Cancer Research

# Increased Caffeine Intake Is Associated with Reduced Risk of Basal Cell Carcinoma of the Skin

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## Abstract

Studies in animals suggest that caffeine administration helps prevent squamous cell skin cancer development, but there have been limited epidemiologic studies on the association between caffeine consumption and skin cancer risk. Using data from the Nurses' Health Study and the Health Professionals Follow-up Study, we prospectively examined risks of basal cell carcinoma (BCC, 22,786 cases), squamous cell carcinoma (SCC, 1,953 cases), and melanoma (741 cases) in relation to caffeine intake. Cox proportional hazard models were used to calculate relative risks (RR) and 95% confidence intervals (CI). The amount of caffeine intake from all dietary sources was inversely associated with BCC risk. Compared with the lowest quintile, the highest quintile had the lowest risk (RR, 0.82 in women; 95% CI:,0.77–0.86 and RR, 0.87 in men; 95% CI, 0.81–0.94; $P_{trend} < 0.0001$ in both). A significant inverse association was also found between caffeinated coffee consumption and BCC risk. Compared with individuals who consumed caffeinated coffee less than 1 cup per month, women who consumed more than 3 cups/d had the lowest risk (RR, 0.79; 95% CI, 0.74–0.85; $P_{trend} < 0.0001$) and the RR for men was 0.90 (95% CI, 0.80–1.01; $P_{trend} = 0.003$). Caffeine from other dietary sources (tea, cola, and chocolate) was also inversely associated with BCC risk. Decaffeinated coffee consumption was not associated with a similar decrease in BCC risk. In contrast, caffeine intake was not found to be inversely associated with risks of SCC or melanoma. Our findings argue that caffeine intake in men and women is inversely associated with risk of BCC. *Cancer Res; 72(13); 3282–9.* ©*2012 AACR.*

## Introduction

Skin cancers, broadly divided into basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma, are the most frequently diagnosed malignant tumors among white people in the United States. One in 5 Americans develops skin cancer in his or her lifetime (1). An individual's risk of developing skin cancer depends on both constitutional and environmental factors. Constitutional risk factors include skin phototype, eye and hair color, and tanning ability (2), which represents certain component of genetic susceptibility. UV radiation is an established environmental risk factor for both melanoma and nonmelanoma skin cancer (3).

Animal studies have consistently shown that oral or topical administration of caffeine inhibits SCC development in mice treated with UV light (4–8). Oral administration of tea inhibited UV-induced carcinogenesis in mice, whereas decaffeinated tea elicited substantially less inhibitory activity, which was restored by caffeine (6). One potential mechanism for the inhibitory effect of caffeine is the induction of apoptosis in UV-damaged keratinocytes (9, 10). Apoptosis is an important pathway for keratinocytes to prevent tumor transformation (11). It was shown that topical caffeine administration to mice after UV-B exposure increased the number of apoptotic keratinocytes as evaluated by sunburn cell formation and other markers of programmed cell death (12, 13). These findings suggest that caffeine intake might protect against the development of skin cancer in humans.

However, the results of epidemiologic studies about the association between coffee and skin cancer have been far from convincing. A prospective study from Norway first reported an inverse association between coffee and nonmelanoma skin cancer risk in 1986 (14). Further studies of this cohort with 108 cases of melanoma reported a significant inverse association between coffee consumption and melanoma risk in women [relative risk (RR) = 0.4; 95% confidence interval (CI), 0.2–0.8] but not in men (RR, 1.8; 95% CI, 0.4–3.2; refs. 15, 16). However, a case–control study from Italy did not confirm the inverse association for melanoma (17). An inverse association for nonmelanoma skin cancer was also found in a cross-sectional analysis of 93,676 Caucasian women, which reported a 30% lower prevalence of nonmelanoma skin cancer for those drinking 6 cups or more than nondrinkers (18). There were also studies suggesting a protective effect of tea consumption against the risk of skin cancer (19, 20). However, these prior

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**Note:** Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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**doi:** 10.1158/0008-5472.CAN-11-3511

studies did not distinguish between caffeinated and decaffeinated coffee or tea. Therefore, it was unknown whether the inverse association was due to caffeine or other components of coffee. We thus conducted a prospective analysis to evaluate the association between the intake of caffeine, caffeinated coffee, decaffeinated coffee, and other foods known to be high in caffeine and the risk of melanoma and nonmelanoma skin cancer in the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

## Patients and Methods

### Study population

The NHS was established in 1976, when 121,700 registered nurses aged 30 to 55 years in 11 U.S. states responded to a baseline questionnaire about risk factors for cancer and cardiovascular diseases. Participants completed self-administered, mailed follow-up questionnaires biennially with updated information on their lifestyle, diet, and medical history. The original response rate of the NHS was 70%, and the follow-up response rate is 90%. The HPFS began in 1986 when 51,529 U.S. male health professionals, including dentists, veterinarians, pharmacists, and optometrists aged 40 to 75 years completed a baseline questionnaire on lifestyle, diet, and newly diagnosed diseases. The information was updated biennially with follow-up questionnaires. The original response rate of the HPFS was 30%, and the follow-up response rate is 92%. These studies were approved by the Human Research Committee at the Brigham and Women's Hospital (Boston, MA) with written informed consent from all participants.

### Assessment of caffeine intake and skin cancer risk factors

To assess dietary intake including coffee and other foods known to be high in caffeine, we used a food-frequency questionnaire that inquired about the average use of foods and beverages during the past 2 years. The dietary questionnaires including caffeinated coffee and decaffeinated coffee, tea, cola, and chocolate intake were completed in 1984, 1986, 1990, 1994, 1998, 2002, and 2006 for the NHS, and in 1986, 1990, 1994, 1998, 2002, and 2006 for the HPFS. On all questionnaires, participants were asked how many times on average during the previous year they had consumed each food and beverage. The participants could choose from 9 frequency responses (never, 1–3 per month, 1 per week, 2–4 per week, 5–6 per week, 1 per day, 2–3 per day, 4–5 per day, and $\leq$6 per day). We assessed the total intake of caffeine by summing the caffeine content for a specific amount of each caffeinated food during the previous year (1 cup for coffee or tea, one 12-ounce bottle or can for carbonated beverages, and 1 ounce for chocolate) multiplied by a weight proportional to the frequency of its use. Using the U.S. Department of Agriculture food composition sources, we estimated that the caffeine content was 137 mg per cup of caffeinated coffee, 47 mg per cup of tea, 46 mg per bottle or can of cola beverage, and 7 mg per serving of chocolate candy. Food and nutrient intakes assessed by this dietary questionnaire, including caffeine, have been validated previously against two 1-week diet records. The observed correlation between the questionnaire and the diet record was about 0.9 for caffeine consumption (21, 22).

Data on skin cancer risk factors were obtained from cohort questionnaires in both cohorts in the 1980s. These risk factors included adolescent sunburn reactions, family history of melanoma, number of severe sunburns, mole count on the left arm, natural hair color, and UV index at birth, age 15, and age 30. In 2008, we asked how many hours per week were spent outdoors in direct sunlight in the middle of the day in summer months, including work and recreation at different age intervals (high school/college, 25–35, 36–59, 60–65) in both cohorts.

### Identification of skin cancer cases

Skin cancer identification was conducted routinely in both cohorts (24 years of follow-up from 1984 in the NHS and 22 years of follow-up from 1986 in the HPFS). Participants reported new diagnoses biennially. With their permission, participants' medical records were obtained and reviewed by physicians to confirm their self-reported diagnosis. Only pathologically confirmed cases of invasive melanoma and SCC were included in this study. Medical records were not obtained for self-reported cases of BCC, and the validity of BCC self-reports was more than 90% in our study (23, 24).

### Statistical analysis

To represent long-term intake of caffeine, caffeinated coffee, decaffeinated coffee, and other foods known to be high in caffeine, as well as caffeine intake patterns of individuals, we used cumulative average intakes based on the information from food frequency questionnaires in different years.

Participants contributed person-time from the date of return of the baseline questionnaire (1984 in NHS and 1986 in HPFS) until date of self-report of the first BCC, date of diagnosis of confirmed SCC or melanoma, date of death, or the end of follow-up (May 31, 2008), whichever came first. For those who were lost to follow-up, we censored them at the return date of the last questionnaire. We used Cox proportional hazard models to assess the association between the incidence of skin cancers and the consumption of caffeine, caffeine from coffee, caffeine from other food sources, caffeinated coffee, and decaffeinated coffee. For these analyses, coffee consumption was categorized into 5 groups: less than 1 cup per month, 1 cup per month to 1 cup per day, 1–2 cups per day, 2–3 cups per day, and more than 3 cups per day. Caffeine intake was categorized into quintiles. Caffeine from coffee and caffeine from other food sources were assessed as continuous variables. Trends in skin cancer risk across the amount of coffee or caffeine intake were assessed in Cox proportional hazard models by using coffee (cup) and caffeine (mg) intake as continuous variables. Covariates were adjusted in the multivariate analysis, including body mass index (BMI, 3 groups), physical activity (quintiles), the BMI and physical activity were associated with sun exposure and skin cancer risk (25), smoking status (never, past, current 1–14 cigarettes per day, 15+ cigarettes per day), childhood reaction to sun, severe sunburns, moles, hair color, family history of melanoma, sun exposures at different age intervals, UV index at birth, age 15, and age 30, and history of

nonskin cancer. We conducted meta-analyses (26) to combine the results from the NHS and HPFS. Because the heterogeneity was not statistically significant between women and men, the fixed-effects model was used to estimate the summary RR and 95% CI. We used the continuous measure of cumulative average caffeine intake per day (from all sources, mg) to fit a restricted cubic spline model and to obtain a smooth representation of the RR as a function of caffeine intake with adjustment for the above-mentioned confounders. We used 3 knots to divide continuous caffeine intake. We deleted the observations with caffeine intake higher than the 99th percentile (905 mg/d).

To summarize multiple variables, we constructed a multivariate confounder score (27) to create a susceptibility score for BCC, SCC, and melanoma. Briefly, we applied the Cox regression coefficients from a multivariate model including age, hair color, severe sunburns, moles, and family history of melanoma to each individual's values for the latter 4 of these variables and summed the values to compute a susceptibility risk score. We used this score to identify participants with low and high susceptibility based on the quintile value of score. The score was positively associated with the risk of each type of skin cancer. The highest quintile had the highest risk compared with the lowest quintile. For BCC, the RR was 1.93 in men (95% CI, 1.80–2.07) and 2.15 in women (95% CI, 2.04–2.28). For SCC, the RR was 2.99 in men (95% CI, 2.36–3.79) and 2.77 in women (95% CI, 2.23–3.44). For melanoma, the RR was 3.57 in men (95% CI, 2.47–5.14) and 4.49 in women (95% CI, 3.11–6.48). To test the interaction between the susceptibility score and caffeine intake, we coded both as continuous variables using the median value among controls for each quintile. For the interaction by individual risk factors, we coded these risk factors as ordinal variables and tested them individually for interaction with caffeine intake. We tested a single multiplicative interaction term by the likelihood ratio test comparing the model with the single interaction term against the model containing just the main effects of the susceptibility score (or each individual risk factor) and caffeine intake along with the same covariates. We also specifically analyzed SCC and melanoma at different body sites: head and neck, trunk, upper extremity, and lower extremity. Statistical analyses were conducted using SAS software (version 9, SAS Institute). All statistical tests were 2-sided.

## Results

A total of 112,897 eligible participants were included in the analyses (72,921 female nurses and 39,976 male health professionals). Characteristics of participants in 1986 were similar among the 5 groups of caffeine intake in both cohorts except for smoking, which was correlated with caffeine intake (Table 1).

During 24 years of follow-up in the NHS and 22 years of follow-up in the HPFS, a total of 22,786 participants developed BCC, 1,953 participants developed SCC, and 741 participants developed melanoma. The associations between caffeine intake and the risks of BCC, SCC, and melanoma are shown in Table 2. The amount of caffeine intake per day was inversely associated with BCC risk. Compared with the lowest quintile, the highest quintile of intake had the lowest risk. The RR was 0.82 in women (95% CI, 0.77–0.86) and was 0.87 in men (95% CI, 0.81–0.94; $P_{trend} < 0.0001$ in both). The RR was 0.84 (95% CI, 0.80–0.87) for men and women combined by meta-analysis. The restricted cubic spline curve (Fig. 1) confirms the inverse association between caffeine intake and the risk of BCC. The consumption of caffeine was not significantly associated with SCC risk or melanoma risk (Table 2).

A significant inverse association was also observed between caffeinated coffee consumption and BCC risk. The dose–response relationship was significant ($P_{trend} < 0.0001$ in women, and $P_{trend} = 0.003$ in men). Compared with individuals who consumed caffeinated coffee less than 1 cup per month, women who consumed more than 3 cups per day had the lowest risk (RR, 0.79; 95% CI, 0.74–0.85), and the RR for men was 0.90 (95% CI, 0.80–1.01). The RR was 0.83 (95% CI, 0.77–0.87) for men and women combined by meta-analysis. However, decaffeinated coffee consumption was not associated with a decreased risk of BCC (Table 3).

The association between caffeine intake per day (mg, continuous variable) from different sources and the risk of BCC is shown in Table 4. Caffeine from coffee, which accounted for 78.5% of total caffeine intake in our study population, was inversely associated with the risk of BCC in both women (RR for 100 mg/d = 0.97; 95% CI, 0.97–0.98) and men (RR for 100 mg/d = 0.99; 95% CI, 0.98–0.998). Caffeine from other dietary sources (tea, 18%; cola, 3%; and chocolate, 0.5%), which accounts for 21.5% of total caffeine intake, was also inversely associated with BCC risk with nonsignificant RR comparable with that of caffeine from coffee. The RR for 100 mg/d was 0.88 (95% CI, 0.75–1.04) in women and 0.93 (95% CI, 0.18–4.84) in men.

The consumption of caffeinated coffee or decaffeinated coffee was not significantly associated with risk of SCC (Supplementary Table S1) or melanoma (Supplementary Table S2).

No significant interactions were found between the susceptibility score (or individual risk factor) and caffeine intake on the risk of BCC, SCC, or melanoma. The association between caffeine intake and the risk of SCC or melanoma did not vary across different body sites (data not shown).

## Discussion

Previous studies were inconsistent about the association between coffee or tea consumption and the risk of skin cancer, whereas an overall decreased risk was suggested for nonmelanoma skin cancer (14–20, 28). In this study, we found an inverse association between coffee consumption and the risk of BCC, which is likely due to the effect of caffeine. No association was found for SCC or melanoma. Our study has extended previous findings by adding a clearer attribution of the risk reduction for BCC to caffeine intake as distinct from coffee consumption and highlighting differences between BCC and SCC.

UV radiation induces DNA damage in epidermal cells. If the DNA damage is not repaired or the damaged cells are not eliminated by apoptosis, the consequences can be cell transformation, uncontrolled proliferation, and eventually skin

**Table 1.** Age-adjusted variables by quintiles of caffeine intake in the NHS and HPFS

| | Caffeine intake per day in NHS (quintile median) | | | | | Caffeine intake per day in HPFS (quintile median) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q5 | Q1 | Q2 | Q3 | Q4 | Q5 |
| Characteristics | 31 mg (N = 14,586) | 122 mg (N = 14,589) | 232 mg (N = 14,597) | 372 mg (N = 14,566) | 604 mg (N = 14,583) | 8 mg (N = 8,146) | 59 mg (N = 7,895) | 154 mg (N = 7,951) | 321 mg (N = 8,010) | 584 mg (N = 7,974) |
| Age (1986), y[a] | 52.7 (7.4) | 52.7 (7.3) | 52.6 (7.2) | 52.6 (7.0) | 51.9 (6.9) | 54.5 (10.0) | 53.5 (9.9) | 54.1 (9.9) | 53.3 (9.6) | 52.4 (8.9) |
| BMI (1986), kg/m$^2$ | 25.8 (5.2) | 25.5 (4.9) | 25.3 (4.8) | 25.1 (4.5) | 24.9 (4.5) | 25.1 (3.3) | 25.6 (3.4) | 25.6 (3.4) | 25.7 (3.5) | 25.8 (3.3) |
| Physical activity (1986), met-h/wk[b] | 15.1 (19.4) | 14.4 (20.0) | 14.1 (19.2) | 13.6 (20.0) | 12.5 (20.2) | 22.6 (29.1) | 21.9 (33.1) | 20.7 (27.4) | 19.7 (25.5) | 18.4 (30.0) |
| Current smoker (1986), % | 11 | 15 | 18 | 22 | 38 | 5 | 6 | 8 | 11 | 17 |
| Family history of melanoma, % | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Number of sun burns 6+, % | 50 | 51 | 52 | 52 | 51 | 33 | 35 | 34 | 35 | 36 |
| Number of moles on the left arm 6+, % | 5 | 5 | 5 | 5 | 4 | 5 | 5 | 5 | 5 | 5 |
| Tanning ability, % | 30 | 31 | 31 | 30 | 31 | 21 | 21 | 20 | 21 | 23 |
| Red or blonde hair, % | 15 | 16 | 15 | 16 | 16 | 14 | 13 | 12 | 14 | 14 |
| College/high school sun exposure 11+ h, % | 13 | 14 | 14 | 14 | 15 | 50 | 51 | 48 | 51 | 49 |
| Age 25–35 sun exposure 11+ h, % | 12 | 13 | 13 | 14 | 14 | 31 | 32 | 31 | 33 | 32 |
| Age 36–59 sun exposure 11+ h, % | 9 | 10 | 10 | 10 | 10 | 26 | 26 | 27 | 29 | 28 |
| Age 60+ sun exposure 11+ h, % | 7 | 8 | 7 | 8 | 8 | 25 | 27 | 25 | 29 | 27 |
| At Birth UV index ≥7, % | 11 | 9 | 10 | 10 | 11 | 23 | 25 | 25 | 27 | 28 |
| Age 15 UV index ≥7, % | 11 | 9 | 10 | 10 | 11 | 24 | 26 | 26 | 28 | 29 |
| Age 30 UV index ≥7, % | 15 | 13 | 14 | 15 | 15 | 27 | 31 | 30 | 33 | 33 |

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

[a]Value is not age adjusted.

[b]Metabolic equivalents from recreational and leisure-time activities.

**Table 2.** Association between caffeine intake per day and the risk of BCC, SCC, and melanoma in the NHS (1984–2008) and the HPFS (1986–2008)

| | Women (NHS) | | | | Men (HPFS) | | | |
|---|---|---|---|---|---|---|---|---|
| Caffeine, mg | Cases | Person-years | Age-adjusted RR | MV-adjusted RR | Cases | Person-years | Age-adjusted RR | MV-adjusted RR |
| BCC | | | | | | | | |
| Quintile 1 | 3,106 | 294,086 | 1.00 | 1.00 | 1,879 | 136,819 | 1.00 | 1.00 |
| Quintile 2 | 3,033 | 292,991 | 0.97 (0.93–1.02) | 0.97 (0.92–1.01) | 1,878 | 137,656 | 0.97 (0.91–1.04) | 0.96 (0.90–1.03) |
| Quintile 3 | 3,072 | 293,707 | 0.97 (0.92–1.02) | 0.96 (0.91–1.01) | 1,895 | 138,136 | 0.96 (0.90–1.02) | 0.95 (0.89–1.02) |
| Quintile 4 | 2,765 | 293,891 | 0.93 (0.88–0.98) | 0.92 (0.87–0.97) | 1,709 | 138,543 | 0.88 (0.82–0.94) | 0.87 (0.81–0.93) |
| Quintile 5 | 2,254 | 294,490 | 0.81 (0.77–0.86) | 0.82 (0.77–0.86) | 1,459 | 137,426 | 0.82 (0.76–0.88) | 0.87 (0.81–0.94) |
| $P_{trend}$ | | | <0.0001 | <0.0001 | | | <0.0001 | <0.0001 |
| SCC | | | | | | | | |
| Quintile 1 | 222 | 295,620 | 1.00 | 1.00 | 171 | 138,502 | 1.00 | 1.00 |
| Quintile 2 | 226 | 294,455 | 1.01 (0.83–1.21) | 0.96 (0.80–1.16) | 189 | 139,383 | 1.05 (0.85–1.29) | 1.03 (0.83–1.28) |
| Quintile 3 | 208 | 295,189 | 0.89 (0.74–1.07) | 0.85 (0.70–1.03) | 192 | 139,887 | 1.04 (0.84–1.27) | 0.99 (0.80–1.23) |
| Quintile 4 | 195 | 295,229 | 0.95 (0.79–1.15) | 0.91 (0.75–1.11) | 198 | 140,067 | 1.10 (0.89–1.34) | 1.07 (0.86–1.33) |
| Quintile 5 | 192 | 295,652 | 1.08 (0.89–1.31) | 1.03 (0.84–1.26) | 157 | 138,736 | 0.98 (0.79–1.22) | 0.91 (0.71–1.15) |
| $P_{trend}$ | | | 0.56 | 0.81 | | | 0.87 | 0.45 |
| Melanoma | | | | | | | | |
| Quintile 1 | 78 | 295,739 | 1.00 | 1.00 | 77 | 138,581 | 1.00 | 1.00 |
| Quintile 2 | 78 | 294,566 | 1.00 (0.73–1.37) | 1.00 (0.73–1.37) | 67 | 139,473 | 0.85 (0.61–1.19) | 0.88 (0.62–1.25) |
| Quintile 3 | 81 | 295,313 | 1.02 (0.75–1.39) | 1.04 (0.76–1.43) | 60 | 139,999 | 0.75 (0.54–1.06) | 0.86 (0.60–1.23) |
| Quintile 4 | 77 | 295,325 | 1.00 (0.73–1.37) | 1.01 (0.73–1.39) | 71 | 140,183 | 0.90 (0.65–1.24) | 1.08 (0.76–1.51) |
| Quintile 5 | 89 | 295,739 | 1.19 (0.88–1.62) | 1.31 (0.95–1.79) | 59 | 138,817 | 0.79 (0.56–1.11) | 0.91 (0.62–1.32) |
| $P_{trend}$ | | | 0.25 | 0.09 | | | 0.35 | 0.93 |

NOTE: MV-adjusted RR: multivariate-adjusted for BMI (3 groups), physical activity (quintiles), smoking status (never, past, current 1–14 cigarettes per day, 15+ cigarettes per day), childhood reaction to sun, severe sunburns, moles, hair color, family history of melanoma, sun exposures at different age intervals, UV index at birth, age 15, and age 30, and history of nonskin cancer.

tumor formation (29). Mouse studies have shown that oral or topical caffeine administration promotes elimination of UV-damaged keratinocytes (the cells from which nonmelanoma skin cancer arises) via apoptosis and markedly reduces the risk of subsequent skin cancer development (8, 30–32).

The mechanisms and molecular targets for the proapoptotic effect of caffeine after DNA damage have been investigated in cultured cell lines (human osteosarcoma cells). Studies indicate that the ATR (ataxia telangiectasia mutated- and Rad3-related) protein is an important proapoptotic target for caffeine (33). ATR has higher affinity for DNA in UV-damaged cells than in undamaged cells, and damaged DNA stimulates the kinase activity of ATR significantly more than undamaged DNA (34). Caffeine either directly disrupts the ATR/Chk1 checkpoint pathway (35) or inhibits UV-induced phosphorylation of Chk1 and prematurely increases the number of mitotic cells with cyclin B1 that are likely to go on to apoptosis (5). In human keratinocytes, inhibition of the ATR-Chk1 pathway with caffeine augmented UV-induced apoptosis in a p53-independent manner, whereas other known and plausible targets of caffeine were not found to be involved in the UV response (9). These effects of caffeine via the ATR/Chk1 pathway may increase UV-induced apoptosis and decrease the risk of UV-induced skin cancer.

Nonmelanoma skin cancers arise via the transformation of keratinocytes from different layers of the skin (SCC from the top layer and BCC from the basal layer; ref. 36). We found an inverse association between caffeine intake and BCC risk, but not for SCC risk. This is somewhat different from findings in mouse studies, which have suggested a protective effect of caffeine for SCC (4, 6, 8). BCC was not specifically examined in these studies. Clear differences exist between BCC and SCC in their pathogenesis. Intermittent UV exposure and exposure during childhood was causative for the development of BCC, whereas chronic UV exposure is more closely associated with SCC development (37). The UV exposure pattern for BCC is similar to that reported in animal models. Squamous cells have a lower tolerance for DNA damage and a lower apoptotic threshold, which makes apoptosis a predominant protective mechanism against SCC. The less-differentiated basal cells have less tendency than squamous cells to undergo apoptosis (38). Hence, the triggering effect of caffeine on apoptosis may be apparent only in basal cells but not in squamous cells.

We did not find an association between caffeine intake and melanoma risk. Melanoma originates from pigment-producing melanocytes in the basal layer of the epidermis (36). Damaged melanocytes limit their proliferation and mutation accumulation by entering the senescence state instead of undergoing

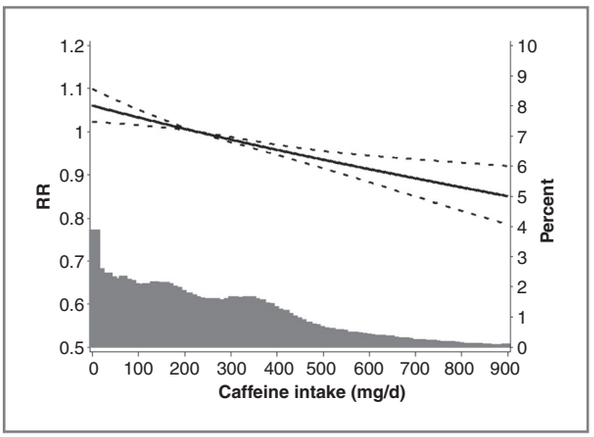


Figure 1. Multivariate RR of BCC among women and men as a function of caffeine intake in the NHS (1984–2008) and the HPFS (1986–2008). Data were fitted by a restricted cubic spline Cox proportional hazards model controlling for covariates listed in Table 2. The RR is indicated as the solid line and the upper and lower bounds of 95% CI as dotted lines (*y*-axis, left). The histogram shows the proportion of individuals (*y*-axis, right) with the same amount of caffeine intake in 10-mg increments. The sum of proportions is 100%.

apoptosis (39, 40). There is no evidence that caffeine promotes elimination of UV-damaged melanocytes via apoptosis; it is possible that this effect is restricted to keratinocytes.

The strengths of our study include the prospective and updated assessment of coffee, long follow-up, and a large number of incident skin cancer cases. Coffee intake was accurately reported on food frequency questionnaires (22), and because any misclassification in coffee intake due to differences in cup size or brewing strength would be expected to bias observed associations toward the null, such bias would not explain the inverse associations that we found. Our use of repeated measures of diet over time captured changes in diet and reduced measurement error; however, we were not able to assess coffee intake in young adulthood or total lifetime coffee intake. We had detailed data on relevant covariates to comprehensively adjust for potential confounders. Nevertheless, we cannot completely rule out the potential for residual confounding.

This study also has some limitations. First, the identification of BCC cases was based on self-report without pathologic confirmation. However, the participants in the 2 cohorts were nurses and health professionals, so the validity of their reports was expected to be high and has been proven in validation studies (23, 24, 41). This validation was conducted on a very small subset of BCC cases and did not include assessment of the underreported BCC. Nevertheless, misclassification of BCC cases would be expected to be nondifferential and to bias any associations toward the null, and thus would not explain the inverse associations. In addition, previous studies of BCC in the NHS using self-reported cases identified both constitutional and sun exposure risk factors as expected, such as lighter pigmentation, less childhood and adolescent tanning tendency, higher tendency to sunburn, and tanning salon attendance (24, 42). We recently confirmed the *MC1R* gene as the top BCC risk locus using the NHS and HPFS samples (43). These data together suggest that the bias due to self-report of BCC is likely to be minimal in our study. Second, the statistical power for

**Table 3.** Association between caffeinated coffee and decaffeinated coffee consumption and BCC risk in the NHS (1984–2008) and the HPFS (1986–2008)

| | Women (NHS) | | | | Men (HPFS) | | | |
|---|---|---|---|---|---|---|---|---|
| | Cases | Person-years | Age-adjusted RR | MV-adjusted RR | Cases | Person-years | Age-adjusted RR | MV-adjusted RR |
| Caffeinated coffee (cup) | | | | | | | | |
| <1/mo | 2,692 | 275,519 | 1.00 | 1.00 | 2,497 | 193,984 | 1.00 | 1.00 |
| 1/mo–1/d | 3,908 | 384,048 | 0.97 (0.92–1.02) | 0.94 (0.89–0.99) | 3,411 | 253,843 | 1.00 (0.95–1.05) | 0.99 (0.93–1.04) |
| 1–2/d | 2,904 | 259,452 | 1.00 (0.95–1.06) | 0.95 (0.89–1.00) | 1,244 | 94,533 | 0.92 (0.86–0.99) | 0.90 (0.84–0.97) |
| 2–3/d | 3,053 | 325,444 | 0.93 (0.88–0.98) | 0.91 (0.85–0.96) | 1,007 | 99,846 | 0.86 (0.80–0.92) | 0.92 (0.85–1.00) |
| >3/d | 1,673 | 224,704 | 0.78 (0.74–0.83) | 0.79 (0.74–0.85) | 397 | 46,090 | 0.80 (0.72–0.90) | 0.90 (0.80–1.01) |
| $P_{trend}$ | | | <0.0001 | <0.0001 | | | <0.0001 | 0.003 |
| Decaffeinated coffee (cup) | | | | | | | | |
| <1/mo | 4,515 | 537,832 | 1.00 | 1.00 | 3,027 | 274,276 | 1.00 | 1.00 |
| 1/mo–1/d | 6,052 | 584,911 | 1.12 (1.08–1.16) | 1.06 (1.01–1.11) | 3,855 | 288,074 | 1.12 (1.07–1.18) | 1.08 (1.03–1.14) |
| 1–2/d | 2,165 | 192,084 | 1.16 (1.10–1.22) | 1.12 (1.06–1.19) | 880 | 57,689 | 1.15 (1.06–1.24) | 1.07 (0.99–1.16) |
| 2–3/d | 1,109 | 110,430 | 1.13 (1.06–1.20) | 1.08 (1.00–1.17) | 568 | 47,644 | 1.04 (0.95–1.13) | 1.06 (0.96–1.16) |
| >3/d | 389 | 43,910 | 1.03 (0.93–1.14) | 0.98 (0.87–1.10) | 226 | 20,613 | 0.95 (0.83–1.09) | 1.00 (0.87–1.15) |
| $P_{trend}$ | | | 0.003 | 0.01 | | | 0.78 | 0.81 |

NOTE: MV-adjusted RR: multivariate-adjusted for BMI (3 groups), physical activity (quintiles), smoking status (never, past, current 1–14 cigarettes per day, 15+ cigarettes per day), childhood reaction to sun, severe sunburns, moles, hair color, family history of melanoma, sun exposures at different age intervals, UV index at birth, age 15, and age 30, and history of nonskin cancer.

**Table 4.** Caffeine intake from different sources and the risk of BCC in the NHS (1984–2008) and the HPFS (1986–2008)

| | Women (NHS) | | Men (HPFS) | |
|---|---|---|---|---|
| **Characteristics** | **MV-adjusted RR for 100 mg/d[c]** | ***P*** | **MV-adjusted RR for 100 mg/d[c]** | ***P*** |
| Caffeine from coffee (78.5%)[a] | 0.97 (0.97–0.98) | <0.0001 | 0.99 (0.98–0.998) | 0.016 |
| Caffeine from tea, cola, and chocolate (21.5%)[b] | 0.88 (0.75–1.04) | 0.13 | 0.93 (0.18–4.84) | 0.93 |

[a]Caffeine from coffee accounts for 78.5% of total caffeine intake in our study population.
[b]Caffeine from tea (18%), cola (3%), and chocolate (0.5%) accounts for 21.5% of total caffeine intake in our study population.
[c]MV-adjusted RR: multivariate-adjusted for BMI (3 groups), physical activity (quintiles), smoking status (never, past, current 1–14 cigarettes per day, 15+ cigarettes per day), childhood reaction to sun, severe sunburns, moles, hair color, family history of melanoma, sun exposures at different age intervals, UV index at birth, age 15, and age 30, and history of nonskin cancer.

melanoma and SCC in our study was much lower, due to the substantially smaller number of cases. Third, we are not able to rule out other differences between caffeinated and decaffeinated coffee that could also be etiologically relevant. Decaffeinated coffee has been artificially treated so as to remove caffeine, and other possibly cancer protective compounds might also be removed in that process. Fourth, we are not able to address a number of possibly relevant issues about tea consumption, such as green or black tea, or brewing strength because of the lack of detailed information about tea consumption on the food frequency questionnaires.

The incidence of BCC, which accounts for approximately 80% of newly diagnosed skin cancers and 30% of all newly diagnosed cancers in the United States, is still increasing by 4% to 8% per year, suggesting that the prevalence of BCC will soon equal that of all other cancers combined (44). Furthermore, an estimated 40% to 50% of patients with a primary carcinoma will develop one or more additional basal cell carcinomas within 5 years (45), causing considerable morbidity and placing a huge burden on healthcare systems. Given the nearly one million new cases diagnosed each year in the United States (46, 47), modification in daily dietary factors with even small protective effects may have great public health impact. Further studies specifically confirming this association are warranted.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Authors' Contributions

**Conception and design:** A. Qureshi, J. Han
**Development of methodology:** J. Han
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** F. Song, J. Han
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** F. Song, J. Han
**Writing, review, and/or revision of the manuscript:** F. Song, J. Han
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** J. Han
**Study supervision:** J. Han

## Acknowledgments

The authors thank Tricia Li for her help in data analysis and Dr. Walter Willett for his insightful input. They are indebted to the participants in the NHS and HPFS for their dedication to this study and thank the following state cancer registries 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.

## Grant Support

This work was supported by Departmental Funding and NIH CA87969 and CA055075.

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Received October 21, 2011; revised May 2, 2012; accepted May 7, 2012; published July 2, 2012.

## References

1. Robinson JK. Sun exposure, sun protection, and vitamin D. JAMA 2005;294:1541–3.
2. Netscher DT, Leong M, Orengo I, Yang D, Berg C, Krishnan B. Cutaneous malignancies: melanoma and nonmelanoma types. Plast Reconstr Surg 2011;127:37e–56e.
3. Karagas MR, Weinstock MA, Nelson HH. Keratinocyte carcinomas (basal and squamous cell carcinomas of the skin). In:Schottenfeld D, Fraumeni JF Jr, editors. Cancer epidemiology and prevention, 3rd ed. Oxford; New York: Oxford University Press; 2006. p. 1230–51.
4. Lu YP, Lou YR, Xie JG, Peng QY, Liao J, Yang CS, et al. Topical applications of caffeine or (-)-epigallocatechin gallate (EGCG) inhibit carcinogenesis and selectively increase apoptosis in UVB-induced skin tumors in mice. Proc Natl Acad Sci U S A 2002;99:12455–60.
5. Lu YP, Lou YR, Peng QY, Xie JG, Nghiem P, Conney AH. Effect of caffeine on the ATR/Chk1 pathway in the epidermis of UVB-irradiated mice. Cancer Res 2008;68:2523–9.
6. Huang MT, Xie JG, Wang ZY, Ho CT, Lou YR, Wang CX, et al. Effects of tea, decaffeinated tea, and caffeine on UVB light-induced complete carcinogenesis in SKH-1 mice: demonstration of caffeine as a biologically important constituent of tea. Cancer Res 1997;57:2623–9.
7. Kerzendorfer C, O'Driscoll M. UVB and caffeine: inhibiting the DNA damage response to protect against the adverse effects of UVB. J Invest Dermatol 2009;129:1611–3.

8. Lou YR, Lu YP, Xie JG, Huang MT, Conney AH. Effects of oral administration of tea, decaffeinated tea, and caffeine on the formation and growth of tumors in high-risk SKH-1 mice previously treated with ultraviolet B light. Nutr Cancer 1999;33:146–53.
9. Heffernan TP, Kawasumi M, Blasina A, Anderes K, Conney AH, Nghiem P. ATR-Chk1 pathway inhibition promotes apoptosis after UV treatment in primary human keratinocytes: potential basis for the UV protective effects of caffeine. J Invest Dermatol 2009;129:1805–15.
10. Han W, Ming M, He YY. Caffeine promotes ultraviolet B-induced apoptosis in human keratinocytes without complete DNA repair. J Biol Chem 2011;286:22825–32.
11. Erb P, Ji J, Kump E, Mielgo A, Wernli M. Apoptosis and pathogenesis of melanoma and nonmelanoma skin cancer. Adv Exp Med Biol 2008;624:283–95.
12. Koo SW, Hirakawa S, Fujii S, Kawasumi M, Nghiem P. Protection from photodamage by topical application of caffeine after ultraviolet irradiation. Br J Dermatol 2007;156:957–64.
13. Lu YP, Lou YR, Li XH, Xie JG, Lin Y, Shih WJ, et al. Stimulatory effect of topical application of caffeine on UVB-induced apoptosis in mouse skin. Oncol Res 2002;13:61–70.
14. Jacobsen BK, Bjelke E, Kvale G, Heuch I. Coffee drinking, mortality, and cancer incidence: results from a Norwegian prospective study. J Natl Cancer Inst 1986;76:823–31.
15. Stensvold I, Jacobsen BK. Coffee and cancer: a prospective study of 43,000 Norwegian men and women. Cancer Causes Control 1994;5:401–8.
16. Veierod MB, Thelle DS, Laake P. Diet and risk of cutaneous malignant melanoma: a prospective study of 50,757 Norwegian men and women. Int J Cancer 1997;71:600–4.
17. Naldi L, Gallus S, Tavani A, Imberti GL, La Vecchia C. Risk of melanoma and vitamin A, coffee and alcohol: a case-control study from Italy. Eur J Cancer Prev 2004;13:503–8.
18. Abel EL, Hendrix SO, McNeeley SG, Johnson KC, Rosenberg CA, Mossavar-Rahmani Y, et al. Daily coffee consumption and prevalence of nonmelanoma skin cancer in Caucasian women. Eur J Cancer Prev 2007;16:446–52.
19. Rees JR, Stukel TA, Perry AE, Zens MS, Spencer SK, Karagas MR. Tea consumption and basal cell and squamous cell skin cancer: results of a case-control study. J Am Acad Dermatol 2007;56:781–5.
20. Hakim IA, Harris RB, Weisgerber UM. Tea intake and squamous cell carcinoma of the skin: influence of type of tea beverages. Cancer Epidemiol Biomarkers Prev 2000;9:727–31.
21. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26; discussion 1127–36.
22. Feskanich D, Rimm EB, Giovannucci EL, Colditz GA, Stampfer MJ, Litin LB, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc 1993;93:790–6.
23. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, 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.
24. Hunter DJ, Colditz GA, Stampfer MJ, Rosner B, Willett WC, Speizer FE. Risk factors for basal cell carcinoma in a prospective cohort of women. Ann Epidemiol 1990;1:13–23.
25. Pothiawala S, Qureshi AA, Li Y, Han J. Obesity and the incidence of skin cancer in US Caucasians. Cancer Causes Control 2012;23:717–26.
26. Fleiss JL. The statistical basis of meta-analysis. Stat Methods Med Res 1993;2:121–45.
27. Miettinen OS. Stratification by a multivariate confounder score. Am J Epidemiol 1976;104:609–20.
28. Asgari MM, White E, Warton EM, Hararah MK, Friedman GD, Chren MM. Association of tea consumption and cutaneous squamous cell carcinoma. Nutr Cancer 2011;63:314–8.
29. Erb P, Ji J, Wernli M, Kump E, Glaser A, Buchner SA. Role of apoptosis in basal cell and squamous cell carcinoma formation. Immunol Lett 2005;100:68–72.
30. Lu YP, Lou YR, Lin Y, Shih WJ, Huang MT, Yang CS, et al. Inhibitory effects of orally administered green tea, black tea, and caffeine on skin carcinogenesis in mice previously treated with ultraviolet B light (high-risk mice): relationship to decreased tissue fat. Cancer Res 2001;61:5002–9.
31. Conney AH, Zhou S, Lee MJ, Xie JG, Yang CS, Lou YR, et al. Stimulatory effect of oral administration of tea, coffee or caffeine on UVB-induced apoptosis in the epidermis of SKH-1 mice. Toxicol Appl Pharmacol 2007;224:209–13.
32. Conney AH, Kramata P, Lou YR, Lu YP. Effect of caffeine on UVB-induced carcinogenesis, apoptosis, and the elimination of UVB-induced patches of p53 mutant epidermal cells in SKH-1 mice. Photochem Photobiol 2008;84:330–8.
33. Nghiem P, Park PK, Kim Y, Vaziri C, Schreiber SL. ATR inhibition selectively sensitizes G1 checkpoint-deficient cells to lethal premature chromatin condensation. Proc Natl Acad Sci U S A 2001;98:9092–7.
34. Unsal-Kacmaz K, Makhov AM, Griffith JD, Sancar A. Preferential binding of ATR protein to UV-damaged DNA. Proc Natl Acad Sci U S A 2002;99:6673–8.
35. Kumagai A, Guo Z, Emami KH, Wang SX, Dunphy WG. The Xenopus Chk1 protein kinase mediates a caffeine-sensitive pathway of checkpoint control in cell-free extracts. J Cell Biol 1998;142:1559–69.
36. Nakayama K. Growth and progression of melanoma and non-melanoma skin cancers regulated by ubiquitination. Pigment Cell Melanoma Res 2010;23:338–51.
37. Rosso S, Zanetti R, Martinez C, Tormo MJ, Schraub S, Sancho-Garnier H, et al. The multicentre south European study 'Helios'. II: Different sun exposure patterns in the aetiology of basal cell and squamous cell carcinomas of the skin. Br J Cancer 1996;73:1447–54.
38. Gilchrest BA, Eller MS, Geller AC, Yaar M. The pathogenesis of melanoma induced by ultraviolet radiation. N Engl J Med 1999;340:1341–8.
39. Giuliano S, Ohanna M, Ballotti R, Bertolotto C. Advances in melanoma senescence and potential clinical application. Pigment Cell Melanoma Res 2011;24:295–308.
40. Ha L, Merlino G, Sviderskaya EV. Melanomagenesis: overcoming the barrier of melanocyte senescence. Cell Cycle 2008;7:1944–8.
41. van Dam RM, Huang Z, Rimm EB, Weinstock MA, Spiegelman D, Colditz GA, et al. Risk factors for basal cell carcinoma of the skin in men: results from the health professionals follow-up study. Am J Epidemiol 1999;150:459–68.
42. 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.
43. Nan H, Xu M, Kraft P, Qureshi AA, Chen C, Guo Q, et al. Genome-wide association study identifies novel alleles associated with risk of cutaneous basal cell carcinoma and squamous cell carcinoma. Hum Mol Genet 2011;20:3718–24.
44. Donaldson MR, Coldiron BM. No end in sight: the skin cancer epidemic continues. Semin Cutan Med Surg 2011;30:3–5.
45. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol 2000;136:1524–30.
46. Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. J Am Acad Dermatol 1994;30:774–8.
47. Kiiski V, de Vries E, Flohil SC, Bijl MJ, Hofman A, Stricker BH, et al. Risk factors for single and multiple basal cell carcinomas. Arch Dermatol 2010;146:848–55.

# Increased Caffeine Intake Is Associated with Reduced Risk of Basal Cell Carcinoma of the Skin

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*Cancer Res* 2012;72:3282-3289.