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

Fengju Song1,4, Abrar A. Qureshi1,2, and Jiali Han1,2,3

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
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, decaffeinated 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 ≤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, 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, decaffeinated 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 lifestyle factors such as alcohol, physical activity, and BMI.
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; \( P \text{trend} < 0.0001 \) 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 (\( P \text{trend} < 0.0001 \) in women, and \( P \text{trend} = 0.003 \) 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, 0.81–0.84) 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 cancer.
Table 1. Age-adjusted variables by quintiles of caffeine intake in the NHS and HPFS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Caffeine intake per day in NHS (quintile median)</th>
<th>Caffeine intake per day in HPFS (quintile median)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1 (N = 14,586)</td>
<td>Q2 (N = 14,597)</td>
</tr>
<tr>
<td></td>
<td>31 mg</td>
<td>122 mg</td>
</tr>
<tr>
<td></td>
<td>52.7 (7.4)</td>
<td>52.6 (7.2)</td>
</tr>
<tr>
<td></td>
<td>51.9 (6.9)</td>
<td>232 mg</td>
</tr>
<tr>
<td></td>
<td>25.3 (4.8)</td>
<td>25.1 (4.5)</td>
</tr>
<tr>
<td></td>
<td>15.1 (19.2)</td>
<td>13.6 (20.0)</td>
</tr>
<tr>
<td></td>
<td>11.1 (19.6)</td>
<td>12.5 (20.2)</td>
</tr>
<tr>
<td></td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Age (1986), y⁰</td>
<td>52.7 (7.4)</td>
<td>52.6 (7.0)</td>
</tr>
<tr>
<td>BMI (1986), kg/m²</td>
<td>25.6 (5.2)</td>
<td>25.1 (4.5)</td>
</tr>
<tr>
<td>Physical activity (1986), met-h/wk⁰</td>
<td>15.1 (19.4)</td>
<td>14.1 (19.2)</td>
</tr>
<tr>
<td>Current smoker  (1986), %</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Family history of melanoma, %</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Number of sun burns 6+, %</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>Number of moles on the left arm 6+, %</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Tanning ability, %</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Red or blonde hair, %</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>College/high school sun exposure 11+, h, %</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Age 25–35 sun exposure 11+, h, %</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Age 36–59 sun exposure 11+, h, %</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Age 60+ sun exposure 11+, h, %</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>At Birth UV index ≥7, %</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Age 15 UV index ≥7, %</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Age 30 UV index ≥7, %</td>
<td>15</td>
<td>13</td>
</tr>
</tbody>
</table>

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

⁰Value is not age adjusted.

³Metabolic equivalents from recreational and leisure-time activities.
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 by 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 different from 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

### 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)

<table>
<thead>
<tr>
<th>Caffeine, mg</th>
<th>Cases (Women)</th>
<th>Age-adjusted RR</th>
<th>MV-adjusted RR</th>
<th>Cases (Men)</th>
<th>Age-adjusted RR</th>
<th>MV-adjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile 1</td>
<td>3,106</td>
<td>294,086</td>
<td>1.00</td>
<td>1.00</td>
<td>1,879</td>
<td>136,819</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>3,033</td>
<td>292,991</td>
<td>0.97 (0.93–1.02)</td>
<td>0.97 (0.92–1.01)</td>
<td>1,878</td>
<td>137,656</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>3,072</td>
<td>293,707</td>
<td>0.97 (0.92–1.02)</td>
<td>0.96 (0.91–1.01)</td>
<td>1,895</td>
<td>138,136</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>2,765</td>
<td>293,891</td>
<td>0.93 (0.88–0.98)</td>
<td>0.92 (0.87–0.97)</td>
<td>1,709</td>
<td>138,543</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>2,254</td>
<td>294,490</td>
<td>0.81 (0.77–0.86)</td>
<td>0.82 (0.77–0.86)</td>
<td>1,459</td>
<td>137,426</td>
</tr>
</tbody>
</table>

| **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) |

| **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) |

| \( P_{\text{trend}} \) | \( <0.0001 \) | \( <0.0001 \) | \( <0.0001 \) | \( <0.0001 \) | \( <0.0001 \) | \( <0.0001 \) |

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.
accurately reported on food frequency questionnaires (22), number of incident skin cancer cases. Coffee intake was updated assessment of coffee, long follow-up, and a large possible that this effect is restricted to keratinocytes. Elimination of UV-damaged melanocytes via apoptosis; it is apoptosis (39, 40). There is no evidence that caffeine promotes proportion is 100%.

The strengths of our study include the prospective and 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%.

aproportion is 100%.

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%

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>
<thead>
<tr>
<th></th>
<th>Women (NHS)</th>
<th></th>
<th>Men (HPFS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Person-years</td>
<td>Age-adjusted RR</td>
</tr>
<tr>
<td>Caffeinated coffee (cup)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1/mo</td>
<td>2,692</td>
<td>275,519</td>
<td>1.00</td>
</tr>
<tr>
<td>1/mo–1/d</td>
<td>3,908</td>
<td>384,048</td>
<td>0.97 (0.92–1.02)</td>
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<td>1–2/d</td>
<td>2,904</td>
<td>259,452</td>
<td>1.00 (0.95–1.06)</td>
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<td>2–3/d</td>
<td>3,053</td>
<td>325,444</td>
<td>0.93 (0.88–0.98)</td>
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<tr>
<td>&gt;3/d</td>
<td>1,673</td>
<td>224,704</td>
<td>0.78 (0.74–0.83)</td>
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<tr>
<td>$P_{\text{trend}}$</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.003</td>
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<tr>
<td>Decaffeinated coffee (cup)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;1/mo</td>
<td>4,515</td>
<td>537,832</td>
<td>1.00</td>
</tr>
<tr>
<td>1/mo–1/d</td>
<td>6,052</td>
<td>584,911</td>
<td>1.12 (1.08–1.16)</td>
</tr>
<tr>
<td>1–2/d</td>
<td>2,165</td>
<td>192,084</td>
<td>1.16 (1.10–1.22)</td>
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<tr>
<td>2–3/d</td>
<td>1,109</td>
<td>110,430</td>
<td>1.13 (1.06–1.20)</td>
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<tr>
<td>&gt;3/d</td>
<td>389</td>
<td>43,910</td>
<td>1.03 (0.93–1.14)</td>
</tr>
<tr>
<td>$P_{\text{trend}}$</td>
<td>0.003</td>
<td>0.01</td>
<td>0.78</td>
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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.

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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.

References
Caffeine and the Risk of Skin Cancer


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

Fengju Song, Abrar A. Qureshi and Jiali Han

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

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