Cutaneous nevi and risk of melanoma death in women and men: A prospective study

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Background: It was unclear whether an increased number of common nevi (moles) predicts melanoma death.

Objective: We prospectively examined the association between number of common nevi and risk of melanoma death.

Methods: Our study used data from the Nurses' Health Study (n = 77,288 women) and Health Professionals Follow-up Study (n = 32,455 men). In 1986, participants were asked about the number of moles they had with a ≥3-mm diameter on the upper extremity, and we stratified their answers into 3 categories (none, 1-2, or ≥3) on the basis of data distribution.

Results: During follow-up (1986-2012), 2452 melanoma cases were pathologically confirmed; among these, we identified 196 deaths due to melanoma. Increased number of nevi was associated with melanoma death; the hazard ratio (HR) for ≥3 nevi compared with no nevi was 2.49 (95% confidence interval [CI] 1.50-4.12) for women and 3.97 (95% CI 2.54-6.22) for men. Among melanoma cases, increased number of nevi was associated with melanoma death in men (≥3 nevi, HR 1.89, 95% CI 1.17-3.05) but not in women. Similarly, the number of nevi was positively associated with Breslow thickness in men only (P_{trend} = .01).

Limitations: This is an epidemiologic study without examination into mechanisms.

Conclusion: Increased number of cutaneous nevi was significantly associated with melanoma death. High nevus count might serve as an independent prognostic factor to predict the risk of melanoma death particularly among male melanoma patients. (J Am Acad Dermatol 2019;80:1284-91.)

Key words: Breslow thickness; cohort study; common nevi; death; melanoma.

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The increased number of common acquired melanocytic nevi (moles), which predominantly occur in sun-exposed or intermittently sun-exposed skin areas, is a well-known constitutional risk factor of melanoma.[1-9] Meta-analyses have indicated a relative risk of 1.02 (95% confidence interval [CI] 1.01-1.02) for melanoma, representing a 2% incidence in melanoma risk per increase of 1 additional common nevus,[6,7] and an estimated 42% of melanoma cases were attributed to having ≥25 common nevi.[7] However, it is unclear whether nevus count is associated with melanoma death. In addition, although a number of factors have been established as risk factors for skin cancer,[2-5,10] previous studies on phenotypic characteristics associated with melanoma death have been limited.

CAPSULE SUMMARY

- A large number of nevi significantly increased the risk of melanoma death. High nevus count might independently predict melanoma death particularly among male melanoma patients.
- Number of nevi might potentially serve as an independent prognostic factor of melanoma in clinical practices, particularly for men.

We hypothesized that nevi might be a phenotypic predictor of melanoma death and prospectively examined the association between number of common nevi and risk of melanoma death in a cohort of women (the Nurses' Health Study [NHS]) and a cohort of men (the Health Professionals Follow-up Study [HPFS]). We further hypothesized that nevus count would predict melanoma death among melanoma cases. That is, nevus count would be associated with melanoma death not only through its association with melanoma incidence but also its prediction of a worse prognosis among patients.

METHODS

Study participants

Details of NHS and HPFS have been described previously.[10,11] NHS and HPFS participants were asked about the number of nevi on their upper extremities in slightly different ways. In 1986, NHS participants were asked about the total number of cutaneous nevi with a ≥3-mm diameter on their left arm from the shoulder to the wrist and given the option to select 1 of 7 categories (none, 1-2, 3-5, 6-9, 10-14, 15-20, or ≥21). HPFS participants were asked about the total number of cutaneous nevi with a ≥3-mm diameter on both their forearms between the elbow and the wrist and reported this quantity using the same 7 categories as in the NHS. The size-based cutoff of 3 mm was chosen because participants could easily distinguish common nevi from other pigmented lesions. Information on number of nevi was not updated during the follow-up.

Participants report diagnoses of melanoma biennially. Only pathologically confirmed invasive cases were included. We collected information on body site (available for all cases) and major histopathologic factors of melanoma (Breslow thickness [continuous variable] and Clark level [available for about half of the cases]). Some participants without melanoma diagnoses reported in biennial surveys were later confirmed to have melanoma deaths; these participants were also documented as having melanoma cases, and their times of diagnosis were obtained. We did not specifically collect the information on skin cancer screening.

Deaths were reported by next of kin or the post office. Names of nonresponders were searched in the National Death Index. Date of death was ascertained from death certificates, supplemented as needed with medical records. More than 98% of deaths in the cohorts have been identified by these 3 methods.[12] Physician reviewers blinded to information on major participant characteristics ascertained cause of death from death certificates, which were supplemented with medical records or interviews with family or health care providers if necessary. In the case of death due to a cancer metastasis, the primary cancer was recorded as the cause of death.

Statistical analysis

Melanoma cases that occurred before the study baseline (return of the 1986 questionnaire) were excluded from our analyses. Among participants with information on nevi, we restricted the analyses to white persons in the primary analyses because most participants were white and white persons are at increased risk of melanoma.

We first examined the association between melanocytic nevi and risk of melanoma death between the baseline (return of the 1986 questionnaire) and end of follow-up (June 2012 for NHS and January 2012 for HPFS) in the overall cohort. We also assessed risk of melanoma death specifically among melanoma patients only during the same follow-up period.

We evaluated the number of nevi using both continuous and categorical variables. For continuous assessment of nevi frequency for each participant, we assigned the middle value to each of the 7 originally reported categories. For example, if 1

Abbreviations used:

CI: confidence interval
HPFS: Health Professionals Follow-up Study
HR: Hazard ratio
NHS: Nurses' Health Study
SD: standard deviation

participant reported the nevus count of 3-5, a count of 4 was assigned to this individual. In the categorical assessment, number of nevi was reclassified into 3 categories (none, 1-2, or ≥3). Because the number of melanoma cases with nevi frequencies of 6-9, 10-14, 15-20, and ≥21 was limited, restricting the statistical power, these categories were combined with the 3-5 nevi category.

All analyses were carried out by using SAS (version 9.2; SAS Institute Inc, Cary, NC). All *P* values were 2-tailed, with the significance level set at $P < .05$.

Analyses of the overall cohort. The analyses were conducted in the overall NHS or HPFS cohort first. Person-years of follow-up were calculated from baseline to death or end of follow-up, whichever came first. Death due to melanoma was the end point. Deaths from other causes were censored. We calculated hazard ratios (HRs) and 95% CIs for each nevus count category compared with the no nevi category. The analyses were performed by using Cox proportional hazards analysis stratified by age and 2-year interval. We conducted multivariate analyses adjusting for smoking, alcohol intake, physical activity, body mass index, childhood sunburn reaction to sun, childhood tanning ability (NHS only), times of sunburns, hair color, family history of melanoma, cumulative ultraviolet flux, and history of keratinocyte carcinoma. The HR per 1 mole and *P* value for trend were calculated by using the linear trend test and the continuous variable of common nevi. Sensitivity analyses were conducted by including all nonwhite participants.

Analyses only among melanoma cases. We also examined whether number of nevi was associated with worse prognosis in analyses limited to melanoma cases only. Cases were included in the analysis at the time of diagnosis and followed until death or end of follow-up. Death from melanoma was the end point, and deaths from other causes were censored. Cox proportional hazards models, with time since diagnosis (in months) as the underlying time variable, were used to calculate HRs and 95% CIs for the nevus count categories; we adjusted these values for the aforementioned covariates. In a second model, we additionally adjusted for Breslow thickness, Clark level, and body site of melanoma. Sensitivity analyses were also conducted by including all nonwhite participants. Each event (death from melanoma) was compared with only the set of participants who were at exactly the same time since diagnosis (measured in months), which enabled us to tightly control for confounding by time since diagnosis. We also calculated the odds ratios and 95% CIs for the association between nevus count and Breslow thickness of melanoma (≤1 mm or >1 mm, recognized cutoff for defining thin melanoma) using logistic regression analyses.

Stratified analyses were conducted by Breslow thickness and body location of melanoma (head or neck, trunk, or limb), and their possible interactions with nevus count were examined.

RESULTS

A total of 77,288 women in NHS and 32,455 men in HPFS were included. During the follow-up (1986-2012), 2452 cases of melanoma were documented (1545 in NHS and 907 in HPFS, Table I). Men (HPFS) had a higher proportion of melanoma at the head, neck, or trunk, and women (NHS) had more melanoma at the extremities. Melanoma cases in men had slightly higher Breslow thicknesses (mean ± standard deviation [SD], 1.02 ± 1.31 mm) than those in women (mean ± SD, 0.97 ± 1.14 mm) ($P = .53$). A total of 196 deaths due to melanoma (91 in NHS and 105 in HPFS) were identified; the mean ± SD time between diagnosis and death from melanoma was 5.9 ± 6.7 years for NHS and 5.6 ± 6.1 years for HPFS. Melanoma patients with higher numbers of nevi tended to be younger at diagnosis, particularly in women. Participants with higher numbers of nevi were more likely to have had sunburn reactions as a child or adolescent (men) or ≥6 lifetime sunburns (women; Table I).

In the overall cohorts, participants were followed-up for a mean of 24.0 years in the NHS and 22.1 years in the HPFS. Overall risk analyses showed that a higher number of nevi was significantly associated with increased risk of melanoma death ($P_{trend} = .003$ in NHS, $P_{trend} < .0001$ in HPFS, Table II). Compared with no nevi on the upper extremity, the multivariate-adjusted HR (95% CI) was 1.41 (0.86-2.34) for 1-2 nevi and 2.49 (1.50-4.12) for ≥3 nevi in NHS. In HPFS, the association appeared even stronger, with an HR (95% CI) of 2.04 (1.25-3.32) for 1-2 nevi and 3.97 (2.54-6.22) for ≥3 nevi.

Melanoma cases were followed up for a mean of 11.1 years in NHS and 8.5 years in HPFS. In an analysis of only melanoma cases, an increased number of nevi was independently associated with

Table I. Age-standardized baseline characteristics of cases with melanoma by number of common melanocytic nevi in the Nurses' Health Study (1986-2012) and Health Professionals Follow-up Study (1986-2012)*

	Nurses' health study				Health Professionals follow-up study			
Category	**None**	**1-2**	**≥3**	***P*†**	**None**	**1-2**	**≥3**	***P*†**
n	760	417	368		494	211	202	
Age at diagnosis, y, mean (SD)	66.8 (9.7)	65.9 (10.3)	64.3 (9.8)	.0003	70.2 (10.0)	68.2 (9.8)	68.6 (10.9)	.03
Body mass index, kg/m,^{2} mean (SD)	25.7 (4.4)	25.7 (5.0)	27.1 (5.7)	.001	25.5 (3.2)	25.8 (3.4)	25.8 (3.3)	.19
Current smoking, %	9.3	5.8	6.1	.12	3.8	1.5	3.9	.54
Alcohol intake, g/d, mean (SD)	7.3 (11.0)	6.1 (9.5)	6.8 (11.5)	.17	14.4 (18.7)	13.3 (14.9)	11.2 (13.7)	.21
Physical activity, metabolic equivalent hr/wk, mean (SD)	16.5 (18.5)	16.0 (19.6)	14.4 (19.0)	.47	23.0 (25.3)	27.6 (46.7)	18.9 (18.8)	.02
Family history of melanoma, %	9.8	10.5	11.8	.68	7.1	8.7	9.2	.73
Red or blonde hair, %	23.7	22.6	20.4	.74	20.1	18.4	15.0	.44
Childhood and adolescent tendency to sunburn or blistering response, %	47.0	45.2	50.6	.18	79.3	80.8	87.8	.03
Childhood and adolescent tendency for average-to-deep tanning response, %	58.0	59.6	59.0	.90				
No. lifetime sunburns, ≥6, %	59.2	63.4	66.2	.02	44.6	36.6	39.9	.47
UV flux, $\times 10^{-4}$ RB units, mean (SD)	125.3 (26.2)	125.4 (25.8)	124.1 (25.2)	.58	136.0 (29.6)	131.2 (26.9)	136.1 (29.1)	.10
Breslow thickness, mm, mean (SD)	1.0 (1.2)	1.0 (1.3)	1.0 (1.1)	.72	0.9 (0.9)	1.4 (2.1)	1.0 (0.9)	.02
Clark level IV or V, %	29.4	24.1	27.5	.22	20.4	31.1	40.1	.04
Body site, %								
Head or neck	21.0	16.5	15.2	.0006	35.8	30.1	37.6	.43
Trunk	24.2	28.5	34.7		38.9	47.0	40.4	
Limbs	54.8	55.0	50.1		25.3	22.9	22.0	

SD, Standard deviation; *UV*, ultraviolet.

*All values shown are for the information before melanoma diagnosis or at the questionnaire cycle close to the melanoma diagnosis year, except when otherwise noted. All variables except age at diagnosis were adjusted for age at diagnosis.

†*P* values were calculated by using the chi-squared test for categorical variables and 1-way analysis of variance for continuous variables.

Table II. HRs (95% CIs) for the association between number of common melanocytic nevi and risk of melanoma death, by cohort

	No. moles				
Study, outcome	**None**	**1-2**	**≥3**	**Per mole***	P_{trend}*
Nurses' Health Study (1986-2012)					
Melanoma deaths/person-years	43/1,172,683	24/446,457	24/236,664		
Age-adjusted HR (95% CI)	1.00	1.52 (0.92-2.51)	2.90 (1.76-4.79)	1.14 (1.07-1.23)	.0002
Multivariate-adjusted HR† (95% CI)	1.00	1.41 (0.86-2.34)	2.49 (1.50-4.12)	1.12 (1.04-1.20)	.003
Health Professionals Follow-up Study (1986-2012)					
Melanoma deaths/person-years	44/484,399	26/140,184	35/91,531		
Age-adjusted HR (95% CI)	1.00	2.05 (1.26-3.33)	4.01 (2.57-6.26)	1.20 (1.14-1.27)	<.0001
Multivariate-adjusted HR† (95% CI)	1.00	2.04 (1.25-3.32)	3.97 (2.54-6.22)	1.20 (1.14-1.27)	<.0001

CI, Confidence interval; *HR*, hazard ratio.

*The HR per mole and *P* value for trend were calculated by using the linear trend test with a continuous assessment of the number of moles.

†Multivariate-adjusted analyses were adjusted for age, smoking (never, past, or current smokers), physical activity (in quintiles, metabolic equivalent hr/wk), body mass index (<25, 25-29.9, ≥30 kg/m^2), alcohol intake (0, >0-4.9, 5-9.9, or ≥10 g/d), childhood sunburn reaction to sun (tan without burn, burn, or painful burn and blisters), childhood tanning ability (practically none, little tan, average tan, or deep tan), number of sunburns (0, 1-2, 3-5, or ≥6), hair color (red, blonde, light brown, or dark brown/black), family history of melanoma (yes or no), cumulative ultraviolet flux (in quintiles), and history of keratinocyte carcinoma (yes or no).

risk of melanoma death in HPFS melanoma cases (P_{trend} = .004), with an HR of 1.89 (95% CI 1.17-3.05) for ≥3 nevi. The association persisted after adjusting for Breslow thickness, Clark level, and melanoma body site. However, this association was not found in women (P_{trend} = .63, Table III). We further examined the association of Breslow thickness with nevus count. Most cases had Breslow thicknesses ≤1 mm (73.7% in NHS and 73.1% in HPFS). We found that number of nevi was positively associated with Breslow thickness in men only (P_{trend} = .01), not in women (P_{trend} = .42). Compared with no nevi, the odds ratio (95% CI) of having a Breslow thickness >1 mm was 1.58 (0.88-2.83) for 1-2 nevi and 2.28 (1.30-4.02) for ≥3 nevi (Table IV).

No significant interactions were found between melanoma body site and nevus count on risk of melanoma death ($P_{interaction}$ = .98 in NHS, $P_{interaction}$ = .31 in HPFS). Stratified analyses by Breslow thickness were limited by the small number of melanoma deaths among cases with thicknesses ≤1 mm (13 in NHS, 9 in HPFS). However, using a cutoff of 1.5 mm (median Breslow thickness among melanoma deaths in the cohorts), we found significant effect modification by Breslow thickness ($P_{interaction}$ = .03); a significant association was found (in men) between nevi and melanoma death among cases with thicknesses ≤1.5 mm (HR 1.16, 95% CI 1.00-1.35) but not among cases with thicknesses >1.5 mm (HR 0.84, 95% CI 0.62-1.13). The analysis of NHS melanoma cases did not yield similar findings ($P_{interaction}$ = .68).

Sensitivity analyses that included nonwhite participants and additionally adjusted for race did not change the findings. For example, in analyses of the overall cohort associated with melanoma deaths, the multivariate-adjusted HR (95% CI) was 1.40 (0.90-2.19) for 1-2 nevi and 2.20 (1.38-3.50) for ≥3 nevi in NHS (P_{trend} = .002) and 1.99 (1.22-3.23) for 1-2 nevi and 3.92 (2.50-6.12) for ≥3 nevi in HPFS (P_{trend} < .0001). In analyses only among melanoma cases, the HR (95% CI) was 1.13 (0.69-1.83) for 1-2 nevi and 0.98 (0.60-1.59) for ≥3 nevi in NHS (P_{trend} = .49) and 1.42 (0.83-2.44) for 1-2 nevi and 1.90 (1.17-3.09) for ≥3 nevi in HPFS (P_{trend} = .004) after adjusting for race, Breslow thickness, Clark level, body site of melanoma, and other aforementioned covariates.

DISCUSSION

In our study, an increased number of common acquired melanocytic nevi was significantly associated with risk of melanoma death in women and men. A high number of cutaneous nevi might predict the risk of melanoma death among men with melanoma independent of Breslow thickness.

An increased number of common nevi conveys an elevated risk of melanoma,[1-9] but whether nevi predicts the risk of melanoma death was unclear. In 1 study, no association was found between total body nevus count and high mitotic rate of melanoma, a predictor of poor prognosis.[13] In another study, a favorable prognosis was reported for melanoma patients with high nevus counts (n = 2184, nevi number counted at melanoma diagnosis).[14] Considering that study reported significantly thinner melanomas in patients with high nevus counts,[14] a concern was raised that this might reflect greater screening for nevi and earlier diagnosis of melanoma among those with higher nevus counts.[15] In addition, this study did not distinguish common nevi from atypical nevi. Atypical nevi have been associated with superficial-spreading melanomas with a more favorable tumor stage.[16]

Etiologic factors of nevi might help explain the observed association between common nevi and risk of melanoma death, which might represent a late-stage or severe form of melanoma. Prior studies have highlighted the roles of intermittent ultraviolet radiation in the nevogenesis of common nevi[17-22] and melanoma carcinogenesis.[23] High nevus counts might, therefore, serve as an indicator of intermittent sun exposure. Common nevi might be melanoma precursors, and individuals with many nevi might possess a greater number of melanocytes with inherently high propensity for malignant transformation.[24] However, the chance of malignant transformation in common nevi is very rare.[1] High number of nevi might also represent the intermediate sun-sensitive skin phenotypes. Studies have examined the association between pigmentary traits and nevi. Although fair skin, sunburn tendency, and freckling have also been positively associated with the occurrence of melanocytic nevi in some studies,[17,18,20,25] in other studies, red-haired or blonde-haired individuals had significantly fewer moles than individuals with other hair colors.[26-28]

In analyses of melanoma cases only, high nevus counts were associated with worse survival in men but not in women. Indeed, in the analysis of overall cohort risk, the HRs with the HPFS cohort also appeared larger than those with the NHS cohort. The reason for the differential effect by sex is unclear, but there are several points worth noting. First, high nevus counts were associated with thicker melanomas (Breslow thickness >1 mm) in men but not in women in our study. As tumor thickness is the most important factor for melanoma prognosis,[29] the role of high nevus counts in predicting melanoma deaths

Table III. HRs (95% CIs) for the association between number of melanocytic nevi and risk of melanoma death among melanoma cases only, by cohort*

Study, outcome	No. moles			Per mole†	P_{trend}†
	None	1-2	≥3		
Nurses' health study (1986-2012)*					
Melanoma deaths/person-years	43/8242	24/4521	24/4379		
Age-adjusted HR (95% CI)	1.00	1.08 (0.65-1.78)	1.04 (0.63-1.71)	0.98 (0.91-1.06)	.67
Multivariate-adjusted HR‡ (95% CI)	1.00	1.15 (0.69-1.91)	1.02 (0.61-1.71)	0.98 (0.91-1.06)	.63
Multivariate-adjusted HR§ (95% CI)	1.00	1.21 (0.72-2.06)	1.17 (0.69-2.00)	0.99 (0.92-1.08)	.90
Health Professionals Follow-up Study (1986-2012)*					
Melanoma deaths/person-years	44/4143	26/1738	35/1856		
Age-adjusted HR (95% CI)	1.00	1.45 (0.89-2.37)	1.68 (1.07-2.62)	1.08 (1.02-1.14)	.01
Multivariate-adjusted HR‡ (95% CI)	1.00	1.29 (0.77-2.17)	1.89 (1.17-3.05)	1.09 (1.03-1.16)	.004
Multivariate-adjusted HR§ (95% CI)	1.00	1.45 (0.84-2.49)	1.88 (1.15-3.06)	1.09 (1.03-1.16)	.005

CI, Confidence interval; *HR*, hazard ratio.
*Melanoma cases entered follow-up after diagnosis.
†The HR per mole and *P* value for trend were calculated by using the linear trend test with a continuous assessment of the number of moles.
‡Multivariate-adjusted analyses were adjusted for age, smoking (never, past, or current smokers), physical activity (in quintiles, metabolic equivalent hr/wk), body mass index (<25, 25-29.9, or ≥30 kg/m^2), alcohol intake (0, >0-4.9, 5-9.9, or ≥10 g/d), childhood sunburn reaction to sun (tan without burn, burn, or painful burn and blisters), childhood tanning ability (practically none, little tan, average tan, or deep tan, for Nurses' Health Study only), number of sunburns (0, 1-2, 3-5, or ≥6), hair color (red, blonde, light brown, or dark brown/black), family history of melanoma (yes or no), cumulative ultraviolet flux (in quintiles), and history of keratinocyte carcinoma (yes or no).
§Additionally adjusting for Breslow thickness (as a continuous variable), Clark level, and melanoma body site. Adjusting for Breslow thickness as a categorical variable (≤1 or >1 mm) yielded very similar results.

Table IV. ORs (95% CIs) for the association between number of melanocytic nevi and Breslow thickness >1 mm of melanoma in the Nurses' Health Study and Health Professionals Follow-up Study*

Study, outcome	No. moles			Per mole†	P_{trend}†
	None	1-2	≥3		
Nurses' Health Study (1986-2012)*					
Cases with Breslow thickness ≤1 mm	247	143	137		
Cases with Breslow thickness >1 mm	96	47	45		
Age-adjusted OR (95% CI)	1.00	0.86 (0.57-1.30)	0.91 (0.60-1.38)	0.97 (0.91-1.04)	.39
Multivariate-adjusted OR‡ (95% CI)	1.00	0.87 (0.57-1.35)	0.92 (0.60-1.43)	0.97 (0.91-1.04)	.42
Health Professionals Follow-up Study (1986-2012)*					
Cases with Breslow thickness ≤1 mm	174	70	61		
Cases with Breslow thickness >1 mm	45	30	37		
Age-adjusted OR (95% CI)	1.00	1.70 (0.99-2.91)	2.37 (1.40-4.01)	1.11 (1.03-1.19)	.005
Multivariate-adjusted OR‡ (95% CI)	1.00	1.58 (0.88-2.83)	2.28 (1.30-4.02)	1.11 (1.02-1.20)	.01

CI, Confidence interval; *OR*, odds ratio.
*Analysis only among melanoma cases.
†The OR per 1 mole and *P* value for trend were calculated by using the linear trend test with a continuous assessment of the number of moles.
‡Multivariate-adjusted analyses were adjusted for age, smoking (never, past, or current smokers), physical activity (in quintiles, metabolic equivalent hr/wk), body mass index (<25, 25-29.9, ≥30 kg/m^2), alcohol intake (0, >0-4.9, 5-9.9, or ≥10 g/d), childhood sunburn reaction to sun (tan without burn, burn, or painful burn and blisters), childhood tanning ability (practically none, little tan, average tan, or deep tan, for Nurses' Health Study only), number of sunburns (0, 1-2, 3-5, or ≥6), hair color (red, blonde, light brown, or dark brown/black), family history of melanoma (yes or no), cumulative ultraviolet flux (in quintiles), and history of keratinocyte carcinoma (yes or no).

in men with melanoma might be partly explained by the positive association of nevus count with Breslow thickness. Second, it is reasonable to speculate that male patients with melanoma and high nevus counts might tend to have their melanomas diagnosed at later stages. However, although the Breslow thickness appeared slightly higher in men than women, the difference was not statistically significant. Third, our prior study supported a stronger association between number of moles and truncal melanoma

than melanoma at other sites.[30] In our study, melanoma tended to occur at the head, neck, or trunk in men and at the extremities in women, consistent with a prior study of HPFS and NHS with shorter follow-up.[30] Poorer survival in head or neck melanoma and trunk melanoma compared with other sites has been reported.[31] Although we were restricted in statistical power to perform analyses by body site, we found a higher proportion of melanoma deaths in men among melanomas of the head or neck (8.7%, 25/289) and trunk (7.8%, 26/334) than among the extremities (5.0%, 10/199). In women, the proportion of melanoma deaths appeared similar between melanomas of the head or neck (5.7%, 16/282), trunk (4.9%, 21/425), and extremities (4.8%, 39/813). Fourth, NHS and HPFS collected information on common nevi in different ways. The potentially differential validity and the reliability of nevi self-report might have also complicated the comparability of the data between men and women.

The observed differential associations by sex might also reflect other etiologic mechanisms. For example, the number of nevi has been identified as a phenotypic marker for plasma sex hormone levels, with more nevi associated with higher levels of estradiol and testosterone.[32] Considering an androgen-related mechanism has long been hypothesized for melanoma development,[11,33] further studies are warranted to explore whether androgen could help explain the predisposition of men for thick melanomas and the possible interplay between nevi and an androgen-related mechanism.

Our study was strengthened by its prospective design and detailed information on potential confounders. We are aware of some limitations. First, information on common nevi was self-reported. We did not verify the self-report of common nevi and did not collect information on nevi at other body parts and the specific types. Previous studies have shown a substantial agreement between nevus self-counts and the gold standard measure, clinical assessment by dermatologists.[34-36] The number of moles on arms has been used as a proxy for the total body mole count and for systematic melanoma risk in studies that included NHS data and other resources.[37,38] Second, although the number of nevi is highly age-dependent and not static during life, information on moles was not updated during follow-up. However, the increased frequency of growing nevi was thought to be related to the growth hormone–rich environment during adolescence and pregnancy.[39] Number of nevi would have stayed similar because most participants were postmenopausal women and adult men (supported by the mean age in Table I). Even so, it would be interesting to assess the time trends of the examined associations,[40] and further studies were warranted. Third, we lack complete information on melanoma treatment, recurrence, multiple melanomas, and other measures for melanoma prognosis. Fourth, the modest sample size restricted the power for analyses of nevi with finer categories and subgroup analyses. However, the analyses involving the continuous assessment of nevus count yielded findings consistent with the categorical assessment. We only had a limited proportion of melanoma cases with information on ulceration and mitotic counts, which constrained the power of considering these histopathologic factors in our analyses.

In conclusion, our prospective investigation showed that increased number of common nevi was significantly associated with the risk of melanoma death. A high number of nevi was independently associated with risk of melanoma deaths among men with melanoma but not among women, suggesting that nevus count might independently predict the risk of melanoma deaths among men. Our findings inform general practitioners on the early detection of and improved therapeutics for melanoma cases with high numbers of nevi. Further studies are warranted to confirm the differential associations of nevus counts with melanoma prognosis by sex and to elucidate the underlying mechanisms.

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