cumulative sun exposure (Weiker et al., 2003; Bauer et al., 2005) have all been proposed as important types of sun exposure associated with increasing number of nevi. Tendency to burn (Green et al., 1986; Heenan et al., 1991; Whiteman et al., 2005), freckling (Green et al., 1986; Darlington et al., 2002; Whiteman et al., 2005), light eye color (Whiteman et al., 2005; Wachsmuth et al., 2005), light hair color (Whiteman et al., 2005; Wachsmuth et al., 2005), and light skin color (Patvlotsky et al., 1997; Whiteman et al., 2005) have also all been positively associated with number of nevi, although these findings vary between studies. A higher prevalence of nevi has been found among individuals with moderately dark skin compared to the those with pale skin (Armstrong et al., 1986). Increasing age has been shown to be associated with a

decreasing number of nevi (Green et al., 1986; Dennis et al., 1996; Schafer et al., 2006) and individuals with melanoma arising from the head or neck tend to have fewer nevi than those with melanoma arising on the trunk (Whiteman et al., 2003).

We wanted to examine whether nevi might be a marker for a type of melanoma that has escaped growth controls and thus might be associated with survival with the disease. Therefore, we conducted long-term follow up (average 16 years) of subjects who had been enrolled in a population-based case control study in Connecticut (Berwick et al., 1996; Berwick et al., 2005).

Methods

The original study on melanoma was approved by the Institutional Review Boards at Yale University, the State of Connecticut Department of Health and the University of New Mexico Health Sciences Center, as well as the hospitals where patients had been diagnosed. Potential subjects with melanoma were identified through the Rapid Case Ascertainment System (RCA), a shared resource of the Cancer Prevention Research Unit for Connecticut and acts as an agent of the Connecticut Tumor Registry (CTR). All participating subjects signed informed consent. Eligibility was based on diagnosis of a first primary invasive melanoma between the dates of January 15, 1987 and May 15, 1989, residence in the state of Connecticut, being of Caucasian race, and being 18 years old or greater. All biopsies and re-excisions were reviewed by a single dermatopathologist (R.L. Barnhill) for standardization. 650 eligible patients, or 75% of

those eligible, were interviewed and of these nevus counts were obtained for 80 percent of subjects

Trained, registered nurses conducted in-person interviews with all the selected study participants. They interviewed the patients with a structured questionnaire to assess the following information: age at melanoma diagnosis, sex, level of educational attainment, history of severe sunburns, skin examination practices, skin awareness, site of melanoma, use of sunlamps, sunscreen use within the last 10 years, sunscreen use before age 15, tanning ability, skin color, and lifetime intermittent sun exposure. The sun exposure index that we used quantified sun exposure history by summing the total intermittent recreational sun exposure histories and has been previously described in detail (Berwick et al., 1996). Intermittent sun exposure was measured as described previously (Berwick et al., 1996). Nurses trained in techniques of skin examination recorded skin color on the inner aspect of the upper arm. Information regarding skin type, sunburn history, skin examination and skin awareness was gathered by asking the following questions:

Skin type. After repeated and prolonged exposure to sunlight, would your skin become: tan, very brown and deeply tanned or moderately tanned or only mildly tanned due to a tendency to peel; no tan, only freckled or no suntan at all.

Sunburn history. Have you ever been sun burnt severely enough to cause pain for 2 or more days or blisters?

Skin examination. Individuals were classified as skin self-examiners if they answered positively to either of the following two questions: 1) Did you ever (in your life) carefully examine your own skin? By this I mean actually check surfaces of your skin deliberately and purposefully?; or 2) Has someone other than a physician ever carefully examined areas of your skin on purpose?

Skin awareness. [Before your recent biopsy] did you ever think about your skin, how it looked, whether there were any changes, or whether there were any abnormal marks? Individuals that answered that they were aware of changes or abnormalities were classified as having skin awareness, while those that answered negatively or answered that they were aware only of cosmetic or other changes were not classified as having skin awareness.

The trained, registered nurses also counted and recorded nevi greater than 2mm in largest diameter on the arms and backs of subjects who consented. A standardized method was used that only included the counting of nevi proximal to the styloid process on both arms. Each arm was divided into four sections and the nurses recorded which sections were examined for nevi. Flat nevi of 2 mm or more in diameter and greater were recorded, and raised nevi of any size were included if they were visibly raised. Nevus counts were performed in an organized fashion beginning with the counting of raised true nevi on both arms followed by inspection for junctional or lentigo simplex nevi and finally, nevi 5mm or greater in largest diameter were counted for both arms. The patients

were examined for palpable nevi by visual inspection first, while palpation was only utilized to distinguish between raised and flat nevi. Inspection of the arms was concluded with observation and recording of the color of the skin on the inner aspect of the upper arm of the patient (dark/black, moderately dark, medium, fair, very fair). The back was assessed in a similar manner and the proportion of the back that was able to be examined was noted by the interviewer and classified as one the following categories: none, all, upper quarter, upper half, and upper ¾ of the back. This allowed for the differences in the proportion of the back that was examined to be taken into account in the analysis. All large nevi on the arms and back were diagramed by the interviewer and the largest mole from the patient's back was recorded on a mannequin.

Pathologic characteristics of melanoma that were recorded included tumor thickness, number of mitoses per millimeter squared (mitotic index), presence of solar elastosis, and Clark level. Presence of a co-existing nevus and the type of nevus (dermal, congenital, dysplastic and other) was also recorded. Follow-up was performed by the RCA throughout the study period up until the August 2008 in all diagnosing institutions in Connecticut. Follow-up included a review of death certificates and reports to the CTR, as well as mailings and telephone calls to patients, their spouses, and their primary physicians if necessary. The National Death Index was queried for all those for whom we did not have death certificates. The median follow up for all case subjects was 16.1 years and the range was 0 to 19.9 years.

Statistical analysis consisted of frequency distributions, and cross-tabulations. Covariates that were determined to have a significant correlation with number of nevi were included in univariate models measuring death as the outcome. If the *p*-value from a specific univariate model was less than 0.16, then that covariate was included in the multivariate analysis, using Cox proportional hazard modeling with time to mortality from melanoma as the outcome. Potential confounders were assessed by comparing the hazard ratio for survival and nevi with each variable that might modify the hazard ratio by 15% or more.

We evaluated the distribution of nevi and divided nevi into two groups based on the top 25th percentile and the lower 75th percentile. We then compared selected variables by the two groups of nevi (Table 1). The following covariates were included: sex, age at diagnosis, ability to tan, history of sunburn, skin color, presence of solar elastosis (a histologic indicator of cutaneous sun damage), anatomic site of melanoma, history of sun exposure, skin examination, sunlamp use, tumor thickness, presence of mitosis, Clark level, education, co-existing nevus, dermal nevus and skin awareness.

Results

In follow up of this cohort, 98 (18.8%) of the 520 patients died of melanoma and 126 (24.2%) died of other causes over the twenty-year period. Younger participants were significantly more likely to possess more than 28 nevi on their arms and back ($P = <.01$) as were those with the ability to tan after prolonged sun exposure ($P = .03$). Individuals

with melanoma arising from the head or neck were significantly more likely to be in the low nevus group (P = .01). Skin examination was associated with more nevi (P = .07) and solar elastosis was associated with fewer nevi (P = .05), but these were of borderline significance. Time to death from melanoma was modeled using univariate Cox hazard models to obtain the hazard ratio for each covariate (Table 2). Eleven variables were significant in this analysis. High nevus count was associated with an increased risk of death from melanoma (HR = 1.7, 95% CI = 1.1 to 2.6, P = .01). Men were more likely to die from melanoma than were women (HR = 1.5, 95% CI = 1.0 to 2.3, P =.04). Increasing age at diagnosis was associated with a decrease in survival (HR for every 1-year increase in age = 1.02, 95% CI = 1.01 to 1.03, P = < .01), as was melanoma of the head and neck compared to melanoma of other sites (HR= 1.8, 95% CI = 1.1 to 3.0, P = .02), the presence of mitoses (HR = 8.9, 95% CI = 4.3 to 18.3, P = <.01), and increasing Breslow thickness and Clark level (see Table 2). Several factors associated with sun exposure were protective: A higher amount of sun exposure (HR for heavy or very heavy sun exposure compared to light or moderate sun exposure = 0.6, 95% CI = 0.4 to 0.9, P = 0.02), the use of sunlamps (HR = 0.3, 95% CI = 0.2 to 0.7, P = <0.01), skin awareness (HR = 0.5, 95% CI = 0.3 to 0.8, P = <0.01) and education greater than high school (HR = 0.7, 95% CI = 0.4 to 1.0, P = .03). The presence of solar elastosis was also protective (HR = 0.7, 95% CI = 0.5 to 1.0, P = .06) but of borderline significance. Additional covariates in the univariate analyses were prognostic, but not statistically significant: The presence of a dermal nevus at the site of melanoma (HR = 1.5, 95% CI = 0.9 to 2.5, P = 0.16) and history of a severe sunburn (HR = 0.7, 95% CI = 0.5 to 1.1, P = 0.14).

For the multivariate analysis (Table 3), we included all variables from the univariate models (Chi-square and Cox univariate) with a *P* value ≤ 0.16. Sex was forced into the model due to its importance in the literature as a prognostic indicator for death from melanoma. Clark level was excluded from the multivariate analysis because Clark level and Breslow thickness had a Spearman correlation coefficient of 0.79 and were considered to be collinear. In multivariate analysis a high number of nevi (HR = 2.4, 95% CI 1.5-3.7), older age at diagnosis (HR = 1.03, 95% CI 1.01-1.04, melanoma on the head or neck (HR = 2.0, 95%, CI = 1.2 to 3.4), presence of solar elastosis (HR = 0.6, 95%, CI = 0.3 to 0.9), greater Breslow thickness (HR for 0.76 mm to ≤3.60 mm = 3.1, 95% CI = 1.9 to 5.2; HR > 3.60mm = 4.7, 95% CI = 2.6 to 8.5), any mitoses (HR = 4.2, 95% CI 1.9-9.1) , presence of a dermal nevus (HR = 1.8, 95%, CI = 1.0 to 3.3), and skin awareness (HR = 0.5, 95%, CI = 0.3 to 0.9) were all significantly associated with melanoma mortality.

Discussion

The results of this melanoma mortality study with twenty years of follow up further support the significance of previously known prognostic indicators. In our multivariate analysis, age at diagnosis, melanoma of the head and neck, increasing Breslow thickness and presence of mitoses all were associated with poorer survival. Existence of a dermal nevus at the site of melanoma was also associated with poorer survival in our study, but to our knowledge this characteristic has not been well studied. Presence of solar elastosis and skin awareness were associated with improved survival, as

was noted in a five-year follow-up study using the same patient database (Berwick et al., 2005). Interestingly, our study suggests that having a large number of nevi increases the risk of death from melanoma more than two-fold. The association of increasing number of nevi with mortality from melanoma was independent of its significant associations with age at diagnosis, skin type and anatomic site of melanoma. In the previous five-year follow-up study with this data, the association between nevus counts and death from melanoma was not statistically significant (Berwick et al., 2005), but this has changed with the longer follow-up period. To our knowledge, number of nevi has not previously been evaluated as a prognostic factor.

In the US, New Zealand and Canada, incidence rates of the more aggressive melanoma on the ears, scalp and neck were higher in males compared to females (Bulliard et al., 1997). The differences in common melanoma sites between males and females likely reflects distinct patterns of site-specific UV radiation (Green et al., 1993; Bulliard et al., 1997; Elwood et al., 1998).

There are multiple factors that could confound the association between nevi and mortality. For example, age is related to both mortality and number of nevi, because as people age past a certain point, their chance of dying tends to increase, while their number of nevi tends to decrease (Dennis et al., 1996). These factors might mitigate against each other. Inevitably, additional confounders may exist that could potentially contribute to error in the study. For example, there is a possibility that use of sunscreen and protective clothing could be inversely associated with mortality from melanoma.

These variables were not included in the multivariate analysis even though their quantification was attempted in the survey but people generally have poor memory of these factors and in a reproducibility study, sunscreen use was not reliably recalled (unpublished data).[1] In addition, sunscreen use was not frequent in the 1980's, when the study was conducted. Other data that were gathered, such as sun exposure, could be relatively unreliable either because of recall bias or because people simply have poor memories of sunburn history. Finally, nevus counts are complete for only 80% of the cohort, because this process was initiated after the study had begun.

Despite the presence of certain limitations in this study, there are a number of inherent strengths. The fifteen-year follow-up allowed for a greater number of outcomes of interest (death) as compared to a previous study using the same data with a five-year follow-up. The long time frame also increased the chance that covariate patterns related to mortality of melanoma would be elucidated and adjusted for more appropriately. The study design strengthened the analysis of our data because a comprehensive initial survey was used to collect information from participants. A unique feature of this study was that skin examination characteristics were collected and could be adjusted for in the multivariate analysis. The vital status for participants who did not respond to mailed follow-up questionnaires was ascertained by phone calls to the patient, patient's spouse or patient's physician. Using this method instead of solely relying upon death certificate information minimized misclassifications of cause of death, which allowed for more complete and accurate evaluation of the relationship between number of nevi and

[1] Berwick M, unpublished data. A kappa for memory of sunscreen use was 0.1

survival. Finally, the use of a single pathologist for the collection of melanoma characteristics such as associated solar elastosis and Clark level also helped to standardize results and avoid inter-observer variation.

The association of a high number of nevi with increased mortality from melanoma may be explained by two hypotheses. First, a separate, more aggressive oncogenic pathway may be associated with patients in the high nevi group. The divergent pathway model developed by Whiteman classifies the pathogenesis of melanoma into two pathways, one characterized by environmental induction and p53 over-expression and another characterized by pigment cell instability (Whiteman et al., 1998). It has been suggested that individuals with fewer nevi require repeated exposure to sunlight in order to drive carcinogenesis because they are more likely to develop melanomas on high sun exposure areas such as the head and neck, while those with many nevi, who are more likely to develop melanoma of the trunk, may possess host factors that drive carcinogenesis after minimal sunlight exposure (Whiteman et al., 2003). Therefore, it is plausible that the oncogenic pathway characterized by pigment cell instability is associated with a higher number of nevi, and may lead to more aggressive melanoma and a worse prognosis.

Alternatively, the pathogenesis of melanoma in patients of both the high and low nevi groups may follow very similar pathways, but patients in the high nevi group may be missing a genetic checkpoint. The absence of this checkpoint may allow for a more aggressive progression of melanoma and may also permit the development of a higher

number of nevi. The etiology of nevi and melanoma appear to be similar in some respects, as the gene CDKN2A has been associated with the development of melanoma (Kefford et al., 1999; Zhu et al., 1999; Chaudru et al., 2004) and possibly with the development of nevi as well (Zhu et al., 1999). For example, a subset of people with certain familial nevus disorders such as dysplastic nevus syndrome (DNS) possess a *CDKN2A* mutation and go on to develop melanoma (Zhu et al., 1999). Further characterization of the biochemical pathways leading to the development of both nevi and melanoma will be necessary, however, before either of these hypothesis can be appropriately supported.

In summary, we found that a high number of nevi is associated with poorer survival from melanoma, though little is known about the specific mechanism by which this may occur. Confirmation of our results may contribute to evidence in the field of oncology that suggests that genetic susceptibility in patients with cancer may possess distinct features of natural history that affect prognosis. Prognostic variables that can be inexpensively and non-invasively obtained from patients may provide welcome new capabilities in clinical medicine. A related example is the finding that women who were diagnosed with breast carcinoma and who had a first-degree family history of breast carcinoma had half the risk of dying compared to those in sporadic cases (Malone et al., 1996). Like family history, the number of nevi present on a patient can easily be obtained clinically. Further research elucidating the prognostic implications of a high number of nevi in melanoma patients could potentially lead to advances in the classification, diagnosis, therapy, and prognosis of melanoma.

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Tables

1. Effect of covariates on nevus count.

	Number of Nevi[a]		
	Low (n =453) n (%)	High (n = 96) n (%)	*P* value
Sex			
Male	194 (72.9)	72 (27.1)	.22
Female	197 (77.6)	57 (22.4)	
Age at diagnosis			
<30	19 (79.2)	5 (20.8)	**<.01**
30-39	47 (64.4)	26 (35.6)	
40-49	59 (62.1)	36 (37.9)	
50-59	79 (76.0)	25 (24.0)	
60-69	90 (81.8)	20 (18.2)	
70+	97 (85.1)	17 (14.9)	
Skin type			
Tan	240 (72.1)	93 (27.9)	**.03**
No tan	139 (80.8)	33 (19.2)	
Skin color			
Very fair/fair	277 (75.3)	91 (24.7)	.95
Medium	114 (79.1)	38 (20.9)	
Anatomic site			
Head and neck	65 (86.7)	10 (13.3)	**.01**
Other	326 (73.3)	119 (26.7)	
Solar elastosis			
Absent	135 (71.1)	55 (28.9)	.05
Present	236 (80.4)	69 (19.6)	
Breslow thickness			
< 0.76	174 (75.7)	56 (24.3)	.91
0.76 – 1.69	113 (73.4)	41 (26.6)	
1.70 – 3.60	65 (74.7)	22 (25.3)	
> 3.60	36 (78.3)	10 (21.7)	
Clark level			
II	139 (80.3)	34 (19.7)	.26
III	101 (71.6)	40 (28.4)	
IV	124 (72.5)	47 (27.5)	
V	15 (75.0)	5 (25.0)	
Mitotic figure(s)			
Absent	149 (74.9)	50 (25.1)	.73
Present	216 (76.4)	78 (23.6)	
Co-existing nevus			
Yes	110 (71.0)	45 (29.0)	.25
No	261 (75.9)	83 (24.1)	
Dermal nevus[2]			
Yes	43 (69.4)	19 (30.6)	.33
No	332 (75.1)	110 (24.9)	
Total sun exposure			
Light/moderate	150 (79.4)	39 (20.6)	.08
Heavy/very heavy	232 (72.5)	88 (27.5)	
Severe sunburn			
Yes	264 (77.4)	77 (22.6)	.09
No	125 (70.6)	52 (29.4)	
Sunlamp use			
Yes	87 (77.0)	26 (23.0)	.62
No	304 (74.7)	103 (25.3)	
Education			
Up to high school	157 (75.5)	51 (24.5)	.90
Greater than high school	234 (75.0)	78 (25.0)	
Skin examination			
Yes	95 (69.3)	42 (30.7)	.07
No	296 (77.3)	87 (22.7)	
Skin awareness			
Yes	119 (75.8)	38 (24.2)	.83
No	272 (74.9)	91 (25.1)	

[2] Dermal nevus is a subset of co-existing nevus. Please see text.

2. Predictors of risk of death from melanoma in a population-based study of residents from Connecticut.

Variable	Total no.[3]	No. of melanoma deaths	Hazard ratio (95% confidence interval)	*P* value
Number of nevi				
< 28	171	64	1.0 (referent)	.01
28+	53	34	1.7 (1.1 to 2.6)	
Sex				
Female	85	40	1.0 (referent)	.04
Male	139	58	1.5 (1.0 to 2.3)	
Age at diagnosis[4]				
1-year increase			1.02 (1.01 to 1.03)	<.01
Skin type				
No tan	75	31	1.0 (referent)	1.0
Tan	139	62	1.0 (0.6 to 1.5)	
Skin color				
Medium	63	25	1.0 (referent)	.30
Very fair/fair	161	73	1.3 (0.8 to 1.0)	
Anatomic site				
Other	174	77	1.0 (referent)	.02
Head and neck	50	21	1.8 (1.1 to 3.0)	
Solar elastosis				
Absent	64	46	1.0 (referent)	.06
Present	152	49	0.7 (0.5 to 1.0)	
Breslow thickness				
< 0.76	76	10	1.0 (referent)	
0.76 – 1.69	59	28	4.3 (2.1 to 8.9)	<.01
1.70 – 3.60	53	37	12.4 (6.2 to 25.0)	<.01
> 3.60	35	23	17.9 (8.5 to 37.6)	<.01
Clark level				
II	53	4	1.0 (referent)	
III	57	23	7.5 (2.6 to 21.6)	<.01
IV/V	107	65	17.9 (6.5 to 49.2)	<.01
Mitotic figure(s)				
Absent	65	8	1.0 (referent)	<.01
Present	150	88	8.9 (4.3 to 18.3)	
Co-existing nevus				
No	156	65	1.0 (referent)	.97
Yes	59	29	1.0 (0.6 to 1.5)	
Dermal nevus				
No	191	80	1.0 (referent)	.16
Yes	27	16	1.5 (0.9 to 2.5)	
Total sun exposure				
Light/moderate	109	43	1.0 (referent)	.02
Heavy/very heavy	108	50	0.6 (0.4 to 0.9)	
Severe sunburn				
No	81	39	1.0 (referent)	.14
Yes	142	59	0.7 (0.5 to 1.1)	
Sunlamp use				
No	189	89	1.0 (referent)	<.01
Yes	35	9	0.3 (0.2 to 0.7)	
Education				
Up to high school	111	47	1.0 (referent)	.03
Greater than high school	113	51	0.7 (0.4 to 1.0)	
Skin examination				
No	175	74	1.0 (referent)	.60
Yes	49	24	.9 (0.6 to 1.4)	
Skin awareness				
No	169	80	1.0 (referent)	<.01
Yes	55	18	0.5 (0.3 to 0.8)	

[3] Numbers may vary because of missing data for some variables.

[4] Age is continuous variable.

3. Independent predictors of death from melanoma in a multivariable model.[5]

Variable	Hazard ratio (95% confidence interval)	*P* value
Number of nevi		
<30	1.0 (referent)	<.001
30+	2.4 (1.5 to 3.7)	
Sex[6]		
Female	1.0 (referent)	.82
Male	1.1 (0.7 to 1.6)	
Age at diagnosis		
1-year increase	1.03 (1.01 to 1.04)	<.001
Anatomic site		
Other	1.0 (referent)	.01
Head/Neck	2.0 (1.2 to 3.4)	
Solar elastosis		
Absent	1.0 (referent)	.01
Present	0.6 (0.3 to 0.9)	
Breslow thickness		
< 0.76	1.0 (referent)	
≤3.60	3.1 (1.9 to 5.2)	<.001
> 3.60	4.7 (2.6 to 8.5)	<.001
Mitoses		
None	1.0 (referent)	<.001
Any	4.2 (1.9 to 9.1)	
Dermal nevus		
No	1.0 (referent)	.04
Yes	1.8 (1.0 to 3.3)	
Skin awareness		
No	1.0 (referent)	.01
Yes	0.5 (0.3 to 0.9)	

[5] This model was run with all variables with $P < .15$ in table 2. Variables that remained statistically significant are shown.

[6] Sex was forced into the model.