Published in final edited form as:

J Am Acad Dermatol. 2019 May ; 80(5): 1284–1291. doi:10.1016/j.jaad.2018.12.058.

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

Wen-Qing Li, PhD^{1,2,3}, Eunyong Cho, ScD^{2,3,4}, Martin A. Weinstock, MD^{2,3,5}, Suyun Li, PhD^{2,6}, Meir J. Stampfer, MD, DrPH^{4,7,8}, and Abrar A. Qureshi, MD, MPH^{2,3,4}

¹Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Cancer Epidemiology, Peking University Cancer Hospital & Institute, Beijing, China

²Department of Dermatology, Warren Alpert Medical School, School of Public Health, Brown University, Providence, RI

³Department of Epidemiology, School of Public Health, Brown University, Providence, RI

⁴Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

⁵Center for Dermatoepidemiology, VA Medical Center, Providence, RI, USA

⁶School of Public Health, Institute for Chemical Carcinogenesis, Guangzhou Medical University, 195 Dongfengxi Road, Guangzhou 510182, China

⁷Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

⁸Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

Abstract

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

*Correspondence: Wen-Qing Li, nhwli@channing.harvard.edu.

Author contributions: Wen-Qing Li - study concept and design; statistical analysis; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; Eunyong Cho- study concept and design; critical revision of the manuscript for important intellectual content; Martin A. Weinstock- analysis and interpretation of data; critical revision of the manuscript for important intellectual content; Suyun Li - statistical analysis; critical revision of the manuscript for important intellectual content; Meir J. Stampfer - study concept and design; critical revision of the manuscript for important intellectual content; Abrar A Qureshi - study concept and design; acquisition of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; funding support; study supervision.

Potential conflicts of interest: The authors declare no conflicts of interest.

Institutional Review Board (IRB) Approval: The study was approved by the Human Research Committee at Brigham and Women's Hospital and Harvard School of Public Health (Boston, MA)

Clinical Trial Registration: not applicable

Statement on prior presentation: A poster on this project was presented in the American Association for Cancer Research 2017 meeting (Apr 1–5, 2017, Washington, D.C.) and the Society for Investigative Dermatology 2017 meeting (Apr 26–29, 2017, Portland, OR).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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

Methods: Our study was based on the Nurses' Health Study (n=77,288 women) and Health Professionals Follow-up Study (n=32,455 men). Number of moles with ≥ 3 mm diameter on the upper extremity was asked in 1986 and was re-classified into three categories (none, 1–2, or ≥ 3) based on data distribution.

Results: During follow-up (1986–2012), 2,452 melanoma cases were pathologically confirmed, among whom 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, number of nevi was positively associated with Breslow thickness in men only ($P_{\text{trend}}=0.01$).

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

Conclusions: Increased number of cutaneous nevi was significantly associated with melanoma death. High nevi count may serve as an independent prognostic factor, which predicts the risk of melanoma death particularly among male melanoma cases.

Keywords

melanoma; common nevi; death; Breslow thickness; cohort study

Introduction

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 reported a relative risk of 1.02 [95% confidence interval (CI), 1.01–1.02] for melanoma, representing a 2% incidence in melanoma risk, per the increase of one additional common nevus^{6, 7} and estimated that 42% of melanoma can be attributed to having ≥ 25 common nevi⁷. However, it is unclear whether nevus count would be associated with melanoma death. In addition, while a number of factors have been established for risk of skin cancer^{2–5, 10}, previous studies on phenotypic characteristics associated with melanoma death have been limited.

We hypothesized that nevus may 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 cases.

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 the upper extremity in slightly different ways. In 1986, NHS participants were asked about the total number of cutaneous nevi with 3 mm diameter on the left arm from the shoulder to the wrist, selecting one of the following seven 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 3 mm diameter on both forearms between the elbow and the wrist, and reported this using the same seven categories with NHS. The size-based cutoff of 3mm was defined so that participants can 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 recorded major histopathological factors of melanoma (Breslow thickness in continuous variable and Clark's level, available for about half of the cases). For diagnoses of melanoma that were not originally reported in any of the biennial surveys, if the participants were confirmed to be melanoma deaths later on, they have also been documented as melanoma cases with the diagnosis time 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 non-responders 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 three methods¹². 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 the 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 the analyses. Among participants with information on nevi, we restricted the analyses to Whites in the primary analyses, as most participants are Whites and Whites are at additionally increased risk for 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 Jan 2012 for HPFS) in the overall cohort. We also assessed risk of melanoma death specifically among melanoma cases only during the same follow-up period.

We evaluated number of nevi in both continuous and categorical variables. For continuous assessment of nevi frequency of each participant, we assigned the median value to each of the seven originally reported categories. For example, if one participant reported the nevi

count of 35, a count of 4 was assigned to this individual. In the categorical assessment, number of nevi was re-classified into three categories (none, 1–2, or 3). Because the number of melanoma cases with nevi frequency of 6–9, 10–14, 15–20, and 21 was limited, restricting the statistical power, these categories were incorporated with the category of 3–5.

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 $P < 0.05$.

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 the 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 the hazard ratios (HRs) and 95% confidence intervals (CIs) for each category of nevi count, compared with no nevi. The analyses were conducted using Cox proportional hazards analysis stratified by age and 2-year interval. Multivariate-adjusted analyses were conducted additionally 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 UV flux, and history of keratinocyte carcinoma. The HR per one mole and *P* for trend were calculated by using the linear trend test, based on the continuous variable of common nevi. Sensitivity analyses were conducted by including all non-Whites.

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 since time of diagnosis, and were 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 categories of nevi count, adjusting for the aforementioned covariates. In a second model, we additionally adjusted for Breslow thickness, Clark's level, and body site of melanoma. Sensitivity analyses were also conducted by including all non-Whites. Each event (death from melanoma) was compared only with the risk set of participants who were at exactly the same time since diagnosis measured in months, providing for tight control of confounding by time since diagnosis. We also calculated the odds ratios (ORs) and 95% CIs for the association between nevi counts and Breslow thickness of melanoma (≤ 1 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 and neck, trunk, or limb), and their possible interactions with nevi 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), 2,452 cases of melanoma were documented (1,545 in NHS and 907 in HPFS, Table 1). Men (HPFS) had a higher proportion of melanoma at head and neck or

trunk while women (NHS) had more melanoma at extremities. Melanoma cases in men had slightly higher Breslow thickness (mean 1.02, SD 1.31) than those in women (mean 0.97, SD 1.14) ($P=0.53$). A total of 196 deaths due to melanoma (91 in NHS and 105 in HPFS) were identified, with the mean (SD) years between diagnosis and deaths from melanoma 5.9 (6.7) for NHS and 5.6 (6.1) for HPFS. Melanoma cases with higher number of nevi tended to be younger at diagnosis, particularly in women. Cases with higher nevus count were more likely to have sunburn reactions as a child or adolescent in men, and have 6 or more lifetime sunburns in women (Table 1).

In the overall cohorts, the participants were followed-up for a mean of 24.0 years in NHS and 22.1 years in HPFS. Overall risk analyses found that higher number of nevi was significantly associated with increased risk of melanoma death ($P_{\text{trend}}=0.003$ in NHS and <0.0001 in HPFS) (Table 2). 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 a 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 the analysis only among melanoma cases, increased number of nevi was independently associated with risk of melanoma death in HPFS melanoma cases ($P_{\text{trend}}=0.004$), with a HR of 1.89 (95% CI: 1.17–3.05) for ≥ 3 nevi. The association persisted after adjusting for Breslow thickness, Clark's level and melanoma body sites. However, the association was not found in women ($P_{\text{trend}}=0.63$, Table 3). We further examined the association of Breslow thickness with nevi count. A majority of cases had Breslow thickness ≤ 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 (HPFS) only ($P_{\text{trend}}=0.01$), but not in women (NHS) cases ($P_{\text{trend}}=0.42$). Compared with no nevi, the OR (95% CI) of having Breslow thickness >1 mm was 1.58 (0.88–2.83) for 1–2 nevi and was 2.28 (1.30–4.02) for ≥ 3 nevi (Table 4).

No significant interactions were found between melanoma body sites and nevi counts on risk of melanoma deaths ($P_{\text{interaction}}=0.98$ in NHS and 0.31 in HPFS). Stratified analyses by Breslow thickness were limited by the small number of melanoma deaths among cases with thickness ≤ 1 mm ($n=13$ in NHS and $n=9$ 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 ($P_{\text{interaction}}=0.03$), with a significant association between nevi and melanoma death among cases with thickness ≤ 1.5 mm (HR=1.16, 95% CI: 1.00–1.35), but not among cases with thickness >1.5 mm (HR=0.84, 95% CI: 0.62–1.13) in men. The analysis of NHS melanoma cases did not yield similar findings ($P_{\text{interaction}}=0.68$).

Sensitivity analyses which included non-Whites and additionally adjusted for race did not change the findings materially. 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 ($P_{\text{trend}}=0.002$), and 1.99 (1.22–3.23) for 1–2 nevi and 3.92 (2.50–6.12) for ≥ 3 nevi in HPFS ($P_{\text{trend}}<0.0001$). 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 ($P_{\text{trend}}=0.49$), and 1.42 (0.83–2.44) for 1–2 nevi and 1.90 (1.17–3.09) for

3 nevi in HPFS ($P_{\text{trend}}=0.004$), after adjusting for race, Breslow thickness, Clark's level, body site of melanoma, and other aforementioned covariates.

Discussion

In our study, 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 may predict the risk of melanoma death among men with melanoma independent of Breslow thickness of melanoma.

Increased number of common nevi conveys elevated risk of melanoma¹⁻⁹, but whether nevi would predict the risk of melanoma death was unclear. In one study, no association was found between total body nevus count and high mitotic rate of melanoma, a predictor of poor prognosis¹³. In another study, a favorable prognosis was reported for melanoma patients with high nevi counts (n=2184, nevi number counted at melanoma diagnosis)¹⁴. As that study reported significantly thinner melanoma in patients with high nevus count¹⁴, a concern was raised that this might reflect greater screening for nevi and earlier diagnosis of melanoma among those with higher nevus count¹⁵. 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 stage¹⁶.

Etiologic factors of nevi may help explain the observed association between common nevi and risk of melanoma deaths, which may represent a late-stage or severe form of melanoma. Prior studies have highlighted the roles of intermittent UV radiation in the nevogenesis of common nevi¹⁷⁻²² and melanoma carcinogenesis²³. High nevus counts may therefore serve as an indicator of intermittent sun exposure. Common nevi may be melanoma precursors and individuals with many nevi may possess a greater number of melanocytes with inherently high propensity for malignant transformation²⁴. However, the chance of malignant transformation in common nevi is very rare¹. High number of nevi may also represent the intermediate sun-sensitive skin phenotypes. Studies have examined the association between pigmentary traits and nevi. While fair skin, sunburn tendency, and freckling have also been positively associated with occurrence of melanocytic nevi in some studies^{17, 18, 20, 25}, others reported that red or blonde-haired individuals had significantly fewer moles than individuals with other hair colors²⁶⁻²⁸.

In analyses of melanoma cases only, high nevi counts were associated with worse survival in men, but not in women. Indeed, in the analysis of overall cohort risk, the HRs in HPFS also appeared larger than NHS. The reason for the differential effect by gender is unclear but there are several points worth noting. First, high nevi counts were associated with thicker melanoma (Breslow thickness >1 mm) in men but not in women in our study. As tumor thickness is the most important factor for melanoma prognosis²⁹, the role of high nevi counts in predicting melanoma deaths in male cases of melanoma might be partly explained by the positive association of nevi count with Breslow thickness. Second, it is reasonable to speculate that melanoma cases with high nevus count may tend to have the melanomas diagnosed at a later stage in men. However, although the Breslow thickness appeared slightly higher in men than in women, the difference was not statistically significant. Third,

our prior study has supported a stronger association with number of moles for truncal melanoma than other sites³⁰. Compared with women, melanoma of men tended to occur at head and neck or trunk while melanoma of women tended to occur at extremities in our study, consistent with a prior study of HPFS and NHS with shorter follow-up³⁰. Poorer survival in head and neck melanoma and trunk melanoma compared with other sites has been reported³¹. Although we were restricted in statistical power for the analyses by body sites, we found a higher proportion of melanoma deaths for melanoma of head and neck (8.7%, 25/289) and trunk (7.8%, 26/334) than extremities (5.0%, 10/199) in men. In women, the proportion of melanoma deaths appeared similar between melanoma of head and 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 reliability of nevi self-report may have also complicated the comparability of the data between men and women.

The observed differential associations by gender may 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 testosterone³². As androgen-related mechanism has long been hypothesized for melanoma^{11, 33}, further studies are warranted to explore whether androgen basis could help explain the thick melanoma predisposition in men only and the possible interplays of nevi and 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 counts and systematic melanoma risk in studies based on NHS and other resources^{37, 38}. Second, number of nevi is highly age-dependent and not static during life, but information on moles was not updated during the follow-up. However, increased frequency of growing nevi was thought to be related to the growth hormone-rich environment in adolescence and pregnancy³⁹. Number of nevi would stay similar since most participants were postmenopausal women and adult men (supported by the mean age in Table 1). Even so, it would be interesting to assess the time trends of the examined associations⁴⁰ and further studies were warranted. Third, we lack complete information on melanoma treatment, recurrence, multiple melanomas, and other measures for melanoma prognosis. Fourth, a modest sample size has restricted the power for analyses of nevi with finer categories and subgroup analyses. However, the analyses using continuous assessment of nevi count have 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 risk of melanoma deaths. A high number of nevi was independently associated with risk of melanoma deaths among men with melanoma but not

among women, suggesting that nevi count may independently predict the risk of melanoma deaths among men. Our findings may inform general practitioners on the early detection and improved therapeutics for melanoma cases with high number of nevi. Further studies are warranted to confirm the differential associations of nevi counts with melanoma prognosis by gender and to elucidate the underlying mechanisms.

Acknowledgments:

We would like to thank the participants and staff of the Nurses' Health Study and Health Professionals Follow-up Study, for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, and WY. The authors assume full responsibility for analyses and interpretation of these data. The views presented in this manuscript do not necessarily represent the views of the Department of Veteran Affairs.

Funding: The work was supported by the Research Career Development Award of Dermatology Foundation, the National Institute of Health grants for Nurses' Health Study (P01 CA87969 and UM1 CA186107), Nurses' Health Study II (UM1 CA176726) and Health Professionals Follow-up Study (UM1 CA167552). The funding sources had no role in study design and conduct; in the collection, management, analysis, and interpretation of data; in the preparation, review, or approval of the report; or in the decision to submit the article for publication.

Abbreviations:

BMI	body mass index
CI	confidence interval
HPFS	Health Professionals Follow-up Study
HR	Hazard ratios
NHS	Nurses' Health Study

References

- Goldstein AM, Tucker MA. Dysplastic nevi and melanoma. *Cancer Epidemiol Biomarkers Prev* 2013;22:528–32. [PubMed: 23549396]
- Cho E, Rosner BA, Feskanich D, Colditz GA. Risk factors and individual probabilities of melanoma for whites. *J Clin Oncol* 2005;23:2669–75. [PubMed: 15837981]
- Han J, Colditz GA, Hunter DJ. Risk factors for skin cancers: a nested case-control study within the Nurses' Health Study. *Int J Epidemiol* 2006;35:1514–21. [PubMed: 16943234]
- Qureshi AA, Zhang M, Han J. Heterogeneity in host risk factors for incident melanoma and non-melanoma skin cancer in a cohort of US women. *J Epidemiol* 2011;21:197–203. [PubMed: 21515942]
- Wu S, Han J, Laden F, Qureshi AA. Long-term ultraviolet flux, other potential risk factors, and skin cancer risk: a cohort study. *Cancer Epidemiol Biomarkers Prev* 2014;23:1080–9. [PubMed: 24876226]
- Gandini S, Sera F, Cattaruzza MS, Pasquini P, Abeni D, Boyle P et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur J Cancer* 2005;41:28–44. [PubMed: 15617989]
- Olsen CM, Carroll HJ, Whiteman DC. Estimating the attributable fraction for cancer: A meta-analysis of nevi and melanoma. *Cancer Prev Res (Phila)* 2010;3:233–45. [PubMed: 20086181]
- Chang YM, Newton-Bishop JA, Bishop DT, Armstrong BK, Bataille V, Bergman W et al. A pooled analysis of melanocytic nevus phenotype and the risk of cutaneous melanoma at different latitudes. *Int J Cancer* 2009;124:4208.

9. Newton-Bishop JA, Chang YM, Iles MM, Taylor JC, Bakker B, Chan M et al. Melanocytic nevi, nevus genes, and melanoma risk in a large case-control study in the United Kingdom. *Cancer Epidemiol Biomarkers Prev* 2010;19:2043–54. [PubMed: 20647408]
10. Li WQ, Cho E, Weinstock MA, Mashfiq H, Qureshi AA. Epidemiological Assessments of Skin Outcomes in the Nurses' Health Studies. *Am J Public Health* 2016;106:1677–83. [PubMed: 27459457]
11. Li WQ, Qureshi AA, Ma J, Goldstein AM, Giovannucci EL, Stampfer MJ et al. Personal history of prostate cancer and increased risk of incident melanoma in the United States. *J Clin Oncol* 2013;31:4394–9. [PubMed: 24190118]
12. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. *Am J Epidemiol* 1994;140:1016–9. [PubMed: 7985649]
13. Shen S, Wolfe R, McLean CA, Haskett M, Kelly JW. Characteristics and associations of high-mitotic-rate melanoma. *JAMA dermatology* 2014;150:1048–55. [PubMed: 25142970]
14. Ribero S, Davies JR, Requena C, Carrera C, Glass D, Rull R et al. High nevus counts confer a favorable prognosis in melanoma patients. *Int J Cancer* 2015;137:1691–8. [PubMed: 25809795]
15. Autier P, Funck-Brentano E, Aegerter P, Boniol M, Saiag P. Re: High nevus counts confer a favorable prognosis in melanoma patients by S ribero and co-workers, published in the *International Journal of Cancer*, 2015 (online 21 march 2015). *Int J Cancer* 2015;137:3006–7. [PubMed: 26095813]
16. Black WC. Residual dysplastic and other nevi in superficial spreading melanoma. Clinical correlations and association with sun damage. *Cancer* 1988;62:163–73. [PubMed: 3383113]
17. Harrison SL, MacLennan R, Speare R, Wronski I. Sun exposure and melanocytic naevi in young Australian children. *Lancet* 1994;344:1529–32. [PubMed: 7983952]
18. Whiteman DC, Brown RM, Purdie DM, Hughes MC. Melanocytic nevi in very young children: the role of phenotype, sun exposure, and sun protection. *J Am Acad Dermatol* 2005;52:40–7. [PubMed: 15627079]
19. Harrison SL, MacLennan R, Buettner PG. Sun exposure and the incidence of melanocytic nevi in young Australian children. *Cancer Epidemiol Biomarkers Prev* 2008;17:2318–24. [PubMed: 18768500]
20. Buendia-Eisman A, Palau-Lazaro MC, Arias-Santiago S, Cabrera-Leon A, Serrano-Ortega S. Prevalence of melanocytic nevi in 8- to 10-year-old children in Southern Spain and analysis of associated factors. *J Eur Acad Dermatol Venereol* 2012;26:1558–64. [PubMed: 22097897]
21. Baron AE, Asdigian NL, Gonzalez V, Aalborg J, Terzian T, Stiegmenn RA et al. Interactions between ultraviolet light and MC1R and OCA2 variants are determinants of childhood nevus and freckle phenotypes. *Cancer Epidemiol Biomarkers Prev* 2014;23:2829–39. [PubMed: 25410285]
22. Oliveria SA, Satagopan JM, Geller AC, Dusza SW, Weinstock MA, Berwick M et al. Study of Nevi in Children (SONIC): baseline findings and predictors of nevus count. *Am J Epidemiol* 2009;169:41–53. [PubMed: 19001133]
23. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer* 2005;41:45–60. [PubMed: 15617990]
24. Tsao H, Bevona C, Goggins W, Quinn T. The transformation rate of moles (melanocytic nevi) into cutaneous melanoma: a population-based estimate. *Archives of dermatology* 2003;139:282–8. [PubMed: 12622618]
25. Bauer J, Buttner P, Wiecker TS, Luther H, Garbe C. Risk factors of incident melanocytic nevi: a longitudinal study in a cohort of 1,232 young German children. *Int J Cancer* 2005;115:121–6. [PubMed: 15645451]
26. Aalborg J, Morelli JG, Byers TE, Mokrohisky ST, Crane LA. Effect of hair color and sun sensitivity on nevus counts in white children in Colorado. *J Am Acad Dermatol* 2010;63:430–9. [PubMed: 20584558]
27. Dellavalle RP, Johnson KR, Hester EJ, Deas AM, Mokrohisky S, Morelli JG et al. Children with red hair have more freckles but fewer melanocytic nevi: results from a cohort study of 280 three-year-olds. *Archives of dermatology* 2005;141:1042–3. [PubMed: 16103341]

28. Naldi L, Randi G, Di Landro A, La Vecchia C. Red hairs, number of nevi, and risk of cutaneous malignant melanoma: results from a case-control study in Italy. *Archives of dermatology* 2006;142:935–6. [PubMed: 16847220]
29. Shaikh WR, Dusza SW, Weinstock MA, Oliveria SA, Geller AC, Halpern AC. Melanoma Thickness and Survival Trends in the United States, 1989 to 2009. *Journal of the National Cancer Institute* 2016;108.
30. Cho E, Rosner BA, Colditz GA. Risk factors for melanoma by body site. *Cancer Epidemiol Biomarkers Prev* 2005;14:1241–4. [PubMed: 15894679]
31. Lachiewicz AM, Berwick M, Wiggins CL, Thomas NE. Survival differences between patients with scalp or neck melanoma and those with melanoma of other sites in the Surveillance, Epidemiology, and End Results (SEER) program. *Archives of dermatology* 2008;144:515–21. [PubMed: 18427046]
32. Zhang M, Zhang X, Qureshi AA, Eliassen AH, Hankinson SE, Han J. Association between cutaneous nevi and breast cancer in the Nurses' Health Study: a prospective cohort study. *PLoS medicine* 2014;11:e1001659. [PubMed: 24915186]
33. Rampen FH, Mulder JH. Malignant melanoma: an androgen-dependent tumour? *Lancet* 1980;1:562–4. [PubMed: 6102285]
34. Buettner PG, Garbe C. Agreement between self-assessment of melanocytic nevi by patients and dermatologic examination. *Am J Epidemiol* 2000;151:72–7. [PubMed: 10625176]
35. Little P, Keefe M, White J. Self screening for risk of melanoma: validity of self mole counting by patients in a single general practice. *BMJ* 1995;310:912–6. [PubMed: 7719184]
36. Mikkilineni R, Weinstock MA. Is the self-counting of moles a valid method of assessing melanoma risk? *Archives of dermatology* 2000;136:1550–1. [PubMed: 11115171]
37. Weinstock MA, Colditz GA, Willett WC, Stampfer MJ, Bronstein BR, Mihm MC, Jr., et al. Moles and site-specific risk of nonfamilial cutaneous malignant melanoma in women. *Journal of the National Cancer Institute* 1989;81:948–52. [PubMed: 2733040]
38. Gallus S, Naldi L, Carli P, La Vecchia C, Italian Group for Epidemiologic Research in D. Nevus count on specific anatomic sites as a predictor of total body count: a survey of 3,406 children from Italy. *Am J Epidemiol* 2007;166:472–8. [PubMed: 17584758]
39. Zalaudek I, Schmid K, Marghoob AA, Scope A, Manzo M, Moscarella E et al. Frequency of dermoscopic nevus subtypes by age and body site: a cross-sectional study. *Archives of dermatology* 2011;147:663–70. [PubMed: 21690528]
40. Welch HG, Brawley OW. Scrutiny-Dependent Cancer and Self-fulfilling Risk Factors. *Ann Intern Med* 2018;168:143–4. [PubMed: 29297002]

Capsule Summary

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

Table 1.

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)^a

	Nurses' Health Study				Health Professionals Follow-up Study			
	None	1-2	3	<i>b</i> <i>p</i>	None	1-2	3	<i>b</i> <i>p</i>
n	760	417	368		494	211	202	
Age at diagnosis, years, mean (SD)	66.8 (9.7)	65.9 (10.3)	64.3 (9.8)	0.0003	70.2 (10.0)	68.2 (9.8)	68.6 (10.9)	0.03
Body mass index, kg/m ² , mean (SD)	25.7 (4.4)	25.7 (5.0)	27.1 (5.7)	0.001	25.5 (3.2)	25.8 (3.4)	25.8 (3.3)	0.19
Current smoking, %	9.3	5.8	6.1	0.12	3.8	1.5	3.9	0.54
Alcohol intake, g/d, mean (SD)	7.3 (11.0)	6.1 (9.5)	6.8 (11.5)	0.17	14.4 (18.7)	13.3 (14.9)	11.2 (13.7)	0.21
Physical activity, metabolic equivalents hours/week, mean (SD)	16.5 (18.5)	16.0 (19.6)	14.4 (19.0)	0.47	23.0 (25.3)	27.6 (46.7)	18.9 (18.8)	0.02
Family history of melanoma, %	9.8	10.5	11.8	0.68	7.1	8.7	9.2	0.73
Red or blonde hair, %	23.7	22.6	20.4	0.74	20.1	18.4	15.0	0.44
Childhood/adolescent tendency to sunburn or blistering response, %	47.0	45.2	50.6	0.18	79.3	80.8	87.8	0.03
Childhood/adolescent tendency to average to deep tanning response, %	58.0	59.6	59.0	0.90				
Number of lifetime sunburns, 6 or more, %	59.2	63.4	66.2	0.02	44.6	36.6	39.9	0.47
UV flux, $\times 10^{-4}$ RB units, mean (SD)	125.3 (26.2)	125.4 (25.8)	124.1 (25.2)	0.58	136.0 (29.6)	131.2 (26.9)	136.1 (29.1)	0.10
Breslow thickness, mm, mean (SD)	1.0 (1.2)	1.0 (1.3)	1.0 (1.1)	0.72	0.9 (0.9)	1.4 (2.1)	1.0 (0.9)	0.02
n	760	417	368		494	211	202	
Clark's level IV or V, %	29.4	24.1	27.5	0.22	20.4	31.1	40.1	0.04
Body site (%)								
Head and neck	21.0	16.5	15.2	0.0006	35.8	30.1	37.6	0.43
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	

^a All values shown were for the information before melanoma diagnosis or at the questionnaire cycle close to the melanoma diagnosis year except otherwise noted. All variables other than age at diagnosis were age (at diagnosis)-adjusted.

^b *P* values were calculated using chi-square test for categorical variables and one-way ANOVA for continuous variables.

Table 2.

HRs (95% CIs) for the association between number of common melanocytic nevi and risk of melanoma deaths: analyses in the overall cohort

	Number of moles			Per one mole ^b	P for trend ^b
	None	1-2	3		
Nurses' Health Study (1986–2012)					
Melanoma Deaths/Person-years	43/1172683	24/446457	24/236664		
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)	0.0002
Multivariate-adjusted HR ^a (95% CI)	1.00	1.41 (0.86–2.34)	2.49 (1.50–4.12)	1.12 (1.04–1.20)	0.003
Health Professionals Follow-up Study (1986–2012)					
Melanoma Deaths/Person-years	44/484399	26/140184	35/91531		
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)	<0.0001
Multivariate-adjusted HR ^a (95% CI)	1.00	2.04 (1.25–3.32)	3.97 (2.54–6.22)	1.20 (1.14–1.27)	<0.0001

^aMultivariate-adjusted analyses were performed adjusting for age, smoking (never, past, or current smokers), physical activity (in quintiles, metabolic equivalent hours/wk), body mass index (<25, 25–29.9, 30 kg/m²), 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/blisters), childhood tanning ability (practically none, little tan, average tan, or deep tan), times 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 UV flux (in quintiles), and history of keratinocyte carcinoma (yes or no).

^bThe HR per one mole and P for trend were calculated by using the linear trend test, based on the continuous assessment of number of moles

Table 3.

HRs (95% CIs) for the association between number of melanocytic nevi and risk of melanoma deaths: analyses among melanoma cases only^a

	Number of moles			Per one mole ^d	P for trend ^d
	None	1-2	3		
Nurses' Health Study (1986–2012) ^a					
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)	0.67
Multivariate-adjusted HR ^b (95% CI)	1.00	1.15 (0.69–1.91)	1.02 (0.61–1.71)	0.98 (0.91–1.06)	0.63
Multivariate-adjusted HR ^c (95% CI)	1.00	1.21 (0.72–2.06)	1.17 (0.69–2.00)	0.99 (0.92–1.08)	0.90
Health Professionals Follow-up Study (1986–2012) ^a					
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)	0.01
Multivariate-adjusted HR ^b (95% CI)	1.00	1.29 (0.77–2.17)	1.89 (1.17–3.05)	1.09 (1.03–1.16)	0.004
Multivariate-adjusted HR ^c (95% CI)	1.00	1.45 (0.84–2.49)	1.88 (1.15–3.06)	1.09 (1.03–1.16)	0.005

^aMelanoma cases entered the followed-up only after they were diagnosed.

^bMultivariate-adjusted analyses were performed adjusting for age, smoking (never, past, or current smokers), physical activity (in quintiles, metabolic equivalent hours/wk), body mass index (<25, 25–29.9, 30 kg/m²), 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/blisters), childhood tanning ability (practically none, little tan, average tan, or deep tan, for Nurses' Health Study only), times 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 UV flux (in quintiles), and history of keratinocyte carcinoma (yes or no).

^cAdditionally adjusting for Breslow thickness (in continuous variables), Clark's level and melanoma body sites. Adjusting for Breslow thickness in a categorical variable (<1 or ≥1mm) yielded very similar results.

^dThe HR per one mole and P for trend were calculated by using the linear trend test, based on the continuous assessment of number of moles.

Table 4.

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^a

	OR (95% CI) by number of moles			OR (95% CI) Per one mole ^c	P for trend ^c
	None	1-2	3		
Nurses' Health Study (1986–2012)^a					
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)	0.39
Multivariate-adjusted OR ^b (95% CI)	1.00	0.87 (0.57–1.35)	0.92 (0.60–1.43)	0.97 (0.91–1.04)	0.42
Health Professionals Follow-up Study (1986–2012)^a					
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)	0.005
Multivariate-adjusted OR ^b (95% CI)	1.00	1.58 (0.88–2.83)	2.28 (1.30–4.02)	1.11 (1.02–1.20)	0.01

^aAnalysis only among melanoma cases.

^bMultivariate-adjusted analyses were performed adjusting for age, smoking (never, past, or current smokers), physical activity (in quintiles, metabolic equivalent hours/wk), body mass index (<25, 25–29.9, 30 kg/m²), 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/blisters), childhood tanning ability (practically none, little tan, average tan, or deep tan, for Nurses' Health Study only), times 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 UV flux (in quintiles), and history of keratinocyte carcinoma (yes or no).

^cThe OR per one mole and P for trend were calculated by using the linear trend test, based on the continuous assessment of number of moles.