View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by IUPUIScholarWorks

Personal history of keratinocyte carcinoma is associated with reduced risk of death from invasive melanoma in men

Fengju Song, PhD,[a] Steven T. Chen, MD, MPH,[b,c] Xin Li, ScD,[d] and Jiali Han, PhD[a,d]
Tianjin, China; Boston, Massachusetts; and Indianapolis, Indiana

Background: Previous studies have found an increased risk for invasive cutaneous melanoma (CM) among those with a history of keratinocyte carcinoma (KC).

Objective: The aim of this study was to evaluate the risk of CM death after KC.

Methods: The study was based on the Health Professionals Follow-up Study. A Cox proportional hazards model was used to examine the hazard ratio (HR) of death due to CM associated with personal history of KC among the entire study population (primary analysis) and among participants with invasive CM (secondary analysis), respectively.

Results: We documented a total of 908 participants with invasive CM over a total of 0.7 million person-years of follow-up. Among all participants, the risk for development of either lethal or nonlethal invasive CM increased for those with a history of KC. The risk for death due to melanoma based on KC history was not significantly increased, with an HR of 1.53 (95% confidence interval, 0.95-2.46). In the case-only analysis, those with a history of KC had a significantly lower risk for death due to melanoma than those with no such history (HR, 0.60; 95% confidence interval, 0.35-0.94).

Limitations: Because the population covered by the Health Professionals Follow-up Study consists exclusively of male health professionals, the results of this study may not be extended to the entire population.

Conclusion: Personal history of KC is associated with a decreased risk for melanoma-specific death among male patients with invasive CM. (J Am Acad Dermatol 2018;78:957-63.)

Key words: cohort study; epidemiology; invasive cutaneous melanoma; keratinocyte carcinoma; mortality; skin cancer.

Melanoma is the most lethal among common forms of skin cancer. As the fifth most common cancer among males and sixth among females (excluding nonmelanoma skin cancers), the estimated number of new melanoma cases in the United States in 2017 was 87,110 and the estimated number of deaths of melanoma was 9730.[1] The prognosis of melanoma is highly

---

From the Department of Epidemiology and Biostatistics, Key Laboratory of Cancer Prevention and Therapy, Tianjin, National Clinical Research Center of Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin[a]; Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston[b]; Department of Internal Medicine, Massachusetts General Hospital, Harvard Medical School, Boston[c]; and Department of Epidemiology, Fairbanks School of Public Health, Indiana University, Indianapolis.[d]

Funding sources: Supported by National Institutes of Health grant UM1 CA167552.

Conflicts of interest: None disclosed.

Accepted for publication December 25, 2017.

Reprints not available from the authors.

Correspondence to: Jiali Han, PhD, Health Sciences Building (RG), 1050 Wishard Boulevard, Room 5112, Indianapolis, IN 46202-2872. E-mail: jialhan@iu.edu.

Fengju Song, PhD, Huanhuxi Road, Hexi District, Tianjin Medical University Cancer Institute and Hospital, Tianjin 300060, China. E-mail: songfengju@163.com.

Published online January 6, 2018.

0190-9622

© 2018 by the American Academy of Dermatology, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

https://doi.org/10.1016/j.jaad.2017.12.075

heterogeneous.[2] Patients whose melanoma is diagnosed in stage I have a much favorable prognosis, with a higher than 90% 5-year survival rate whereas the 5-year survival rate for patients with stage IV (distant) disease is around 15%.[3] There has been a discrepancy between melanoma incidence and mortality over the past 2 decades; melanoma incidence has dramatically risen, but melanoma mortality has recently stabilized.[4,5]

Keratinocyte carcinoma (KC), including cutaneous basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most commonly diagnosed malignancies in the United States, with 3.5 million cases each year.[6] It has been suggested that KC and other cancers may share common carcinogenic exposures or molecular mechanisms in their etiology, such as DNA repair deficiency and immune suppression, implying that a history of KC may indicate an increased risk for subsequent cancer development. We previously reported an increased risk for cancer associated with history of KC, including melanoma in men and breast cancer, lung cancer, and melanoma in women.[7] In addition, Wu et al recently reported that a personal history of KC was associated with increased risk for melanoma (hazard ratio [HR], 2.22; 95% confidence interval [CI], 1.73-2.85),[8] which is consistent with previous reports from registry-based, case-control, and prospective cohort studies.[9-12]

Although the association of a personal history of KC with melanoma risk has been consistently reported, its association with melanoma mortality remains undetermined. A study 2 decades ago reported that increased mortality due to overall cancer and melanoma after the diagnosis of KC may be due to shared exposures or susceptibilities.[13] However, this association was not further replicated in later years.[14] Does a history of KC increase the risk for melanoma death, and do patients with melanoma with a history of KC have poorer prognoses? To answer these questions, we conducted a prospective cohort study using data from the Health Professionals Follow-up Study (HPFS).

CAPSULE SUMMARY

- Previous studies have found an increased risk for invasive cutaneous melanoma among persons with a personal history of keratinocyte carcinoma (KC).
- We found that individuals with invasive cutaneous melanoma who had a history of KC had better survival than those without a history of KC.
- Information regarding a patient's personal history of KC is relevant for melanoma prognosis.

METHODS

Study population

The HPFS was started in 1986 and enrolled 51,529 American male health care professionals age 40 to 75 years. Participants receive a biennial survey regarding their personal health information and lifestyle. Response rates are higher than 90%. Our study period includes data collected from the cohort in surveys from 1986 to 2012. Only white patients (both Hispanic and non-Hispanic whites) were included in our analysis, given the different risks for development of melanoma among different races.[15] Our study was approved by the Human Research Committee of the Harvard T.H. Chan School of Public Health (Boston, MA).

Assessment of exposure

In the HPFS, participants were asked about having received a diagnosis of BCC and SCC. Medical and pathological reports were obtained from participants who reported SCC to confirm the diagnosis. Medical records were not obtained for BCC cases because of a large number of cases in our cohort and because previous validation studies reported a more than 90% accuracy of self-reported BCC among subsets of cohort participants.[16]

Assessment of melanoma and death

Similar to assessment of exposure as already detailed, participants in both cohorts self-reported a diagnosis of melanoma. Afterward, permission was sought to access their medical records so that pathologic reports could be reviewed. We focused only on the mortality of confirmed invasive cases, and excluded those participants with lentigo maligna melanoma and melanoma in situ from this analysis because of their favorable prognosis. Self-reported cases that could not be confirmed were excluded. Information collected aside from melanoma diagnosis included major histopathologic factors, such as Breslow depth and Clark level. All information was updated up to 2012.

Death events were reviewed in 1 of 3 ways. Deaths were reported by next of kin or by the US Postal Service. Additionally, a search was made in the National Death Index for participants who did not respond to their surveys. Death certificates and when necessary, medical records, were used to determine the date of death. More than 98% of deaths in these 2 cohorts were confirmed by 1 of these methods.[17] Furthermore, cause of death was determined by

Abbreviations used:

BCC:	basal cell carcinoma
CI:	confidence interval
CM:	cutaneous melanoma
HPFS:	Health Professionals Follow-up Study
HR:	hazard ratio
KC:	keratinocyte carcinoma
OR:	odds ratio
SCC:	squamous cell carcinoma
UV:	ultraviolet

blinded physician reviewers who reviewed death certificates. This was supplemented with family or health care provider interviews, as well as with medical records. The primary cancer was recorded as cause of death in cases of metastatic disease causing death.

Assessment of covariates

Covariate information was collected by self-reported questions on the biennial surveys. This included information on smoking, alcohol intake, body mass index, and physical activity. Questions about certain factors were asked at certain time points in the cohort. These included the following factors: number of blistering sunburns and tendency to burn as a child or adolescent, natural hair color, and family history of melanoma in first-degree relatives. Additionally, ultraviolet (UV) flux was calculated for each participant on the basis of his state of residence and by using a previously described method.[18]

Statistical analysis

We calculated person-years of follow-up from baseline to death or end of follow-up period, whichever came first. The year 1986 was set as the study baseline, and association of a history of KC with subsequent diagnosis of invasive cutaneous melanoma (CM) and melanoma death were examined until 2012 for the cohort. Melanoma deaths were considered the major end point, whereas deaths from other causes were censored. By using a Cox proportional hazards model stratified by age and follow-up cycles, we calculated HRs for melanoma death, comparing participants with and without a history of KC. The analyses were adjusted for the predetermined covariates (body mass index, smoking, alcohol intake, physical activity, childhood reaction to sun, number of sunburns, family history for melanoma, hair color, UV flux, and frequency of physical examination). Missing data for any covariate required creation of an indicator. In a secondary analysis, we looked at history of KC and its effect on incident cases of lethal melanoma and nonlethal melanoma. In this analysis, follow-up time was determined by the basis of date of melanoma diagnosis, death from any cause, or end of follow-up time, whichever came first. Similarly, we used a Cox proportional hazards model with adjustment for the same covariates.

Moreover, we analyzed the rate of death from melanoma among invasive melanoma cases to examine whether a history of KC is associated with a worse prognosis. In this analysis, we included participants from time of diagnosis of invasive melanoma and followed them until either the predetermined end time or death from any cause, whichever came first. Any death from all causes other than melanoma death was censored. As already described, HRs were calculated by using a Cox proportional hazards model with time in months since diagnosis as the time variable, adjusting for the same covariates. All analyses were carried out using SAS software (version 9.3, SAS Institute Inc, Cary, NC). All *P* values were 2 tailed with the significance level set at *P* less than .05.

RESULTS

A total of 579 of participants with invasive CM had no personal history of KC in the cohort, versus 329 who did carry a prior diagnosis of KC over 0.7 million years of follow-up. Baseline characteristics for the 2 groups are mostly similar (as shown in Table I), except that the mean age at diagnosis for participants with invasive CM with a history of KC was older than that of participants without a history of KC: 72.9 years versus 66.5 years.

We examined the risk for development of either a lethal or nonlethal melanoma depending on history of KC. The age-adjusted HR for development of a lethal melanoma for those with a history of KC was 1.63 (95% CI, 1.01-2.61) when compared with those who had no such history. In multivariate analysis, this HR was 1.97 (95% CI, 1.21-3.20). For the risk of nonlethal melanoma, the HRs for age-adjusted and multivariate-adjusted modeling were 1.70 (95% CI, 1.44-2.01) and 1.61 (95% CI, 1.36-1.90) (Table II).

When the HR of melanoma mortality was evaluated on the basis of a personal history of KC, the age-adjusted HR was 1.26 (95% CI, 0.79-2.00) in the HPFS. When covariates other than age were included in the model, the multivariate-adjusted HR was 1.53 (95% CI, 0.95-2.46) (Table III). In addition, no significant association was found between a history of KC and melanoma thickness or invasiveness. We calculated the odds ratios (ORs) (95% CIs) for the association between personal history of KC and Breslow thickness of melanoma of 0.8 mm or

Table I. Age-standardized baseline characteristics of cases with invasive melanoma by personal history of KC in the Health Professionals Follow-up Study (1986-2012)

	Personal history of KC	
Characteristic	**No**	**Yes**
No. of participants	579	329
Age at diagnosis, y, mean (SD)	66.5 (10.8)	72.9 (8.5)
Body mass index, kg/m^2, mean (SD)	25.6 (3.5)	25.8 (3.0)
Current smoking, %	2.9	4.6
Family history of melanoma, %	5.8	6.5
Red or blonde hair, %	18.0	21.8
Childhood/adolescent tendency to sunburn or blistering response, %	81.2	83.1
≥6 sunburns, % per *United States Cancer Statistics: 1999-2014 Incidence and Mortality Web-based Report*	41.8	44.9
UV flux, $\times 10^{-4}$ RB units, mean (SD)	134.1 (29.0)	138.0 (28.7)
Breslow thickness, mm, mean (SD)	1.0 (1.1)	1.0 (1.5)
<1 mm, %	74.6	73.9
1-2 mm, %	17.3	19.3
>2 mm, %	9.9	8.5
Clark level IV or V, %	23.3	29.8
Body site (%)		
Head and neck	36.1	36.3
Trunk	40.6	41.5
Limbs	23.3	22.2
Physical examination frequency	67.1 (29.9)	76.5 (22.6)

All values shown were for the information at melanoma diagnosis or the questionnaire cycle closest to the melanoma diagnosis year except where otherwise noted. All variables other than age at diagnosis were adjusted for age at diagnosis.
KC, Keratinocyte melanoma; *RB*, Robertson-Berger; *SD*, standard deviation; *UV*, ultraviolet.

Table II. HRs (95% CIs) for the association between personal history of KC and risk for incident lethal melanoma and nonlethal melanoma in the Health Professionals Follow-up Study (1986-2012)

	Personal history of KC	
Lethal vs nonlethal melanoma	**No**	**Yes**
Lethal melanoma		
Cases per 1000 person-years	0.1 (74/611067)	0.27 (28/103285)
Age-adjusted HR (95% CI)	1.00	1.63 (1.01-2.61)
Multivariate-adjusted HR (95% CI)*	1.00	1.97 (1.21-3.20)
Nonlethal melanoma		
Cases per 1000 person-years	0.96 (586/611067)	2.04 (211/103285)
Age-adjusted HR (95% CI)	1.00	1.70 (1.44-2.01)
Multivariate-adjusted HR (95% CI)*	1.00	1.61 (1.36-1.90)

CI, Confidence interval; *HR*, hazard ratio; *KC*, keratinocyte melanoma.
*Multivariate-adjusted analyses were performed with adjustment for age, smoking (never-smokers, past smokers, or current smokers), physical activity (in quintiles, metabolic equivalent h/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 reaction to sun (tan without burn, burn, or painful burn/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 physical examination frequency. An indicator variable was created for the missing value of each covariate.

more; the multivariate OR was 1.18 (95% CI, 0.76-1.83). We calculated the ORs (95% CIs) for the association between personal history of KC and Clark levels IV and V melanoma; the multivariate OR was 1.69 (95% CI, 0.91-3.15).

Furthermore, in the melanoma case—only analysis, we found that a personal history of KC conferred an HR of 0.59 (95% CI, 0.37-0.94) in the age-adjusted model. Multivariate modeling revealed an HR of 0.60 (95% CI, 0.37-0.99), and in the more

Table III. HRs (95% CIs) for the association between personal history of KC and risk for death from melanoma death in the Health Professionals Follow-up Study

	Personal history of KC	
Characteristic	**No**	**Yes**
Deaths per 1000 person-years	0.13 (77/612246)	0.27 (28/103592)
Age-adjusted HR (95% CI)	1.00	1.26 (0.79-2.00)
Multivariate-adjusted HR (95% CI)*	1.00	1.53 (0.95-2.46)

CI, Confidence interval; *HR*, hazard ratio; *KC*, keratinocyte melanoma.

*Multivariate-adjusted analyses were performed with adjustment for age, smoking (never- smokers, past smokers, or current smokers), physical activity (in quintiles, metabolic equivalent hours/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 reaction to sun (tan without burn, burn, or painful burn/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 physical examination frequency. An indicator variable was created for the missing value of each covariate.

Table IV. HRs (95% CIs) for the association between personal history of KC and risk for death from melanoma death in the Health Professionals Follow-up Study (1986-2012): among melanoma cases only

	Personal history of KC	
Characteristic	**No**	**Yes**
Deaths per 1000 person-years	16.7 (77/4603)	8.9 (28/3136)
Age-adjusted HR (95% CI)	1.00	0.59 (0.37-0.94)
Multivariate-adjusted HR (95% CI)*	1.00	0.60 (0.37-0.99)
Multivariate-adjusted HR (95% CI)†	1.00	0.60 (0.35-0.94)

Patients with melanoma entered follow-up only after their melanoma was diagnosed.

CI, Confidence interval; *HR*, hazard ratio; *KC*, keratinocyte melanoma.

*Multivariate-adjusted analyses were performed with adjustment for age, smoking (never-smokers, past smokers, or current smokers), physical activity (in quintiles, metabolic equivalent hours/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 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), 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 physical examination frequency. An indicator variable was created for the missing value of each covariate.

†Additionally adjusting for Breslow thickness (<1, 1-2, or >2 mm) and Clark level.

complex multivariate model, which additionally controlled for Breslow thickness and Clark level, the HR was 0.60 (95% CI, 0.35-0.94) (Table IV).

DISCUSSION

It has been reported that a personal history of KC is associated with an increased risk for invasive melanoma. In this prospective cohort study, we found no significantly increased mortality from melanoma among patients with a history of KC. Interestingly, in the melanoma case—only analysis, melanoma cases with such a history had significantly better survival than cases without a history of KC, suggesting a protective effect of a history of KC on melanoma death.

This could be explained logically by the idea that once a patient has a KC, they are more likely to undergo serial skin examinations with a dermatologist,[19] making the diagnosis of CM not only more likely but also more likely to be made earlier. Patients with a history of KC visit their dermatologists more often, thus having a better chance of having CMs diagnosed before the tumors start to metastasize.[20] This, combined with the previously described data showing an increase in melanoma diagnosis after a history of KC, suggests a detection bias leading to higher CM diagnosis rates. However, we did not observe that patients with a history of KC had thinner or less invasive melanomas.

It has been proposed that a history of KC is a marker for previous UV exposure,[21] which would explain both the increased incidence and diagnosis of lethal and nonlethal melanoma.[22] However, a population-based study of survival after a melanoma diagnosis suggests that some factors associated with high levels of sun exposure, such as solar elastosis and, to a lesser extent, sunburns and intermittent sun exposure, are inversely associated with death from melanoma.[23] Our data were consistent with this finding. Sun exposure is necessary for synthesis of 25-hydroxy vitamin D_3 in the skin, which is then converted to 1,25-dihydroxyvitamin D, which has antiproliferative and proapoptotic properties. It would be plausible to speculate that the inverse relationship between sun exposure and survival of melanoma could be mediated by vitamin D.

Additionally, melanomas that develop in patients with prior KC likely occur because of similar pathways involving UV exposure. However, melanomas that occur in patients without a history of KC or with lower levels of sun exposure are more likely due to nonmodifiable host factors, such as genetic predisposition and nevus count.[24-26] The latter group may have more aggressive melanomas leading to death in a shorter period of follow-up. In essence, a history of KC does increase the risk of CM and death from it. However, if people develop a CM without a history of KC, they are at higher risk for death, given the possibility of a more aggressive tumor.

Our study has both limitations and strengths. One limitation is that because the HPFS population consists solely of male health professionals, who may have sun exposure-related or other behaviors different from those of the general population, the results of this study may not be applicable to the whole population. For example, a participant in the HPFS study is less likely to be a current smoker compared with the general population[27] but more likely to be a moderate or heavy drinker.[28,29] In addition, HPFS participants have higher levels of health awareness and are more likely to undergo screening and early detection. Furthermore, we have documented previously that the incidence of melanoma is higher in our cohort[30] than in the general population,[31] as high socioeconomic status and intermittent sun exposure patterns have been associated with an increased risk for melanoma.[32] For KC, the HPFS has an incidence similar to that in the general population.[33-35]

Another limitation is that patients were studied from 1986 to 2012, and advances in therapy for metastatic melanoma have improved dramatically in the past few years. As such, it is reasonable to conjecture that if a study were to begin now, the rate of death due to melanoma might be lower, or at least we might see a longer time to death from melanoma after the date of diagnosis. However, one could also posit that with longer survival from advanced therapies come higher costs, indicating that prevention and early detection are still of the utmost importance for both mortality and health care spending. In addition, we did not have complete information on subtype of melanoma, which is an important factor for melanoma prognosis. Furthermore, recall bias regarding factors such as childhood reaction to sun, childhood tanning ability, and times of sunburns may exist during data collection. As for strengths, participants in the HPFS are all health care professionals. As such, their own likelihood of following up with physicians after an event such as KC is higher. Our calculations likely represent true estimates in ideal circumstances, which is helpful when quoting risks for patients.

In summary, we found no significantly increased mortality among people with a personal history of KC. However, among patients with invasive melanoma, those with a history of KC were found to have better survival than patients without a history of KC. Further studies are warranted to investigate the mechanism underlying this inverse association.

We acknowledge the Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School. We are indebted to the participants in the HPFS for their dedication and commitment. We thank the cancer registries of the following states for their help: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, and Wyoming. The authors assume full responsibility for analyses and interpretation of these data.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67:7-30.
2. Gershenwald JE, Ross MI. Sentinel-lymph-node biopsy for cutaneous melanoma. *N Engl J Med*. 2011;364:1738-1745.
3. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol*. 2009;27:6199-6206.
4. Jemal A, Saraiya M, Patel P, et al. Recent trends in cutaneous melanoma incidence and death rates in the United States, 1992-2006. *J Am Acad Dermatol*. 2011;65:S17-S25.
5. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64:9-29.
6. Rogers HW, Weinstock MA, Harris AR, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. *Arch Dermatol*. 2010;146:283-287.
7. Song F, Qureshi AA, Giovannucci EL, et al. Risk of a second primary cancer after non-melanoma skin cancer in white men and women: a prospective cohort study. *PLoS Med*. 2013;10:e1001433.
8. Wu S, Cho E, Li WQ, Qureshi AA. History of keratinocyte carcinoma and risk of melanoma: a prospective cohort study. *J Natl Cancer Inst*. 2017;109.
9. Rees JR, Zens MS, Gui J, Celaya MO, Riddle BL, Karagas MR. Non melanoma skin cancer and subsequent cancer risk. *PLoS One*. 2014;9:e99674.
10. Nugent Z, Demers AA, Wiseman MC, Mihalcioiu C, Kliewer EV. Risk of second primary cancer and death following a diagnosis of nonmelanoma skin cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14:2584-2590.
11. Wheless L, Black J, Alberg AJ. Nonmelanoma skin cancer and the risk of second primary cancers: a systematic review. *Cancer Epidemiol Biomarkers Prev*. 2010;19:1686-1695.
12. Chen J, Ruczinski I, Jorgensen TJ, et al. Nonmelanoma skin cancer and risk for subsequent malignancy. *J Natl Cancer Inst*. 2008;100:1215-1222.
13. Kahn HS, Tatham LM, Patel AV, Thun MJ, Heath CJ. Increased cancer mortality following a history of nonmelanoma skin cancer. *JAMA*. 1998;280:910-912.
14. Jensen AO, Bautz A, Olesen AB, Karagas MR, Sorensen HT, Friis S. Mortality in Danish patients with nonmelanoma skin cancer, 1978-2001. *Br J Dermatol*. 2008;159:419-425.

15. Wu XC, Eide MJ, King J, et al. Racial and ethnic variations in incidence and survival of cutaneous melanoma in the United States, 1999-2006. *J Am Acad Dermatol*. 2011;65:S26-S37.
16. van Dam RM, Huang Z, Giovannucci E, et al. Diet and basal cell carcinoma of the skin in a prospective cohort of men. *Am J Clin Nutr*. 2000;71:135-141.
17. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. *Am J Epidemiol*. 1994;140:1016-1019.
18. 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;23:1080-1089.
19. Bath-Hextall F, Jenkinson C, Kumar A, et al. Longitudinal, mixed method study to look at the experiences and knowledge of non melanoma skin cancer from diagnosis to one year. *BMC Dermatol*. 2013;13:13.
20. Rhodes AR. Public education and cancer of the skin. What do people need to know about melanoma and nonmelanoma skin cancer? *Cancer*. 1995;75:613-636.
21. Brondum-Jacobsen P, Nordestgaard BG, Nielsen SF, Benn M. Skin cancer as a marker of sun exposure associates with myocardial infarction, hip fracture and death from any cause. *Int J Epidemiol*. 2013;42:1486-1496.
22. Mancebo SE, Wang SQ. Skin cancer: role of ultraviolet radiation in carcinogenesis. *Rev Environ Health*. 2014;29:265-273.
23. Berwick M, Armstrong BK, Ben-Porat L, et al. Sun exposure and mortality from melanoma. *J Natl Cancer Inst*. 2005;97:195-199.
24. Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC. Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. *J Natl Cancer Inst*. 2003;95:806-812.
25. Olsen CM, Zens MS, Stukel TA, et al. Nevus density and melanoma risk in women: a pooled analysis to test the divergent pathway hypothesis. *Int J Cancer*. 2009;124:937-944.
26. Gibbs DC, Orlow I, Bramson JI, et al. Association of interferon regulatory factor-4 polymorphism rs12203592 with divergent melanoma pathways. *J Natl Cancer Inst*. 2016;108.
27. Jamal A, King BA, Neff LJ, Whitmill J, Babb SD, Graffunder CM. Current cigarette smoking among adults—United States, 2005-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65:1205-1211.
28. Wu S, Li WQ, Qureshi AA, Cho E. Alcohol consumption and risk of cutaneous basal cell carcinoma in women and men: 3 prospective cohort studies. *Am J Clin Nutr*. 2015;102:1158-1166.
29. Dayoub E, Jena AB. Chronic disease prevalence and healthy lifestyle behaviors among US health care professionals. *Mayo Clin Proc*. 2015;90:1659-1662.
30. Wei EX, Qureshi AA, Han J, et al. Trends in the diagnosis and clinical features of melanoma in situ (MIS) in US men and women: a prospective, observational study. *J Am Acad Dermatol*. 2016;75:698-705.
31. US Cancer Statistics Working Group. *United States Cancer Statistics: 1999-2014 Incidence and Mortality Web-based Report*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2017. Available at: www.cdc.gov/uscs.
32. Pion IA, Rigel DS, Garfinkel L, Silverman MK, Kopf AW. Occupation and the risk of malignant melanoma. *Cancer*. 1995;75:637-644.
33. Wu S, Han J, Li WQ, Li T, Qureshi AA. Basal-cell carcinoma incidence and associated risk factors in U.S. women and men. *Am J Epidemiol*. 2013;178:890-897.
34. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. *J Am Acad Dermatol*. 2013;68:957-966.
35. Wysong A, Linos E, Hernandez-Boussard T, Arron ST, Gladstone H, Tang JY. Nonmelanoma skin cancer visits and procedure patterns in a nationally representative sample: National Ambulatory Medical Care Survey 1995-2007. *Dermatol Surg*. 2013;39:596-602.