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Niacin intake and risk of skin cancer in US women and men

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Abstract

A recent clinical trial found a protective role of niacinamide, a derivative of niacin, against skin cancer recurrence. However, there is no epidemiologic study to assess the association between niacin intake and risk of skin cancer [basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma]. We prospectively evaluated whether total, dietary and supplemental niacin intake was associated with skin cancer risk based on 72,308 women in the Nurses' Health Study (1984–2010) and 41,808 men in the Health Professionals Follow-up Study (1986–2010). Niacin intake was assessed every 2 to 4 years during follow-up and cumulative averaged intake. Cox proportional hazard models were used to compute the hazard ratios (HR) and 95% confidence intervals (CI) and cohort-specific results were pooled using a random-effects model. During the

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Additional Supporting Information may be found in the online version of this article.

Author Contributions

Drs. Park and Cho had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors

Analysis and interpretation of data: All authors.

Drafting of the manuscript: Park and Cho.

Critical revision of the manuscript for important intellectual content: All authors.

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Study supervision: Park and Cho.

follow-up, we documented 23,256 BCC, 2,530 SCC and 887 melanoma cases. Total niacin intake was inversely associated with SCC risk; the pooled HR for top vs. bottom quintiles was 0.84 (95% CI = 0.74–0.95; p_{trend} = 0.08). However, there were a marginally positive association between total niacin intake and BCC risk; the pooled HR for top versus bottom quintiles was 1.05 (95% CI = 1.01–1.10; p_{trend} < 0.01). Higher total niacin intake was also marginally positively associated with melanoma risk in men, but not in women. The results were similar in stratified analyses according to sun exposure related factors and by body location of melanoma and SCC. Our study supports a potential beneficial role of niacin intake in relation to SCC but not of BCC or melanoma.

Keywords

niacin intake; skin cancer; basal cell carcinoma; squamous cell carcinoma; melanoma

Niacin (vitamin B3, nicotinic acid) is largely unexplored in relation to risk of cancer.[1–4] Increased skin sensitivity to sun exposure is a well-known symptom of severe niacin deficiency (pellagra) in human,[5] which is related with low nicotinamide-adenine dinucleotide (NAD) status and deficiencies in responding to ultraviolet (UV) damage.[6]

In several animal[7,8] and human studies,[9–11] topical or oral use of niacin and its derivative, nicotinamide(niacinamide) have reduced UV-induced immunosuppression, which was suggested to be a possible risk factor of skin cancer.[12] However, niacin's association with risk of skin cancer including melanoma and keratinocyte carcinoma (KC) is still unclear.

A recent randomized controlled phase 3 trial among KC patients found that oral nicotinamide supplementation of 1 g/d significantly reduced the rates of new KC and premalignant actinic keratosis.[13] The study did not take into account either dietary or supplemental niacin/nicotinaminde intake. To our knowledge, there is no epidemiologic study to assess the associations between dietary niacin intakes and risk of skin cancer.

Therefore, we assessed the association between niacin intake and risk of skin cancer including basal cell carcinoma (BCC), squamous cell cancer (SCC) and melanoma based on prospective data from the Nurses' Health Study (NHS, 1984–2010) and the Health Professionals Follow-up Study (HPFS, 1986–2010).

Material and Methods

Study population

The study population consisted of participants from the NHS and the HPFS. The NHS was initiated in 1976, when 121,700 US female registered nurses who were aged 30–55 years at the time of enrollment completed an initial questionnaire about their lifestyle and medical history. The HPFS consisted of 51,529 male health professionals aged 40–75 years who completed a questionnaire that inquired about medical history and lifestyle practices in 1986. Details of the two cohorts have been described elsewhere.[14–16] The questionnaire data about medical history and lifestyle factors was collected biennially in both cohorts. This study was approved by the Institutional Review Boards of Brigham and Women's Hospital and Harvard School of Public Health.

We followed participants for incident BCC, SCC and melanoma starting from 1984 in the NHS and 1986 in the HPFS. At baseline, 49,617 HPFS men and 81,685 NHS women completed the dietary questionnaire. Participants who had a history of any cancer were excluded. Owing to small number and low risk of skin cancer in nonwhite participants,[17] this study was restricted to participants of Caucasian ancestries. After exclusions, 41,808 men and 72,308 women (total $n = 114,116$) remained in the present study.

Assessment of niacin intake and other dietary consumption

To assess dietary intake, this study used a food frequency questionnaire (FFQ) to collect dietary information in 1984 of the NHS, and in 1986 and every four years thereafter in both the NHS and HPFS. Participants responded to the questions regarding how often on average they had consumed each type of food during the previous year. Participants also reported their current use and dose of multivitamins and use of vitamin supplements biennially. Total niacin intake included intakes from both diet and supplements. In validation studies, dietary intake collected using the FFQ has been shown to be a valid estimator of relative food intake when compared with multiple diet records.[18,19] The correlation coefficients ranged from 0.67–0.78 in the NHS between intakes of major dietary sources and supplementation of niacin assessed on the FFQ and intakes assessed on two 1-week dietary records. Information on other dietary factors, including intakes of total energy, alcohol and citrus consumption, was also collected by the FFQs.

Assessment of other covariates

We collected and updated information on body weight, physical activity and cigarette smoking in men and women and menopausal status and post-menopausal hormone use in women biennially. In 1982 of the NHS and in 1992 of the HPFS, participants responded to questions regarding skin reaction to sun exposure as a child/adolescent; number of lifetime blistering sunburns (never, 1–2 times, 3–5 times or 6 or more times); average time spent in direct sunlight since high school.

Data on the following skin cancer associated factors was collected through the follow-up questionnaires[20–22]: current residence (assessed biennially), family history of melanoma (assessed multiple times); natural hair color (1982 in NHS and 1988 in HPFS); number of arm moles (none, 1–2, 3–5, 6–9, 10–14, 15–20, 21 or more moles; 1986 in NHS and 1987 in HPFS); and routine use of sunscreen (1986 in NHS and 1992 in HPFS). The cumulative UV flux that each study participant could have received over a period of time was estimated by summing then averaging the annual UV flux data based on residential history over the follow-up.[23] Routine sunscreen use was defined as “yes” if the participants reported using sunscreen or sunblock with a Sun Protection Factor of 15 or more always or often when they were outside on a sunny day. The details of information about major skin cancer associated factors were reported previously.[24]

Assessment of BCC, SCC and melanoma cases

Biennially, participants had reported diagnoses of BCC, SCC and melanoma during the previous 2 years. We obtained permission from participants who reported SCC or melanoma to review their medical and pathological reports, which were reviewed by study physicians

to confirm the diagnoses. SCCs and melanomas were further classified into the following two subgroups according to tumor location related with the level of sun exposure: tumors on sites with higher sun exposure (head, neck and extremities), and tumors on sites with lower sun exposure (trunk). Although medical records were not obtained for self-reported cases of BCC, previous validation studies in the two cohorts have demonstrated a high accuracy of self-reported BCC, with around 90% confirmed by histopathology records.[18,25,26]

Statistical analysis

To better estimate long-term dietary intake and to minimize within-person variation, we used cumulative average of niacin intake up to that time prior to every 4-year follow-up interval (from baseline to the time of a censoring event). For example, in the HPFS, skin cancer incidence during 1990–1994 time period was related to the average niacin intake from the 1986 and 1990 questionnaires. We used energy-adjusted niacin intake calculated from regression-residual method to reduce the confounding by energy intake and its correlated measurement error. If nutrients are not adjusted for total caloric intake, some of them may be associated with disease risk simply due to their correlation with total energy intake.[27]

We followed participants for incident BCC, SCC and melanoma starting from 1984 in the NHS and 1986 in the HPFS. Person-time of follow-up were calculated from the return month of the baseline questionnaire to the date of the first report of any cancer, date of death, or end of follow-up (January 1, 2010 for men; June 1, 2010 for women), whichever came first.

Cox proportional hazard models were used to compute the hazard ratios (HR) and 95% confidence intervals (CI) of BCC, SCC and melanoma associated with total, dietary and supplemental niacin intakes. Total and dietary niacin intakes were categorized into quintiles in each cohort with the lowest quintile as the reference. Total niacin intake was also explored into deciles to evaluate wider range of the intake in relation to skin cancer. Supplementary niacin intakes were categorized as following: none, 0.1–2.0, 2.1–10.0, 10.1–18.0 and > 18 mg/d.

Multivariate analyses were performed with adjustment for family history of melanoma (yes *vs.* no), natural hair color (red, blonde, light brown, dark brown and black), number of arm moles (0, 1–2, 3–9 and ≥10),[22] skin reaction to sun exposure as a child/adolescent (none/some redness, burn, painful burn/blisters), number of lifetime blistering sunburns (0, 1–4, 5–9 and ≥10), average time spent in direct sunlight since high school (<2, 2–5, 6–9 and ≥10 hr/wk), cumulative UV flux since baseline (quintiles), body mass index (<25.0, 25.0–29.9, 30.0–34.9 and ≥35.0 kg/m^2), physical activity (quintiles), smoking status (never, past, current with 1–14, 15–24 or ≥25 cigarettes/d), intakes of total energy (quintiles), alcohol (0, 0.1–4.9, 5.0–9.9, 10.0–19.9 and ≥20.0 g/d) and citrus intake (quintiles), which were known as other skin cancer risk factors[20,21] and/or potential confounders.[28–30] Analyses for women were also adjusted for menopausal status and postmenopausal hormone use. The most recent information for time-varying variables *(e.g.*, body mass index) prior to each follow-up interval were used to take into account potential changes over the follow-up. Trend tests were performed by assigning median values for niacin intake categories and treating the new variable as a continuous term in the models. The analyses were performed among men and

women separately while different sets of covariates were adjusted for in NHS and HPFS and then pooled using a random-effects model to summarize the association between niacin intakes and skin cancer risk.

We performed several sensitivity analyses. First, we performed stratified analysis according to major sun exposure variables, including annual UV flux at residence, history of blistering sunburns and average time spent in direct sunlight since high school. Second, we also performed analyses for SCC and melanoma subtypes divided by tumor location (sites with higher sun exposure vs. sites with lower sun exposure). Third, as high-dose niacin has been used as cholesterol-lowering medication,[31] and we did not have information on it, we performed a sensitivity analysis among participants without hypercholesterolemia. Fourth, total niacin intake was also explored into deciles to evaluate wider range of the intake in relation to skin cancer. We used SAS software version 9.2 (SAS Institute, Cary, NC) for all statistical analyses. All statistical tests were two-tailed, and the significance level was set at $p < 0.05$.

Results

Age-adjusted characteristics of participants according to the total niacin intake are shown in Table 1. Participants with higher intake of total niacin tended to be slightly older and to have higher levels of physical activity. Major contributors of total niacin intake included multivitamins, B vitamin supplements, and food items including red meat, poultry, fish, coffee and breakfast cereal in the cohorts. (Supporting Information Table S1)

During 24–26 years of follow-up, we documented 23,256 BCC, 2,530 SCC and 887 melanoma cases. Table 2 presents the associations between total niacin intakes and risk of skin cancer. The mean levels of total niacin intake for bottom versus top quintiles were 17.9 *vs.* 84.1 mg/d for women and 21.5 *vs.* 115.7 mg/d for men. Total niacin intake was inversely associated with risk of SCC in women (HR for top *vs.* bottom quintiles = 0.80; 95% CI = 0.67–0.95), while this trend was not significant in men (HR for top *vs.* bottom quintiles = 0.89; 95% CI = 0.74–1.07). In a pooled analysis, there was a marginally inverse association between total niacin intake and risk of SCC; the pooled HR for top *vs.* bottom quintiles was 0.84 (95% CI = 0.74–0.95; $p_{trend} = 0.08$). Total niacin intake was weakly positively associated with risk of BCC in men only: the adjusted HR for extreme quintiles was 1.08 (95% CI = 1.01–1.15; $p_{trend} = 0.07$). In a pooled analysis, there was no significant association between total niacin intake and melanoma risk; the pooled HR for top *vs.* bottom quintiles was 1.18 (95% CI = 0.77–1.81; $p_{trend} = 0.07$). However, in the HPFS, there was a marginally positive association between total niacin intake and melanoma risk; the adjusted HR for top *vs.* bottom quintiles was 1.48 (95% CI = 1.07–2.05; $p_{trend} = 0.05$). The multivariable pooled HRs for top versus bottom deciles of total niacin intake were 1.05 (95% CI = 0.98–1.11; $p_{trend} < 0.001$) for BCC, 0.74 (95% CI = 0.62–0.90; $p_{trend} = 0.01$) for SCC and 1.14 (95% CI = 0.79–1.64; $p_{trend} = 0.58$) for melanoma.

We assessed the association between niacin intakes from food and from supplements separately and did not find any significant associations between dietary niacin intake and any skin cancer except a week positive association in men only (Supporting Information

Table S2). Niacin intake from supplements was weakly positively associated with increased risk of BCC, but not with SCC and melanoma; the pooled HR for BCC was 1.08 (95% CI = 1.04–1.12; $p_{trend} < 0.001$) for participants who took supplementary niacin >18 mg/d compared with none users (Supporting Information Table S3). In a sensitivity analysis adjusting for both dietary niacin intake and supplemental niacin intake in the model simultaneously, no material differences in trends were found (data not shown).

Stratified analysis according to sun exposure related factors showed similar trends between orally taken niacin and risk of skin cancer (Supporting Information Table S4). When we performed analyses for SCC and melanoma subtypes divided by tumor location (sites with higher sun exposure *vs.* sites with lower sun exposure), the overall pattern of associations remained consistent by body location of SCC and melanoma (Table 3).The multivariable pooled HRs on the body sites with higher sun exposure (head, neck and extremities) for top versus bottom quintiles of total niacin intake were 0.85 (95% CI = 0.73–0.98; $p_{trend} = 0.10$) for SCC and 1.05 (95% CI = 0.77–1.42; $p_{trend} = 0.38$) for melanoma. The results for SCC and melanoma of on the body sites with lower sun exposure (trunk and mucosa) were similar but did not reach statistical significance. When we performed a sensitivity analysis among participants without hypercholesterolemia (Table 4), the inverse association between total niacin intake and risk of SCC seemed to be slightly stronger than primary analysis; the pooled HR for top *vs.* bottom quintiles was 0.80 (95% CI = 0.67–0.96; $p_{trend} = 0.04$). And there was no significant association between total niacin intake and the risks of BCC and melanoma. When we performed a sensitivity analysis by additionally adjusting for use of sunscreen, the overall associations remained similar (data not shown).

Discussion

In this pooled analyses of the two large cohort studies, total niacin intake was associated with modestly decreased risk of SCC, while no protective associations were found for BCC or melanoma. Instead, there was a suggestion of positive association with BCC risk. The associations were similar when body site location of SCC and melanoma were evaluated. When we examined stratified analysis according to sun exposure related factors and sensitivity analysis among participants without hypercholesterolemia, these trends remained similar.

Niacin is a nutrient largely unexplored in relation to cancer risk. Nicotinamide is a niacin derivative. Dietary niacin in natural food converts to nicotinamide in cooking process or in the body. Breakfast cereal, multivitamins, and B vitamin supplements often contain nicotinamide as niacin. Niacin and nicotinamide are considered identical in their role as vitamins and used for coenzymes NADH and NHDPH, which are involved in numerous enzyme reactions including ATP formation.[32] However, they have different pharmacological effect. For example, unlike nicotinamide, high dose of niacin lowers cholesterol and thus has been used as cholesterol-lowering medication and can cause vasodilation, skin flushing, headache and hypotension.[31,33]

Previous studies have suggested a protective role of niacin on development of KC. Several animal studies have demonstrated that nicotinamide treatment reduced UV-induced

immunosuppression.[8,34] Nicotinamide also was known to enhances DNA repair in UV-irradiated human HaCaT keratinocytes and ex vivo human skin.[9] Other studies have suggested that niacin might protect the skin against UV radiation–induced DNA damage through cellular processes including DNA repair, genomic stability and transcription.[35–38] A randomized controlled phase 2 trial in heavily sun-damaged individuals also found that oral nicotinamide significantly reduced premalignant actinic keratosis, a precursor for SCC.[39] Furthermore, a recent phase 3 randomized trial of daily administration of 1 g nicotinamide supplement for 12 months in 386 KC patients also found a chemopreventive effect of nicotinamide on development of new KC, especiallySCC.[13] The estimated reduction in the rate of new SCC was 30% ($p = 0.05$) for nicotinamide group, while that was 20% for new BCC without statistical significance ($p = 0.12$).[13]

Consistent with these findings, there was a modest inverse association between total niacin intake and risk of SCC in our study. The inverse association was consistent by body location of melanoma sun exposure related factors. The association was somewhat stronger in decile analysis and after excluding participants with hypercholesterolemia to reduce misclassification of niacin intake due to those taking niacin as lipid-lowering medication.

However, orally taken niacin from diet and/or supplements was not inversely related but was rather weakly positively associated with BCC risk. As one of the major sources of niacin intake is multivitamins, we cannot exclude the possibility that other components in multivitamins might have masked the inverse association. Earlier studies from our group found that risk of BCC was increased among those with higher intakes of vitamins A, C and E, and folate,[15] while there were weak and nonsignificant inverse associations between intake of retinol and folate and risk of SCC.[16] Although both BCC and SCC originate from keratinocytes, their biological pathways and interactions with niacin intakes could be different. In addition, it might be partially due to the difference of disease confirmation method between SCC and BCC: SCC cases were confirmed by medical records, while the diagnosis of BCC was assessed based on self-reports without pathological validation. Although our participants were nurses or health professionals and validity of their self-report of BCC was proven to be high in previous studies.[18,25,26] There was still a higher possibility of misclassification of BCC. It is possible that people who are more health conscious and taking multivitamins and B vitamin supplements may get skin examination more frequently and diagnosis of BCC. Then, we would find a positive association between higher niacin intake and BCC as we observed.

To our knowledge, there is no prospective epidemiologic study on the association between niacin intake and risk of KC. Niacin intake in our population was much lower than the dose of nicotinamide used in the clinical trials. Recommended Daily Allowance (RDA) of niacin was set to 16 mg/d for adult male and 14 mg/d for adult female with 35 mg/d as upper limit.[40] In our populations, due to common use of multivitamins, the means of bottom quintiles of total niacin intake were close to RDA. This suggests that over 80% of our participants consumed over RDA of niacin. However, the mean values of the top quintiles of total niacin intake were far lower than the dose used in the clinical trials. We still found an inverse association with SCC, especially evaluating decile of total niacin intake. Further studies are needed to investigate this association in other populations and explore the underlying

mechanisms as well as dose-response relationship. It is also unknown whether niacin and nicotinamide would have a similar effect on SCC risk.

We did not find a protective association between niacin intake and melanoma risk. On the other hand, there was a marginally positive association between total niacin intake and melanoma risk in men only. This could be due to chance given that it was found only in one cohort. Or there could be other mechanisms to counterbalance the hypothesized protective effect of niacin on skin cancer development. Niacin is one of the common medication for dyslipidemia,[31] as it is involved in steroid hormone synthesis. Niacin could accentuate sex hormone synthesis, which could lead to melanocyte progression. Melanocytes are known to have estrogen and androgen receptors,[41] and previous studies suggested that cutaneous nevi might be a marker of plasma estrogen hormone level[42,43] and higher estrogen exposure could increase the risk of cutaneous melanoma.[44–46] However, little is known about the association between niacin intake and sex hormone levels, and future studies are needed to identify the underlying mechanisms.

This study has several strengths. Our study had a prospective design, large number of skin cancer cases, long-term follow-up over 24–26 years, repeated assessment of dietary and lifestyle factors, and the ability to adjust for a number of potential confounders. Our study also has several limitations. First, our study population were Caucasians and well-educated health professionals, which may not be representative of the US general population. Future replication studies will be needed with sufficient power to detect similar associations among other ethnicities. Second, although we controlled for several strong predictors of skin cancer risk, we cannot exclude residual confounding by those factors or other unknown factors. Third, the case numbers of melanoma were not as high as that of BCC or SCC, and the possibility of limited power in our study could not be excluded. Fourth, we did not have information on niacin use to lower cholesterol levels. However, the proportion of participants using this medication would be relatively small. Fifth, although random effects model was used to pool the data, the possible heterogeneity due to difference in some variables across the NHS and HPFS cohorts is another important limitation of the meta-analytic approach.

In conclusion, we found a potential beneficial role of orally taken niacin in relation to risk of SCC but not in BCC or melanoma. Further work is warranted to confirm our findings and identify relevant mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Harrison LE, Zhang ZF, Karpeh MS, et al. The role of dietary factors in the intestinal and diffuse histologic subtypes of gastric adenocarcinoma: a case-control study in the U.S. Cancer. 1997; 80:1021–8. [PubMed: 9305701]
2. Slattery ML, Potter JD, Coates A, et al. Plant foods and colon cancer: an assessment of specific foods and their related nutrients (United States). Cancer Causes Control. 1997; 8:575–90. [PubMed: 9242473]
3. Franceschi S, Bidoli E, Baron AE, et al. Maize and risk of cancers of the oral cavity, pharynx, and esophagus in northeastern Italy. J Natl Cancer Inst. 1990; 82:1407–11. [PubMed: 2388291]
4. Shrubsole MJ, Shu XO, Li HL, et al. Dietary B vitamin and methionine intakes and breast cancer risk among Chinese women. Am J Epidemiol. 2011; 173:1171–82. [PubMed: 21447479]
5. Malfait P, Moren A, Dillon JC, et al. An outbreak of pellagra related to changes in dietary niacin among Mozambican refugees in Malawi. Int J Epidemiol. 1993; 22:504–11. [PubMed: 8359968]
6. Benavente CA, Jacobson MK, Jacobson EL. NAD in skin: therapeutic approaches for niacin. Curr Pharm Des. 2009; 15:29–38. [PubMed: 19149600]
7. Gehring W. Nicotinic acid/niacinamide and the skin. J Cosmet Dermatol. 2004; 3:88–93. [PubMed: 17147561]
8. Gensler HL. Prevention of photoimmunosuppression and photocarcinogenesis by topical nicotinamide. Nutr Cancer. 1997; 29:157–62. [PubMed: 9427980]
9. Surjana D, Halliday GM, Damian DL. Nicotinamide enhances repair of ultraviolet radiation-induced DNA damage in human keratinocytes and ex vivo skin. Carcinogenesis. 2013; 34:1144–9. [PubMed: 23349012]
10. Damian DL, Patterson CR, Stapelberg M, et al. UV radiation-induced immunosuppression is greater in men and prevented by topical nicotinamide. J Invest Dermatol. 2008; 128:447–54. [PubMed: 17882270]
11. Lin F, Xu W, Guan C, et al. Niacin protects against UVB radiation-induced apoptosis in cultured human skin keratinocytes. Int J Mol Med. 2012; 29:593–600. [PubMed: 22246168]
12. Welsh MM, Applebaum KM, Spencer SK, et al. CTLA4 variants, UV-induced tolerance, and risk of non-melanoma skin cancer. Cancer Res. 2009; 69:6158–63. [PubMed: 19622768]
13. Chen AC, Martin AJ, Choy B, et al. A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention. N Engl J Med. 2015; 373:1618–26. [PubMed: 26488693]
14. Hunter DJ, Colditz GA, Stampfer MJ, et al. Diet and risk of basal cell carcinoma of the skin in a prospective cohort of women. Ann Epidemiol. 1992; 2:231–9. [PubMed: 1342273]
15. Fung TT, Hunter DJ, Spiegelman D, et al. Vitamins and carotenoids intake and the risk of basal cell carcinoma of the skin in women (United States). Cancer Causes Control. 2002; 13:221–30. [PubMed: 12020103]
16. Fung TT, Spiegelman D, Egan KM, et al. Vitamin and carotenoid intake and risk of squamous cell carcinoma of the skin. Int J Cancer. 2003; 103:110–5. [PubMed: 12455062]
17. Society, AC. Cancer Facts & Figures 2014. Atlanta: American Cancer Society; 2014.
18. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. Am J Epidemiol. 1986; 123:894–900. [PubMed: 3962971]
19. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol. 1989; 18:858–67. [PubMed: 2621022]
20. Cho E, Rosner BA, Feskanich D, et al. Risk factors and individual probabilities of melanoma for whites. J Clin Oncol. 2005; 23:2669–75. [PubMed: 15837981]
21. Wu S, Han J, Li WQ, et al. Basal-cell carcinoma incidence and associated risk factors in U.S. women and men. Am J Epidemiol. 2013; 178:890–7. [PubMed: 23828250]

22. Cho E, Rosner BA, Colditz GA. Risk factors for melanoma by body site. Cancer Epidemiol Biomarkers Prev. 2005; 14:1241–4. [PubMed: 15894679]
23. Fears TR, Bird CC, Guerry D, et al. Average midrange ultraviolet radiation flux and time outdoors predict melanoma risk. Cancer Res. 2002; 62:3992–6. [PubMed: 12124332]
24. Wu S, Cho E, Li WQ, et al. History of Severe Sunburn and Risk of Skin Cancer Among Women and Men in 2 Prospective Cohort Studies. Am J Epidemiol. 2016; 183:824–33. [PubMed: 27045074]
25. Hunter DJ, Colditz GA, Stampfer MJ, et al. Risk factors for basal cell carcinoma in a prospective cohort of women. Ann Epidemiol. 1990; 1:13–23. [PubMed: 1669486]
26. 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; 71:135–41. [PubMed: 10617958]
27. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol. 1986; 124:17–27. [PubMed: 3521261]
28. Pothiawala S, Qureshi AA, Li Y, et al. Obesity and the incidence of skin cancer in US Caucasians. Cancer Causes Control. 2012; 23:717–26. [PubMed: 22450736]
29. Song F, Qureshi AA, Gao X, et al. Smoking and risk of skin cancer: a prospective analysis and a meta-analysis. Int J Epidemiol. 2012; 41:1694–705. [PubMed: 23064412]
30. Wu S, Han J, Feskanich D, et al. Citrus Consumption and Risk of Cutaneous Malignant Melanoma. J Clin Oncol. 2015; 33:2500–8. [PubMed: 26124488]
31. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force. On Practice Guidelines. Circulation. 2014; 129:S1–45. [PubMed: 24222016]
32. Rolfe HM. A review of nicotinamide: treatment of skin diseases and potential side effects. J Cosmet Dermatol. 2014; 13:324–8. [PubMed: 25399625]
33. MacKay D, Hathcock J, Guarneri E. Niacin: chemical forms, bioavailability, and health effects. Nutr Rev. 2012; 70:357–66. [PubMed: 22646128]
34. Thanos SM, Halliday GM, Damian DL. Nicotinamide reduces photodynamic therapy-induced immunosuppression in humans. Br J Dermatol. 2012; 167:631–6. [PubMed: 22709272]
35. Hassa PO, Haenni SS, Elser M, et al. Nuclear ADP-ribosylation reactions in mammalian cells: where are we today and where are we going? Microbiol Mol Biol Rev. 2006; 70:789–829. [PubMed: 16959969]
36. Pollak N, Dolle C, Ziegler M. The power to reduce: pyridine nucleotides-small molecules with a multitude of functions. Biochem J. 2007; 402:205–18. [PubMed: 17295611]
37. Kirkland JB. Niacin and carcinogenesis. Nutr Cancer. 2003; 46:110–8. [PubMed: 14690785]
38. Yiasemides E, Sivapirabu G, Halliday GM, et al. Oral nicotinamide protects against ultraviolet radiation-induced immunosuppression in humans. Carcinogenesis. 2009; 30:101–5. [PubMed: 19028705]
39. Surjana D, Halliday GM, Martin AJ, et al. Oral nicotinamide reduces actinic keratoses in phase II double-blinded randomized controlled trials. J Invest Dermatol. 2012; 132:1497–500. [PubMed: 22297641]
40. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. US: National Academies Press; 1998.
41. Zouboulis CC, Chen WC, Thornton MJ, et al. Sexual hormones in human skin. Horm Metab Res. 2007; 39:85–95. [PubMed: 17326004]
42. Driscoll MS, Grant-Kels JM. Nevi and melanoma in the pregnant woman. Clin Dermatol. 2009; 27:116–21. [PubMed: 19095157]
43. Driscoll MS, Grant-Kels JM. Hormones, nevi, and melanoma: an approach to the patient. J Am Acad Dermatol. 2007; 57:919–31. quiz 32-6. [PubMed: 18021848]
44. Karagas MR, Stukel TA, Dykes J, et al. A pooled analysis of 10 case-control studies of melanoma and oral contraceptive use. Br J Cancer. 2002; 86:1085–92. [PubMed: 11953854]

45. Osterlind A, Tucker MA, Stone BJ, et al. The Danish case-control study of cutaneous malignant melanoma. III. Hormonal and reproductive factors in women. Int J Cancer. 1988; 42:821–4. [PubMed: 3192324]

46. Koomen ER, Joosse A, Herings RM, et al. Estrogens, oral contraceptives and hormonal replacement therapy increase the incidence of cutaneous melanoma: a population-based case-control study. Ann Oncol. 2009; 20:358–64. [PubMed: 18725391]

What's new?

Niacin (vitamin B3) and its derivative niacinamide have been shown to reduce UV-induced immunosuppression, which has been suggested to be a possible risk factor of skin cancer, in both mice and humans when used topically or orally. A recent clinical trial has also found a protective role of niacinamide against skin cancer recurrence. The association between niacin intake and risk of skin cancer however remains unclear. In this prospective U.S. study, the authors found a potential beneficial role of niacin intake in relation to risk of squamous cell carcinoma but not of basal cell carcinoma or melanoma.

Table 1

Baseline characteristics of study participants according to quintile of total niacin intake in women in the NHS and in men in the health professional follow-up study (HPFS)

	Quintile of total niacin intake				
	*Q*1	*Q*2	*Q*3	*Q*4	*Q*5
Women in NHS (1984)					
No. of participants	14,673	15,720	12,508	15,038	14,349
Age (year)[1]	49.8 (7.4)	50.0 (7.1)	50.0 (7.0)	50.6 (7.2)	50.9 (7.1)
Family history of melanoma (%)	6.7	7.0	7.5	7.4	7.0
Red/blonde hair (%)	15.5	15.1	15.4	15.9	16.0
Painful burn/blisters reaction as a child/adolescent (%)	13.8	13.8	15.0	14.4	15.3
No. of blistering sunburns	8.2 (6.9)	8.5 (6.9)	8.7 (7.0)	8.7 (7.0)	8.8 (6.9)
Use of sunscreen (%)	21.2	22.6	23.2	25.9	28.7
Annual UV flux ($\times 10^{-4}$ RB count)	120.1 (22.8)	120.6 (23.6)	121.2 (24.2)	122.4 (24.8)	123.7 (25.5)
Body mass index (kg/m^2)	25.2 (5.0)	25.3 (4.9)	25.2 (4.7)	24.8 (4.5)	24.7 (4.6)
Physical activity level (metabolic-equivalents hr/wk)	12.4 (18.5)	13.3 (20.2)	13.4 (17.7)	15.0 (20.9)	16.3 (24.7)
Current smoking (%)	21.9	24.2	29.1	24.4	23.2
Menopausal status (%)	46.9	47.0	47.6	47.4	47.2
Current postmenopausal hormones use[2] (%)	21.0	21.3	21.2	26.9	30.0
Total niacin intake (mg/day)	15.8 (2.1)	20.5 (1.1)	24.7 (1.4)	35.1 (5.1)	91.6 (41.7)
Diet niacin intake (mg/day)	16.0 (2.1)	20.1 (1.7)	23.3 (3.0)	22.4 (5.6)	21.6 (6.2)
Supplemental niacin intake (mg/day)	0.2 (0.4)	0.3 (0.8)	1.1 (2.8)	12.7 (8.1)	69.9 (40.3)
Total energy intake (kcal/d)	1585.6 (494.7)	1782.5 (511.0)	1854.1 (538.7)	1810.4 (532.3)	1701.4 (532.6)
Alcohol intake (g/d)	6.8 (12.2)	7.3 (11.6)	7.1 (11.3)	7.2 (11.5)	7.0 (11.7)
Total citrus intake (serving/d)	0.8 (0.7)	0.9 (0.7)	0.9 (0.7)	0.9 (0.8)	0.9 (0.8)
Men in HPFS (1986)					
No. of participants	8387	8519	8469	8192	8241
Age (year)[1]	52.8 (9.7)	52.6 (9.3)	53.2 (9.6)	54.3 (9.8)	54.1 (9.6)
Family history of melanoma (%)	3.7	3.9	4.0	4.1	4.3

	Quintile of total niacin intake				
	Q1	***Q2***	***Q3***	***Q4***	***Q5***
Red/blonde hair (%)	13.9	13.6	13.1	13.2	13.0
Painful burn/blisters reaction as a child/adolescent (%)	24.1	22.8	24.1	23.7	23.4
No. of blistering sunburns	12.6 (11.9)	12.9 (12.1)	12.7 (12.0)	13.0 (12.2)	13.0 (12.2)
Use of sunscreen (%)	51.6	56.3	60.1	62.9	63.4
Annual UV flux ($\times 10^{-4}$ RB count)	129.1 (26.8)	128.1 (26.3)	128.0 (26.5)	129.6 (27.2)	130.8 (27.6)
Body mass index (kg/m^2)	25.0 (5.1)	25.2 (5.0)	25.1 (5.2)	24.9 (5.1)	24.7 (4.8)
Physical activity level (metabolic-equivalents hr/wk)	17.9 (26.7)	19.5 (25.9)	21.7 (33.0)	22.8 (30.3)	23.2 (30.2)
Current smoking (%)	12.2	9.7	8.3	8.2	9.6
Total niacin intake (mg/day)	20.0 (2.3)	25.1 (1.2)	30.3 (2.1)	43.5 (6.1)	112.2 (56.7)
Diet niacin intake (mg/day)	20.4 (2.5)	24.9 (2.1)	28.7 (3.8)	28.7 (7.0)	26.9 (7.2)
Supplemental niacin intake (mg/day)	0.1 (0.6)	0.3 (1.2)	1.6 (3.6)	14.3 (8.6)	80.7 (50.8)
Total energy intake (kcal/d)	1798.6 (555.8)	2016.5 (602.4)	2134.0 (637.3)	2044.0 (630.4)	1962.5 (613.3)
Alcohol intake (g/d)	11.7 (16.9)	12.0 (16.1)	11.7 (15.8)	11.6 (15.4)	11.9 (16.0)
Total citrus intake (serving/d)	0.8 (0.9)	0.9 (0.9)	1.0 (0.8)	1.0 (0.9)	1.0 (0.9)

Note: Values are means (SD) or percentages and have been standardized to the age distribution of the study population.

[1]Values are not age adjusted.

[2]Percentages among postmenopausal women.

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Table 2

Harzard Ratio (and 95% CI) of skin cancer by total niacin intake in the NHS (1984–2010), and HPFS (1986–2010)

	Quintile of total niacin intake					*p* for trend
	1	2	3	4	5	
BCC						
NHS						
Mean total niacin (mg/d)	17.9	22.7	28.3	39.6	84.1	
No. of cases/person-years	2,312/282,389	2,616/303,943	2,705/293,419	2,842/286,151	2,861/287,191	
Age-adjusted	1 (referent)	1.03 (0.97, 1.09)	1.10 (1.04, 1.16)	1.17 (1.10, 1.23)	1.16 (1.10, 1.23)	<0.001
Multivariate-adjusted[1]	1 (referent)	0.98 (0.92, 1.03)	1.01 (0.95, 1.07)	1.05 (0.99, 1.11)	1.04 (0.98, 1.10)	0.05
HPFS						
Mean total niacin (mg/d)	21.5	27.2	33.8	48.2	115.7	
No. of cases/person-years	1,705/154,486	1,926/160,196	2,014/157,496	2,170/152,268	2,105/152,513	
Age-adjusted	1 (referent)	1.10 (1.03, 1.17)	1.14 (1.07, 1.22)	1.24 (1.16, 1.32)	1.18 (1.11, 1.26)	<0.001
Multivariate-adjusted[1]	1 (referent)	1.05 (0.98, 1.12)	1.05 (0.99, 1.12)	1.12 (1.05, 1.19)	1.08 (1.01, 1.15)	0.07
Pooled[2]						
Age-adjusted	1 (referent)	1.06 (1.00, 1.13)	1.12 (1.07, 1.17)	1.20 (1.13, 1.27)	1.17 (1.12, 1.22)	<0.001
Multivariate-adjusted[1]	1 (referent)	1.01 (0.94, 1.08)	1.03 (0.99, 1.07)	1.08 (1.01, 1.15)	1.05 (1.01, 1.10)	<0.01
Squamous cell cancer						
NHS						
No. of cases/person-years	267/283,597	257/305,267	264/294,812	266/287,579	271/288,719	
Age-adjusted	1 (referent)	0.86 (0.72, 1.02)	0.91 (0.77, 1.08)	0.95 (0.80, 1.12)	0.94 (0.79, 1.11)	0.90
Multivariate-adjusted[1]	1 (referent)	0.79 (0.66, 0.94)	0.81 (0.68, 0.96)	0.82 (0.69, 0.97)	0.80 (0.67, 0.95)	0.20
HPFS						
No. of cases/person-years	221/155,954	240/161,829	243/159,198	264/154,061	237/154,286	
Age-adjusted	1 (referent)	1.06 (0.88, 1.27)	1.06 (0.88, 1.27)	1.14 (0.95, 1.36)	1.00 (0.83, 1.20)	0.76
Multivariate-adjusted[1]	1 (referent)	0.98 (0.82, 1.18)	0.94 (0.78, 1.13)	1.00 (0.83, 1.19)	0.89 (0.74, 1.07)	0.23
Pooled[2]						

	Quintile of total niacin intake					*p* for trend
	1	**2**	**3**	**4**	**5**	
Age-adjusted	1 (referent)	0.95 (0.77, 1.17)	0.97 (0.84, 1.13)	1.04 (0.86, 1.24)	0.97 (0.85, 1.09)	0.87
Multivariate-adjusted[1]	1 (referent)	0.88 (0.71, 1.09)	0.87 (0.75, 1.01)	0.90 (0.74, 1.09)	0.84 (0.74, 0.95)	0.08
Melanoma						
NHS						
No. of cases/person-years	97/283,730	108/305,385	86/294,976	106/287,725	107/288,842	
Age-adjusted	1 (referent)	1.01 (0.77, 1.33)	0.84 (0.63, 1.12)	1.07 (0.81, 1.40)	1.06 (0.81, 1.40)	0.41
Multivariate-adjusted[1]	1 (referent)	0.92 (0.70, 1.22)	0.75 (0.56, 1.01)	0.95 (0.72, 1.26)	0.96 (0.73, 1.27)	0.67
HPFS						
No. of cases/person-years	60/156,086	75/161,961	92/159,320	57/154,238	99/154,386	
Age-adjusted	1 (referent)	1.23 (0.88, 1.73)	1.51 (1.09, 2.09)	0.94 (0.65, 1.35)	1.63 (1.18, 2.24)	0.01
Multivariate-adjusted[1]	1 (referent)	1.18 (0.84, 1.67)	1.41 (1.01, 1.96)	0.85 (0.59, 1.23)	1.48 (1.07, 2.05)	0.05
Pooled[2]						
Age-adjusted	1 (referent)	1.09 (0.88, 1.35)	1.12 (0.63, 1.99)	1.02 (0.82, 1.27)	1.30 (0.86, 1.98)	0.02
Multivariate-adjusted[1]	1 (referent)	1.02 (0.80, 1.30)	1.02 (0.55, 1.89)	0.91 (0.73, 1.14)	1.18 (0.77, 1.81)	0.07

[1]Adjusted for family history of melanoma (yes *vs.* no), natural hair color (red, blonde, light brown, dark brown and black), number of arm moles (0, 1–2, 3–9 and ≥10), skin reaction to sun exposure as a child/adolescent (none/some redness, burn, painful burn/blisters), number of lifetime blistering sunburns (0, 1–4, 5–9 and ≥10), average time spent in direct sunlight since high school (<2, 2–5, 6–9, and ≥10 hr/wk), cumulative UV flux since baseline (quintiles), body mass index (<25.0, 25.0–29.9, 30.0–34.9, and ≥35.0 kg/m^2), physical activity (quintiles), smoking status (never, past, current with 1–14, 15–24 or ≥25 cigarettes/d), intakes of total energy (quintiles), alcohol (0, 0.1–4.9, 5.0–9.9, 10.0–19.9 and ≥20.0 g/d) and citrus intake (quintiles). Analyses for women were also adjusted for menopausal status and postmenopausal hormone use.

[2]The multivariate-adjusted HR from each cohort were combined with meta-analytic methods using random effects model.

Table 3

Pooled multivariate hazard ratio (HR) of site-specific SCC and melanoma by total niacin intake in the NHS and HPFS

	Quintile of total niacin intake					*p* for trend
	1	2	3	4	5	
Pooled risk on the body sites with higher sun exposure (head, neck, and extremities)						
SCC						
No. of cases	380	403	394	430	397	
Pooled HR[1]	1 (referent)	0.92 (0.69, 1.23)	0.87 (0.71, 1.05)	0.95 (0.70, 1.29)	0.85 (0.73, 0.98)	0.10
Melanoma						
No. of cases	93	106	93	104	115	
Pooled HR[1]	1 (referent)	0.96 (0.72, 1.27)	0.89 (0.48, 1.65)	0.94 (0.71, 1.25)	1.05 (0.77, 1.42)	0.38
Risk of SCC on the body sites with lower sun exposure (trunk and mucosa)						
SCC						
No. of cases	55	59	63	62	68	
Pooled HR[1]	1 (referent)	0.88 (0.61, 1.28)	0.90 (0.62, 1.31)	0.88 (0.49, 1.58)	0.97 (0.68, 1.40)	0.75
Melanoma						
No. of cases	57	71	68	54	76	
Pooled HR[1]	1 (referent)	1.12 (0.74, 1.70)	1.08 (0.67, 1.74)	0.85 (0.58, 1.25)	1.21 (0.63, 2.34)	0.50

[1]The multivariate-adjusted HR from each cohort were combined with meta-analytic methods using random effects model. The HR from each cohorts were adjusted for family history of melanoma (yes *vs.* no), natural hair color (red, blonde, light brown, dark brown and black), number of arm moles (0, 1–2, 3–9 and ≥10), skin reaction to sun exposure as a child/adolescent (none/some redness, burn, painful burn/blisters), number of lifetime blistering sunburns (0, 1–4, 5–9 and ≥10), average time spent in direct sunlight since high school (<2, 2–5, 6–9 and ≥10 hr/wk), cumulative UV flux since baseline (quintiles), body mass index (<25.0, 25.0–29.9, 30.0–34.9 and ≥35.0 kg/m^2), physical activity (quintiles), smoking status (never, past, current with 1–14, 15–24 and or ≥25 cigarettes/d), intakes of total energy (quintiles), alcohol (0, 0.1–4.9, 5.0–9.9, 10.0–19.9 and ≥20.0 g/d) and citrus intake (quintiles). Analyses for women were also adjusted for menopausal status and postmenopausal hormone use (premenopausal, postmenopausal never, past or current use.

Table 4

Hazard Ratio (and 95% CI) of skin cancer by total niacin intake among participants without hypercholesterolemia in the NHS (1984–2010) and HPFS (1986–2010)

	Quintile of total niacin intake					*p* for trend
	1	2	3	4	5	
BCC						
NHS						
No. of cases/person-years	1,252/175,822	1,366/177,761	1,327/166,675	1,443/164,418	1,354/160,764	
Age-adjusted	1 (referent)	1.07 (0.99, 1.15	1.11 (1.03, 1.20)	1.20 (1.11, 1.30)	1.14 (1.06, 1.24)	0.002
Multivariate-adjusted[1]	1 (referent)	1.01 (0.93, 1.09)	1.02 (0.94, 1.10)	1.07 (0.99, 1.15)	1.00 (0.93, 1.09)	0.97
HPFS						
No. of cases/person-years	1,105/108,366	1,148/105,728	1,118/99,163	1,224/94,199	1,130/90,271	
Age-adjusted	1 (referent)	1.08 (0.99, 1.18)	1.11 (1.02, 1.20)	1.23 (1.13, 1.34)	1.19 (1.09, 1.29)	0.0002
Multivariate-adjusted[1]	1 (referent)	1.04 (0.95, 1.13)	1.02 (0.94, 1.11)	1.12 (1.03, 1.21)	1.09 (1.00, 1.19)	0.03
Pooled[2]						
Age-adjusted	1 (referent)	1.08 (1.02, 1.14)	1.11 (1.05, 1.17)	1.22 (1.15 1.28)	1.16 (1.10, 1.23)	<0.0001
Multivariate-adjusted[1]	1 (referent)	1.02 (0.97, 1.08)	1.02 (0.96, 1.08)	1.09 (1.03 1.16)	1.04 (0.96, 1.13)	0.24
Squamous cell cancer						
NHS						
No. of cases/person-years	124/176,482	114/178,480	111/167,381	92/165,187	110/161,527	
Age-adjusted	1 (referent)	0.90 (0.70, 1.16)	0.95 (0.73, 1.23)	0.80 (0.61, 1.05)	0.96 (0.74, 1.24)	0.95
Multivariate-adjusted[1]	1 (referent)	0.81 (0.63, 1.05)	0.82 (0.63, 1.06)	0.68 (0.52, 0.90)	0.80 (0.61, 1.03)	0.25
HPFS						
No. of cases/person-years	138/109,303	133/106,706	130/100,099	135/95,180	107/91,198	
Age-adjusted	1 (referent)	1.02 (0.80, 1.29)	1.04 (0.81, 1.31)	1.08 (0.85, 1.36)	0.90 (0.70, 1.16)	0.32
Multivariate-adjusted[1]	1 (referent)	0.94 (0.74, 1.20)	0.93 (0.72, 1.18)	0.93 (0.73, 1.19)	0.80 (0.74, 1.20)	0.09
Pooled[2]						
Age-adjusted	1 (referent)	0.96 (0.81, 1.14)	0.99 (0.83, 1.18)	0.94 (0.70, 1.25)	0.93 (0.78, 1.11)	0.39

	Quintile of total niacin intake					*p* for trend
	1	**2**	**3**	**4**	**5**	
Multivariate-adjusted[1]	1 (referent)	0.88 (0.74, 1.05)	0.88 (0.73, 1.05)	0.80 (0.59, 1.09)	0.80 (0.67, 0.96)	0.04
Melanoma						
NHS						
No. of cases/person-years	47/176,543	63/178,526	46/167,435	64/165,214	50/161,574	
Age-adjusted	1 (referent)	1.30 (0.89, 1.90)	1.02 (0.68, 1.90)	1.43 (0.98, 2.08)	1.14 (0.77, 1.70)	0.75
Multivariate-adjusted[1]	1 (referent)	1.18 (0.80, 1.72)	0.92 (0.61, 1.38)	1.28 (0.87, 1.87)	1.03 (0.68, 1.54)	0.98
HPFS						
No. of cases/person-years	44/109,383	44/106,775	56/100,161	31/95,279	56/91,242	
Age-adjusted	1 (referent)	1.05 (0.69, 1.60)	1.41 (0.95, 2.10)	0.80 (0.50, 1.27)	1.51 (1.02, 2.25)	0.06
Multivariate-adjusted[1]	1 (referent)	1.01 (0.66, 1.55)	1.35 (0.90, 2.01)	0.73 (0.46, 1.16)	1.42 (0.95, 2.13)	0.11
Pooled[2]						
Age-adjusted	1 (referent)	1.18 (0.89, 1.57)	1.20 (0.87, 1.66)	1.09 (0.61, 1.92)	1.32 (0.99, 1.74)	0.09
Multivariate-adjusted[1]	1 (referent)	1.10 (0.83 1.46)	1.11 (0.76, 1.62)	0.98 (0.57, 1.70)	1.21 (0.88, 1.67)	0.21

[1]Adjusted for family history of melanoma (yes *vs.* no), natural hair color (red, blonde, light brown, dark brown and black), number of arm moles (0, 1–2, 3–9 and ≥10), skin reaction to sun exposure as a child/adolescent (none/some redness, burn and painful burn/blisters), number of lifetime blistering sunburns (0, 1–4, 5–9 and ≥10), average time spent in direct sunlight since high school (<2, 2–5, 6–9 and ≥10 hr/wk), cumulative UV flux since baseline (quintiles), body mass index (<25.0, 25.0–29.9, 30.0–34.9 and ≥35.0 kg/m^2), physical activity (quintiles), smoking status (never, past, current with 1–14, 15–24 or ≥25 cigarettes/d), intakes of total energy (quintiles), alcohol (0, 0.1–4.9, 5.0–9.9, 10.0–19.9 and ≥20.0 g/d) and citrus intake (quintiles). Analyses for women were also adjusted for menopausal status and postmenopausal hormone use.

[2]The multivariate-adjusted HR from each cohort were combined with meta-analytic methods using random effects model.