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Caffeine Intake, Coffee Consumption, and Risk of Cutaneous Malignant Melanoma

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Abstract

Background—Caffeine has been shown to prevent ultraviolet radiation-induced carcinogenesis and to inhibit growth of melanoma cells in experimental studies.

Objectives—We evaluated the association between caffeine intake, coffee consumption, and melanoma risk among three large cohort studies.

Methods—The analysis used data from 163,886 women in the Nurses' Health Study II (NHS II, 1991–2009) and Nurses' Health Study (NHS, 1980–2008) and 39,424 men in the Health Professionals Follow-up Study (HPFS, 1986–2008). We used Cox proportional hazards models to estimate the hazard ratios (HR) with 95% confidence intervals (CI) of melanoma associated with dietary intakes.

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Conflict of Interest

The author(s) indicated no potential conflicts of interest.

Results—We documented 2,254 melanoma cases over 4 million person-years of follow-up. After adjustment for other risk factors, higher total caffeine intake was associated with a lower risk of melanoma (≥393 mg/d vs. <60 mg/d: HR=0.78, 95% CI=0.64–0.96, P_{trend}=0.048). The association was more apparent in women (≥393 mg/d vs. <60 mg/d: HR=0.70, 95% CI=0.58–0.85, P_{trend}=0.001) than in men (HR=0.94, 95% CI=0.75–1.18, P_{trend}=0.81), and more apparent for melanomas occurred on the body sites with higher continuous sun exposure (head, neck and extremities) (≥393 mg/d vs. <60 mg/d: HR=0.71, 95% CI=0.59–0.86, P_{trend}=0.001) than for melanomas occurred on the body sites with lower continuous sun exposure (trunk including shoulder, back, hip, abdomen and chest) (HR=0.90, 95% CI=0.70–1.16, P_{trend}=0.60). This pattern of association was similar to that for caffeinated coffee consumption, whereas no association was found for decaffeinated coffee consumption and melanoma risk.

Conclusions—Increasing caffeine intake and caffeinated coffee consumption may be protective against cutaneous malignant melanomas.

Keywords

caffeine; cancer epidemiology; coffee; melanoma; sun exposure

INTRODUCTION

Cutaneous malignant melanoma is a potentially lethal form of skin cancer, and its incidence has been increasing in the United States and worldwide[1–3]. Numerous studies have identified solar ultraviolet (UV) radiation as the predominant environment risk factor for the development of cutaneous melanoma[4], and the number of UV-induced sunburns is a strong predictor of melanoma incidence[5]. Interestingly, caffeine, a stimulant that is rich in coffee, has been shown to inhibit UV-induced sunburn lesions in the epidermis of mice and thus may mimic the effect of a sunscreen[6–8]. Oral administration of caffeine also has been demonstrated to enhance UV-induced cell apoptosis thereby enhancing the elimination of damaged precancerous cells[9–11]. In addition, both *in vitro* and *in vivo* studies have demonstrated an inhibitory effect of caffeine on the growth of melanoma cells[12–15]. Therefore, there is a good biological rationale for a potential preventive role of caffeine in the development of cutaneous melanoma.

To date, epidemiologic evidence for the association of coffee consumption and risk of cutaneous melanoma has been ambiguous. Limited prior studies have yielded conflicting results. Some studies suggested an inverse association between coffee consumption and risk of melanoma[16–19], while others showed no association[20–23]. The heterogeneous results may be due to differences in study design and range of coffee consumption and inconsistent control for potential confounders. Furthermore, the numbers of melanoma cases have been limited in most previous studies. These studies also did not distinguish caffeinated vs. decaffeinated coffee[16–19,21–23].

It has been documented that the role of sunlight in causing melanoma differs according to anatomic site, which is supportive of the hypothesis that melanomas may arise through divergent etiological pathways[24,25]. However, potential variation in the relation between coffee consumption and risk of melanoma by anatomic site has been unknown. According to

the existing biological evidence that caffeine may prevent UV-induced skin cancer[11], it is plausible that caffeine may have a stronger protective effect against cutaneous carcinogenesis on the body sites receiving higher continuous UV radiation versus that on the body sites receiving lower continuous UV radiation.

To address the hypothesis that caffeine intake and coffee consumption may be associated with a reduced risk of cutaneous malignant melanoma, we investigated these questions of interest by using data from three large cohorts of women and men, including the Nurses' Health Study II (NHS II, 1991–2009), Nurses' Health Study (NHS, 1980–2008), and Health Professionals Follow-up Study (HPFS, 1986–2008).

METHODS

Study Populations

The NHS II was established in 1989 when 116,430 registered female nurses aged 25–42 years were enrolled using a mailed baseline questionnaire which inquired about medical history and lifestyle practices. The NHS was established in 1976 when 121,700 married, registered, female nurses between the ages of 30 and 55 and residing in the United States at the time of enrollment responded to a baseline questionnaire that included questions about their medical history and lifestyle risk factors. The HPFS was established in 1986 when 51,529 US male health professionals aged 40 to 75 years completed a baseline questionnaire on lifestyle, diet, and newly diagnosed diseases. Biennial questionnaires were used to collect data on disease outcomes and health related factors in all three cohorts. We had investigated the association of caffeine intake, coffee consumption and melanoma risk using data from the NHS and HPFS[20], which lacked a detailed investigation for body site information on melanoma and used different cutoffs on caffeine intake levels. Thus, we revisited these studies and performed a meta-analysis of all three studies. The institutional review boards of Partners Health Care System and Harvard School of Public Health approved this study. We consider the participants' completion and return of the self-administered questionnaires as informed consent.

Assessment of Melanoma Cases

Participants reported new diagnoses of skin cancer biennially. Permission is obtained from participants to acquire their medical and pathological reports if melanoma is reported. The medical and pathological records were reviewed by physicians who were unaware of exposure status to retrieve information on tumor histology if available. Melanomas were initially classified as the following three subgroups according to tumor location: head/neck melanomas, extremity melanomas (upper extremities between shoulder and hand fingers and lower extremities between hip and feet) and trunk melanomas (shoulder, back, hip, abdomen, and chest), according to the existing literature that head/neck melanomas may arise through a different causal pathway when compared to trunk melanomas[25], and extremity melanomas may have a risk factor profile intermediate between the profiles for head/neck melanomas and trunk melanomas[24,26]. Because the associations with caffeine intake for melanomas of head/neck and extremities were similar, we then collapsed these two subgroups as a single group. In-situ melanomas were defined as early-stage tumors

restricted to the epidermis, and invasive melanomas were defined as those had grown into the dermis or surrounding tissues based on the pathological reports. A detailed body site and histological description for incident melanomas in each study is shown in eTable 1.

Assessment of Dietary Exposure

The dietary assessment was repeated using a food-frequency questionnaire (FFQ) at least 4 years during the follow-up. Specifically, dietary information was collected in 1991, 1995, 1999, 2003 and 2007 in the NHS II, in 1980, 1984, 1986, 1990, 1994, 1998, 2002 and 2006 in the NHS, and in 1986, 1990, 1994, 1998, 2002 and 2006 in the HPFS. On all FFQs, participants were asked how often on average (i.e., never to 6+ servings/d) during the previous year they had consumed caffeinated and decaffeinated coffee ("one cup"), tea ("one cup or glass"), carbonated beverages ("one glass, bottle, or can"), and other food items. Carbonated beverages included caffeinated and caffeine-free colas and carbonated soft drinks. We calculated the total caffeine intake by summing the caffeine content for a specific amount of each food during the previous year multiplied by a weight proportional to the frequency of its consumption. By using the food-composition database of the US Department of Agriculture, we estimated that the caffeine content was 137 mg per cup of caffeinated coffee, 47 mg per cup of caffeinated tea, 46 mg per bottle or can of caffeinated carbonated beverage, and 7 mg per serving of caffeine-containing chocolate. The validity and reproducibility of the FFQ has been detailed elsewhere[27,28]. Specifically, high correlations were found between FFQ and diet records for coffee and other caffeine-rich beverage intake (coffee: r=0.78; tea: r=0.93; and caffeinated carbonated beverages: r=0.84)[27,28]. In addition, information on other dietary intakes including total energy and alcohol was also collected using the FFQs.

Assessment of Covariates

In the biennial follow-up questionnaires, we inquired and updated information on anthropometric and lifestyle factors for chronic diseases, including body height and weight, cigarette smoking, and physical activity. Data on menopausal status, post-menopausal hormone use, and rotating night shifts were collected in women[29]. Data on the following phenotypic and sun exposure related factors were collected through the follow-up questionnaires: family history of melanoma in first-degree relatives (parents and siblings); natural hair color; number of moles on legs (NHS II) or arms (NHS and HPFS); skin reaction to sun exposure for 2 hours or more as a child/adolescent; number of severe or blistering sunburns; average time spent in direct sunlight since high school; and cumulative UV flux since baseline[30,31].

Statistical Analysis

A total of 95,248 women in the NHS II, 74,666 women in the NHS, and 39,424 men in the HPFS who had completed a dietary questionnaire and had no history of any cancer at baseline were included in the present analysis. We used cumulatively updated intakes in analyses to create the best estimates of long-term intake. That is, at the beginning of every 2-year follow-up cycle, each intake was calculated as the mean of all reported intakes up to that time[32]. Participants contributed to follow-up time from the return month of baseline questionnaire to the month of the first diagnosis of a skin cancer (melanoma, squamous cell

carcinoma, or basal cell carcinoma), month of death, loss to follow-up, or the end of follow-up (June 2009 for NHS II, June 2008 for NHS, and January 2008 for HPFS), whichever came first. We used Cox proportional hazards models to estimate the age-adjusted and multivariate hazard ratios (HRs) with 95% confidence intervals (CIs) of incident melanoma associated with dietary intakes. Multivariate analyses for caffeine intake were conducted with adjustment for known melanoma risk factors and potential lifestyle confounders which have been associated with skin cancer risk in previous studies[29,30,33–35]. Missing data during any follow-up period were coded as a missing indicator category for categorical variables (e.g., smoking status) and with carried-forward values for continuous variables (e.g., body mass index). Trend tests across categories of dietary intake were performed by assigning median values for these categories and treating the variables as continuous terms in the models. Results from different study cohorts were pooled using a random-effect model. P values for heterogeneity between studies were calculated with the use of the Q statistic. We used SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina) for all statistical analyses. All statistical tests were 2-tailed, and the significance level was set at $P<0.05$.

RESULTS

We documented a total of 1,483 incident melanomas among women over 3,302,700 person-years of follow-up (NHS II: 642 cases/1,543,932 person-years; NHS: 841 cases/1,758,768 person-years) and 771 incident melanomas among men over 663,991 person-years of follow-up. Among women, 199 (13.4%) melanomas occurred on head and neck, 793 (53.5%) on extremities, and 457 (30.8%) on trunk. Among men, 233 (30.2%) melanomas occurred on head and neck, 169 (21.9%) on extremities, and 307 (39.8%) on trunk (eTable 1). To control for the heterogeneity in caffeine intake ranges across the study cohorts, we used the caffeine intake quintiles in the NHS II to regroup NHS and HPFS participants. Table 1 shows the characteristics of study participants by quintiles of caffeine intake in the NHS II. Participants with higher caffeine intake had higher consumption levels of caffeinated coffee, caffeinated tea, and caffeinated carbonated beverages; and were more likely to smoke, drink alcohol, and work in night shifts.

We found significant inverse association between increased caffeine intake and risk of overall melanoma in both NHS II and NHS cohorts (Table 2). After adjustment for other risk factors, the pooled multivariate HRs for overall melanoma from the lowest to highest category of caffeine intake in women were 1.00 (reference), 0.84 (95% CI, 0.70 to 1.01), 0.90 (95% CI, 0.75 to 1.07), 0.80 (95% CI, 0.67 to 0.96), and 0.70 (95% CI, 0.58 to 0.85) (P_{trend}=0.001). However, the association was not apparent in men (P_{trend}=0.81). Pooled analysis for all three cohorts also suggested a significant inverse association between caffeine intake and risk of overall melanoma (multivariate HR=0.78 comparing the extreme categories of ≥393 mg/d vs. <60 mg/d, 95% CI, 0.64 to 0.96, P_{trend}=0.048).

Interestingly, the inverse association appeared to be more apparent for melanomas occurred on head/neck and extremities than for melanomas occurred on trunk in all three cohorts. The inverse association for head/neck melanoma was similar with that for extremity melanoma (eTable 2), and the pooled multivariate HRs for melanoma on head, neck and extremities comparing the extreme categories were 0.66 (95% CI, 0.53 to 0.83, P_{trend}=0.001) in women

and 0.71 (95% CI, 0.59 to 0.86, P_{trend}=0.001) in both women and men (Table 3). In contrast, the association trend was not evident for trunk melanoma over the intake categories in the pooled analyses (all pooled P_{trend}>0.20).

Caffeinated coffee consumption was also inversely associated with risk of overall melanoma in women, whereas decaffeinated coffee consumption showed no association with risk of overall melanoma in women (Table 4). Compared to women who abstained from caffeinated coffee, the pooled multivariate HRs for overall melanoma were 0.86 (95% CI, 0.72 to 1.02) for women who consumed less than 1 cup/d, 0.83 (95% CI, 0.70 to 0.98) for 1 to 2 cup/d, and 0.76 (95% CI, 0.64 to 0.89) for more than 2 cup/d (P_{trend}=0.001). There was no apparent association for caffeinated coffee consumption and risk of overall melanoma in men (P_{trend}=0.55). However, caffeinated coffee consumption appeared to be more strongly associated with melanoma on head, neck and extremities in all three cohorts (Table 5), and the pooled multivariate HRs comparing the extreme consumption levels (>2 cup/d vs. never) were 0.70 (95% CI, 0.58 to 0.85, P_{trend}<0.001) in women and 0.74 (95% CI, 0.63 to 0.88, P_{trend}<0.001) in both women and men. The inverse association for head/neck melanoma was also similar with that for extremity melanoma (eTable 3). In contrast, there was no evident association trend for caffeinated coffee consumption and risk of trunk melanoma over the consumption categories (all pooled P_{trend}>0.60, Table 5). There was no apparent association between decaffeinated coffee consumption and melanoma on either head/neck/extremities or trunk (data not shown).

Associations of caffeine intake and caffeinated coffee consumption with in-situ and invasive melanomas were generally similar (eTable 4 and eTable 5). We conducted stratified analyses to evaluate whether the association between caffeine intake and risk of melanoma varied according to potential confounders, such as smoking status, alcohol use, and rotating night shifts in women. Results of subgroup analyses suggested associations generally similar to those from the main analyses, and there was no significant interaction between caffeine intake and these potential confounders (all $P_{interaction}$>0.10, data not shown).

DISCUSSION

Based on data from three large prospective cohorts, we found that higher caffeine intake and caffeinated coffee consumption was associated with a lower risk of cutaneous malignant melanoma. In contrast, no association was found between consumption of decaffeinated coffee and risk of melanoma. Participants in the highest caffeine intake category (≥393 mg/d) had a 22% lower risk of melanoma compared to those in the lowest intake category (<60 mg/d). The inverse association with caffeine intake and caffeinated coffee consumption was more apparent in women than in men, and more apparent for melanomas occurred on head, neck and extremities than for melanomas occurred on trunk . In contrast, no inverse association was found for melanoma on trunk with caffeinated coffee consumption. These findings are consistent with the existing literature from animal studies that caffeine may eliminate sunburn cells by enhancing UV-induced apoptosis and thereby prevent UV-induced carcinogenesis[6–10,36,37].

Caffeine may inhibit UV-induced carcinogenesis through several biological mechanisms. Animal studies indicate that caffeine has a sunscreen effect that inhibits UV-induced formation of thymine dimers and sunburn lesions in the epidermis of mice[7,11]. Caffeine administration enhances UV-induced apoptosis by p53-dependent and p53-independent mechanisms. Pretreatment with oral caffeine enhanced UV-induced increases in p53 positive cells, p21 positive cells, and apoptotic sunburn cells[9]. Oral administration of coffee had a similar stimulatory effect on UV-induced apoptosis[10]. However, oral administration of caffeine had no effect on p53, p21, or apoptosis in the absence of UV irradiation, indicating that caffeine enhanced apoptosis only in DNA damaged epidermis but not in normal epidermis[11]. Previous experimental studies in tumor cells have found that caffeine can arrest cell cycle at the G2 checkpoint and preferentially radiosensitize tumor cells[38,39], and that the radiosensitizing effects of caffeine are related to inhibition of the protein kinase activities of ataxia telangiectasia mutated and Rad3-related (ATR)[40]. A more recent study further demonstrated that administration of caffeine could enhance the removal of DNA-damaged cells by inhibiting the ATR-mediated phosphorylation of checkpoint kinase 1 and prematurely increasing the number of cyclin B1-containing cells that undergo lethal mitosis, and thereby inhibit UV-induced carcinogenesis[37]. In addition, UV-mediated NF-κB activation has been shown to result in acquired resistance to apoptosis and promotes the development of skin cancer[41,42], whereas caffeine can inhibit UV-mediated NF-κB activation in melanoma cells[43]. Notably, caffeine also has been demonstrated to inhibit the growth of melanoma cells *in vitro* and *in vivo*[12–15]. An early study found that caffeine caused murine melanoma cells treated with cisplatin to differentiate, and this inhibited growth[12]. Further studies found that treatment with caffeine not only can inhibit tumor growth, prevent neovascularization, increase apoptosis of melanoma cells[13], but also can inhibit metastatic behavior of melanoma cells[14,15]. Therefore, there exists a convincing biological plausibility that caffeine intake may play an important role in the prevention of cutaneous melanoma.

The findings of the present study are different from that in our previous analysis[20]. Several reasons may help explain the previous null results. First, the ranges of caffeine intake differed between the study cohorts, causing the heterogeneity in the HRs of higher intake groups vs. reference groups over study populations. Specifically, the ranges of the first quintiles were 0–59 mg/d in the NHS II, 0–132 mg/d in the NHS, and 0–42 mg/d in the HPFS. Table 2 shows the results using NHS II intake quintiles for all 3 cohorts, and the HR of the second category 60–140 mg/d vs. the first category 0–59 (<60) mg/d was 0.83 (0.60–1.15) in the NHS. Therefore, when we use the 0–132 mg/d range (equals to <60 mg/d plus 60–140 mg/d approximately) as the reference group for NHS, it will diminish the relative risk difference over intake categories and results in null HR estimates. To control for the heterogeneity in intake ranges over studies, we therefore used the same intake cutoffs for different study cohorts. Second, we treated melanoma as a single outcome in the previous analysis but did not account for the body site categories (head/neck/extremities vs. trunk) of the tumors. In the present study, we performed a more detailed, hypothesis-driven subtype analysis for melanoma, and found that the inverse association between caffeine intake, caffeinated coffee consumption and risk of melanoma was mainly attributable to melanomas occurred on head, neck and extremities with higher continuous sun exposure but not

melanomas occurred on trunk with lower continuous sun exposure. Third, we also expanded the follow-up period to start from 1980 (instead of 1984 in the previous analysis) in the NHS when the first FFQ was used to collect diet information in the NHS participants[32], and thus increased the statistical power. Melanoma was first asked in 1982 in the NHS, and we sought to validate self-reported melanoma diagnoses during 1980–1982 by medical and pathological records.

The association between caffeine intake, caffeinated coffee consumption and melanoma risk was not apparent among men in the HPFS, though the inverse association was also more apparent for melanoma on head, neck and extremities than for melanoma on trunk. This may be due to a modest statistical power for men, and a lower proportion of melanoma on head, neck and extremities and a higher proportion of melanoma on trunk in men than in women (eTable 1). It is evident that sun exposure patterns differ between women and men. Men generally receive less continuous solar UV radiation on extremities as compared to women because of different dressing styles, thereby resulting in different proportions of extremity melanoma over genders (21.9% in men vs. 53.5% in women). Therefore, it is possible that caffeine's protective effect against melanoma among men may not be as apparent as among women when overall melanoma is treated as a single outcome. Similarly, a previous study from Norway also documented a significant inverse association between coffee consumption and melanoma risk in women but not in men[18]. The Norwegian study included 25,049 women and 25,708 men, among whom a total of 108 malignant melanomas were documented[18]. However, this study did not differentiate between caffeinated coffee and decaffeinated coffee and also did not account for the variation in the association by tumor site.

The strengths of this study include its prospective design, large sample size, long-term follow-up, detailed melanoma case ascertainment with clear separation for different subtypes, repeated assessments of dietary and lifestyle factors, and the ability to differentiate between caffeinated coffee and decaffeinated coffee. Our study also has several limitations. The cohorts studied mostly comprised white, well-educated health professionals, which potentially limits the generalizability of the findings. However, restricting the sample to health professionals also reduces potential residual confounding from socioeconomic status. In the present study, caffeine intake was also positively associated with several lifestyle factors including alcohol intake, smoking status and rotating night shifts. However, we did not detect appreciable interaction between caffeine intake, coffee consumption and these potential confounders, suggesting that residual confounding by these variables should not be a substantial concern.

In sum, we found that caffeine intake and caffeinated coffee consumption were inversely associated with risk of cutaneous malignant melanoma based on data from three large cohorts. The association was more apparent in women than in men, and was also more apparent for melanomas occurred on head, neck and extremities than for melanomas occurred on trunk. We did not find any association between decaffeinated coffee consumption and melanoma risk. These findings are consistent with previous biological evidence that caffeine may prevent UV-induced carcinogenesis, and support the hypothesis that melanoma on different body sites may arise through divergent causal pathways[24–26].

Given the highly prevalent coffee consumption and sun exposure behaviors in the general population and the rising melanoma incidence over the decades worldwide[1–3], our findings may help convey important public health implication, and may be potentially useful for the prevention of sun-induced malignant melanomas.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Society, AC., editor. American Cancer Society. Cancer Facts & Figures 2014. Atlanta: 2014.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005; 55(2):74–108. [PubMed: 15761078]
3. Geller AC, Miller DR, Annas GD, Demierre MF, Gilchrest BA, Koh HK. Melanoma incidence and mortality among US whites, 1969–1999. Jama. 2002; 288(14):1719–1720. [PubMed: 12365954]
4. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, Melchi CF. Metaanalysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer. 2005; 41(1):45–60. [PubMed: 15617990]
5. Cho E, Rosner BA, Feskanich D, Colditz GA. Risk factors and individual probabilities of melanoma for whites. J Clin Oncol. 2005; 23(12):2669–2675. [PubMed: 15837981]
6. Lu YP, Lou YR, Peng QY, Xie JG, Conney AH. Stimulatory effect of topical application of caffeine on UVB-induced apoptosis in the epidermis of p53 and Bax knockout mice. Cancer Res. 2004; 64(14):5020–5027. [PubMed: 15256477]
7. Lu YP, Lou YR, Xie JG, Peng QY, Zhou S, Lin Y, Shih WJ, Conney AH. Caffeine and caffeine sodium benzoate have a sunscreen effect, enhance UVB-induced apoptosis, and inhibit UVB-induced skin carcinogenesis in SKH-1 mice. Carcinogenesis. 2007; 28(1):199–206. [PubMed: 16864596]
8. Lu YP, Lou YR, Xie JG, Peng QY, Liao J, Yang CS, Huang MT, Conney AH. 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(19):12455–12460. [PubMed: 12205293]
9. Lu YP, Lou YR, Li XH, Xie JG, Brash D, Huang MT, Conney AH. Stimulatory effect of oral administration of green tea or caffeine on ultraviolet light-induced increases in epidermal wild-type p53, p21(WAF1/CIP1), and apoptotic sunburn cells in SKH-1 mice. Cancer Res. 2000; 60(17): 4785–4791. [PubMed: 10987287]
10. Conney AH, Zhou S, Lee MJ, Xie JG, Yang CS, Lou YR, Lu Y. 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(3):209–213. [PubMed: 17188726]

11. Conney AH, Lu YP, Lou YR, Kawasumi M, Nghiem P. Mechanisms of Caffeine-Induced Inhibition of UVB Carcinogenesis. Front Oncol. 2013; 3:144. [PubMed: 23785666]
12. Tsuchiya H, Tomita K, Yasutake H, Ueda Y, Tanaka M, Sasaki T. Growth inhibition and differentiation of murine melanoma B16-BL6 cells caused by the combination of cisplatin and caffeine. Jpn J Cancer Res. 1989; 80(12):1246–1251. [PubMed: 2516852]
13. Ohta A, Gorelik E, Prasad SJ, Ronchese F, Lukashev D, Wong MK, Huang X, Caldwell S, Liu K, Smith P, Chen JF, Jackson EK, Apasov S, Abrams S, Sitkovsky M. A2A adenosine receptor protects tumors from antitumor T cells. Proc Natl Acad Sci U S A. 2006; 103(35):13132–13137. [PubMed: 16916931]
14. Gude RP, Menon LG, Rao SG. Effect of Caffeine, a xanthine derivative, in the inhibition of experimental lung metastasis induced by B16F10 melanoma cells. J Exp Clin Cancer Res. 2001; 20(2):287–292. [PubMed: 11484989]
15. Lentini A, Kleinman HK, Mattioli P, Autuori-Pezzoli V, Nicolini L, Pietrini A, Abbruzzese A, Cardinali M, Beninati S. Inhibition of melanoma pulmonary metastasis by methylxanthines due to decreased invasion and proliferation. Melanoma Res. 1998; 8(2):131–137. [PubMed: 9610865]
16. Osterlind A, Tucker MA, Stone BJ, Jensen OM. The Danish case-control study of cutaneous malignant melanoma. IV. No association with nutritional factors, alcohol, smoking or hair dyes. Int J Cancer. 1988; 42(6):825–828. [PubMed: 3192325]
17. Stensvold I, Jacobsen BK. Coffee and cancer: a prospective study of 43,000 Norwegian men and women. Cancer Causes Control. 1994; 5(5):401–408. [PubMed: 7999961]
18. 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(4):600–604. [PubMed: 9178814]
19. Fortes C, Mastroeni S, Boffetta P, Antonelli G, Pilla MA, Botta G, Anzidei P, Venanzetti F. The protective effect of coffee consumption on cutaneous melanoma risk and the role of GSTM1 and GSTT1 polymorphisms. Cancer Causes Control. 2013; 24(10):1779–1787. [PubMed: 23860951]
20. Song F, Qureshi AA, Han J. Increased caffeine intake is associated with reduced risk of basal cell carcinoma of the skin. Cancer Res. 2012; 72(13):3282–3289. [PubMed: 22752299]
21. 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(5):823–831. [PubMed: 3457969]
22. Green A, Bain C, McLennan R, Siskind V. Risk factors for cutaneous melanoma in Queensland. Recent Results Cancer Res. 1986; 102:76–97. [PubMed: 3738188]
23. 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(6):503–538. [PubMed: 15548944]
24. Olsen CM, Zens MS, Stukel TA, Sacerdote C, Chang YM, Armstrong BK, Bataille V, Berwick M, Elwood JM, Holly EA, Kirkpatrick C, Mack T, Bishop JN, Osterlind A, Swerdlow AJ, Zanetti R, Green AC, Karagas MR, Whiteman DC. Nevus density and melanoma risk in women: a pooled analysis to test the divergent pathway hypothesis. Int J Cancer. 2009; 124(4):937–944. [PubMed: 19035450]
25. Whiteman DC, Stickley M, Watt P, Hughes MC, Davis MB, Green AC. Anatomic site, sun exposure, and risk of cutaneous melanoma. J Clin Oncol. 2006; 24(19):3172–3177. [PubMed: 16809740]
26. Green AC, Siskind V. Risk factors for limb melanomas compared with trunk melanomas in Queensland. Melanoma Res. 22(1):86–91. [PubMed: 22124166]
27. Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, Willett WC. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol. 1989; 18(4):858–867. [PubMed: 2621022]
28. Willett, WC. Nutritional epidemiology. 1 ed.. New York: Oxford University Press; 1990.
29. Schernhammer ES, Razavi P, Li TY, Qureshi AA, Han J. Rotating night shifts and risk of skin cancer in the nurses' health study. J Natl Cancer Inst. 2011; 103(7):602–606. [PubMed: 21335547]

30. Wu S, Han J, Laden F, Qureshi AA. Long-term ultraviolet flux, other potential risk factors, and skin cancer risk: a cohort study. Cancer Epidemiol Biomarkers Prev. 2014; 23(6):1080–1089. [PubMed: 24876226]
31. Wu S, Han J, Li WQ, Li T, Qureshi AA. Basal-cell carcinoma incidence and associated risk factors in U.S. women and men. Am J Epidemiol. 2013; 178(6):890–897. [PubMed: 23828250]
32. Lopez-Garcia E, van Dam RM, Willett WC, Rimm EB, Manson JE, Stampfer MJ, Rexrode KM, Hu FB. Coffee consumption and coronary heart disease in men and women: a prospective cohort study. Circulation. 2006; 113(17):2045–2053. [PubMed: 16636169]
33. Rota M, Pasquali E, Bellocco R, Bagnardi V, Scotti L, Islami F, Negri E, Boffetta P, Pelucchi C, Corrao G, La Vecchia C. Alcohol drinking and cutaneous melanoma risk: a systematic review and dose-risk meta-analysis. Br J Dermatol. 170(5):1021–1028. [PubMed: 24495200]
34. Freedman DM, Sigurdson A, Doody MM, Rao RS, Linet MS. Risk of melanoma in relation to smoking, alcohol intake, and other factors in a large occupational cohort. Cancer Causes Control. 2003; 14(9):847–857. [PubMed: 14682442]
35. Pothiawala S, Qureshi AA, Li Y, Han J. Obesity and the incidence of skin cancer in US Caucasians. Cancer Causes Control. 2012; 23(5):717–726. [PubMed: 22450736]
36. Huang MT, Xie JG, Wang ZY, Ho CT, Lou YR, Wang CX, Hard GC, Conney AH. 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(13): 2623–2629. [PubMed: 9205068]
37. 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(7):2523–2529. [PubMed: 18381462]
38. Yao SL, Akhtar AJ, McKenna KA, Bedi GC, Sidransky D, Mabry M, Ravi R, Collector MI, Jones RJ, Sharkis SJ, Fuchs EJ, Bedi A. Selective radiosensitization of p53-deficient cells by caffeine-mediated activation of p34cdc2 kinase. Nat Med. 1996; 2(10):1140–1143. [PubMed: 8837615]
39. Russell KJ, Wiens LW, Demers GW, Galloway DA, Plon SE, Groudine M. Abrogation of the G2 checkpoint results in differential radiosensitization of G1 checkpoint-deficient and G1 checkpoint-competent cells. Cancer Res. 1995; 55(8):1639–1642. [PubMed: 7712467]
40. Sarkaria JN, Busby EC, Tibbetts RS, Roos P, Taya Y, Karnitz LM, Abraham RT. Inhibition of ATM and ATR kinase activities by the radiosensitizing agent, caffeine. Cancer Res. 1999; 59(17): 4375–4382. [PubMed: 10485486]
41. Qin JZ, Chaturvedi V, Denning MF, Choubey D, Diaz MO, Nickoloff BJ. Role of NF-kappaB in the apoptotic-resistant phenotype of keratinocytes. J Biol Chem. 1999; 274(53):37957–37964. [PubMed: 10608863]
42. Dhar A, Young MR, Colburn NH. The role of AP-1, NF-kappaB and ROS/NOS in skin carcinogenesis: the JB6 model is predictive. Mol Cell Biochem. 2002; 234–235(1–2):185–193.
43. Ravi D, Muniyappa H, Das KC. Caffeine inhibits UV-mediated NF-kappaB activation in A2058 melanoma cells: an ATM-PKCdelta-p38 MAPK-dependent mechanism. Mol Cell Biochem. 2008; 308(1–2):193–200. [PubMed: 17932622]

Table 1

Baseline Characteristics of Study Participants According to Caffeine Intake in the NHS II (1991–2009), NHS (1980–2008), and HPFS (1986–2008).[a]

	NHS II			NHS			HPFS		
	Q1	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**
Intake range, mg/d[b]	<60	141–246	≥393	<60	141–246	≥393	<60	141–246	≥393
Participants, n	17 750	17 855	17 802	8074	11 557	32 926	11 605	5896	9191
Age, year	35.5(4.8)[c]	35.9(4.7)	37.1(4.4)	46.4(7.5)	45.7(7.5)	46.1(7.0)	53.8(9.9)	53.8(9.8)	52.3(8.9)
Dietary variables									
Alcohol intake, g/d	1.8(4.5)	3.1(5.7)	4.2(7.0)	4.7(9.9)	5.7(10.2)	7.1(11.1)	8.9(14.1)	11.8(15.4)	13.2(16.6)
Caffeinated coffee, servings/d	0.0(0.0)	0.6(0.4)	3.5(1.3)	0.0(0.0)	0.6(0.5)	3.8(1.5)	0.0(0.1)	0.8(0.6)	3.5(1.4)
Decaffeinated coffee, servings/d	0.4(0.9)	0.4(0.8)	0.2(0.7)	0.7(1.2)	0.4(0.9)	0.6(1.2)	0.8(1.3)	0.7(1.1)	0.3(0.9)
Caffeinated tea, servings/d	0.1(0.2)	1.0(1.2)	0.8(1.3)	0.1(0.2)	1.2(1.0)	1.0(1.4)	0.1(0.2)	0.7(0.9)	0.6(1.1)
Decaffeinated tea, servings/d	0.3(0.7)	0.3(0.8)	0.2(0.6)	0.2(0.6)	0.3(0.7)	0.2(0.6)	0.2(0.6)	0.2(0.6)	0.2(0.5)
Caffeinated carbonated beverages, servings/d	0.1(0.2)	0.7(1.0)	0.8(1.0)	0.0(0.1)	0.1(0.2)	0.1(0.2)	0.1(0.1)	0.3(0.4)	0.2(0.4)
Decaffeinated carbonated beverages, servings/d	0.4(0.8)	0.3(0.6)	0.2(0.6)	0.0(0.2)	0.1(0.2)	0.1(0.2)	0.1(0.3)	0.1(0.3)	0.1(0.2)
Caffeine-containing chocolate, servings/d	0.1(0.2)	0.2(0.2)	0.1(0.2)	0.2(0.3)	0.2(0.3)	0.2(0.3)	0.1(0.2)	0.1(0.3)	0.1(0.3)
Total energy intake, kcal	1768(528)	1770(542)	1644(543)	1559(498)	1549(485)	1526(496)	1982(614)	1972(621)	1826(561)
Non-dietary variables									
Family history of melanoma, %	13.4	12.9	11.8	6.8	6.4	6.6	4.5	3.7	3.7
Red/blonde hair, %	20.6	20.0	20.3	15.3	15.8	15.9	13.4	12.4	13.8
Number of moles on legs or arms ≥10, %	16.7	14.6	13.5	2.0	2.1	2.1	2.3	2.8	2.4
Painful/blistering sunburn reaction as a child/adolescent, %	24.5	24.1	24.5	13.9	15.1	15.2	24.7	23.0	23.3
Number of blistering sunburns ≥5, %	9.1	9.7	11.0	58.1	59.4	60.8	18.9	19.3	18.0
Average time spent in direct sunlight since high school ≥5 hrs/wk, %	39.6	42.2	45.5	50.3	52.0	52.8	38.4	35.7	39.9
Annual ultraviolet flux, × 10^{-4} Robertson-Berger unit	124.9(24.0)	125.5(24.4	) 124.1(24.5)	121.1(22.9)	119.3(22.0)	119.8(23.2)	128.7(26.6)	129.7(26.9)	129.2(26.9)
Body mass index, kg/m^2	24.5(5.4)	24.8(5.5)	24.6(4.9)	24.4(4.7)	24.6(4.8)	24.3(4.3)	24.7(4.9)	24.9(5.3)	25.2(5.1)
Current smoking, %	4.6	9.6	27.1	19.1	19.0	38.0	5.7	8.6	16.8
Physical activity, met-hrs/wk	20.9(25.8)	21.0(27.7)	20.7(28.2)	14.4(18.9)	14.0(19.2)	13.5(19.5)	22.6(32.5)	20.3(26.5)	18.7(29.6)
Rotating night shifts, %	57.3	61.6	64.1	9.7	9.6	12.4	-	-	-
Postmenopausal status, %	2.9	3.3	3.5	31.8	31.0	31.7	-	-	-

	NHS II			NHS			HPFS		
	Q1	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**
Postmenopausal hormone use, %[d]	84.5	81.9	84.5	22.4	22.3	18.9	-	-	-

[a] All variables other than age have been standardized to the age distribution of the study population.

[b] Quintile cutoffs based on the NHS II.

[c] Mean (standard deviation) for all such values.

[d] Percentages among postmenopausal women.

Table 2

Hazard Ratios of Incident Melanoma According to Caffeine Intake in the NHS II (1991–2009), NHS (1980–2008), and HPFS (1986–2008).

	Categories of caffeine intake (mg/d)[a]					*P* for Trend	*P* for heterogeneity
	1 (<60)	2 (60–140)	3 (141–246)	4 (247–392)	5 (≥393)		
NHS II							
No. of cases	141	126	142	135	98		
No. of person-years	309 301	308 196	308 808	308 220	309 407		
Age-adjusted HR(95% CI)	1.00	0.87 (0.69–1.11)	0.97 (0.77–1.23)	0.89 (0.71–1.13)	0.66 (0.51–0.85)	0.003	
Multivariate HR (95% CI)[b]	1.00	0.85 (0.67–1.08)	0.93 (0.73–1.18)	0.81 (0.64–1.04)	0.66 (0.51–0.87)	0.004	
NHS							
No. of cases	84	118	187	226	226		
No. of person-years	151 421	226 168	343 546	451 642	585 991		
Age-adjusted HR(95% CI)	1.00	0.87 (0.65–1.14)	0.92 (0.71–1.19)	0.86 (0.67–1.11)	0.75 (0.58–0.97)	0.02	
Multivariate HR (95% CI)[b]	1.00	0.82 (0.62–1.09)	0.85 (0.66–1.11)	0.79 (0.61–1.01)	0.74 (0.57–0.96)	0.04	
HPFS							
No. of cases	191	146	145	152	137		
No. of person-years	163 904	123 280	116 404	119 733	140 670		
Age-adjusted HR(95% CI)	1.00	0.94 (0.76–1.17)	0.97 (0.78–1.20)	1.00 (0.81–1.24)	0.89 (0.71–1.10)	0.41	
Multivariate HR (95% CI)[b]	1.00	0.93 (0.74–1.15)	0.96 (0.77–1.20)	0.99 (0.80–1.24)	0.94 (0.75–1.18)	0.81	
Pooled for women (NHS II and NHS)							
Multivariate HR (95% CI)[b]	1.00	0.84 (0.70–1.01)	0.90 (0.75–1.07)	0.80 (0.67–0.96)	0.70 (0.58–0.85)	0.001	0.31
Pooled for women and men (NHS II, NHS and HPFS)							
Multivariate HR (95% CI)[b]	1.00	0.87 (0.76–1.00)	0.92 (0.80–1.06)	0.87 (0.75–1.01)	0.78 (0.64–0.96)	0.048	0.11

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Quintile cutoffs based on the NHS II.

[b] Multivariate hazard ratios were further adjusted for family history of melanoma (yes or no), personal history of non-skin cancer (yes or no), natural hair color (red, blonde, light brown, dark brown, black), number of moles on legs or arms (none, 1–2, 3–9, ≥10), sunburn reaction as a child/adolescent (none/some redness, burn, painful burn/blisters), number of blistering sunburns (none, 1–2, 3–4, ≥5), time spent in direct sunlight since high school (<1, 1–4, ≥5 hrs/wk), cumulative ultraviolet flux since baseline (quintiles), body mass index (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0 kg/m^2), smoking status (never, past, current with 1–14, 15–24, or ≥25 cigarettes/d), physical activity (quintiles), total energy intake (quintiles), and alcohol intake (none, 0.1–4.9, 5.0–9.9, ≥10.0 g/d). Analyses for women were also adjusted for rotating night shifts (never, 1–2, 3–9, ≥10 years) and menopausal status and postmenopausal hormone use (premenopausal, postmenopausal never, past, or current use).

Table 3

Multivariate Hazard Ratios of Site-Specific Incident Melanoma According to Caffeine Intake in the NHS II (1991–2009), NHS (1980–2008), and HPFS (1986–2008).

	Categories of caffeine intake (mg/d)[a]					*P* for trend	*P* for heterogeneity
	1 (<60)	2 (60–140)	3 (141–246)	4 (247–392)	5 (≥393)		
Risk of overall melanoma on head, neck, and extremities							
NHS II							
No. of cases/person-years	96/309 301	77/308 196	92/308 808	87/308 220	65/309 407		
Multivariate HR (95% CI)[b]	1.00	0.76 (0.56–1.03)	0.88 (0.66–1.18)	0.75 (0.55–1.02)	0.66 (0.47–0.91)	0.02	
NHS							
No. of cases/person-years	62/151 421	88/226 168	123/343 546	153/451 642	149/585 991		
Multivariate HR (95% CI)[b]	1.00	0.83 (0.60–1.15)	0.75 (0.55–1.02)	0.72 (0.53–0.97)	0.67 (0.50–0.91)	0.02	
HPFS							
No. of cases/person-years	110/163	84/123 280	65/116 404	78/119 733	65/140 670		
Multivariate HR (95% CI)[b]	1.00	0.91 (0.68–1.21)	0.74 (0.54–1.02)	0.89 (0.66–1.20)	0.82 (0.59–1.13)	0.29	
Pooled for women (NHS II and NHS)							
Multivariate HR (95% CI)[b]	1.00	0.79 (0.63–0.99)	0.82 (0.66–1.01)	0.73 (0.59–0.91)	0.66 (0.53–0.83)	0.001	0.70
Pooled for women and men (NHS II, NHS and HPFS)							
Multivariate HR (95% CI)[b]	1.00	0.83 (0.70–0.99)	0.79 (0.67–0.95)	0.78 (0.66–0.93)	0.71 (0.59–0.86)	0.001	0.63
Risk of overall melanoma on trunk							
NHS II							
No. of cases/person-years	44/309 301	47/308 196	45/308 808	48/308 220	33/309 407		
Multivariate HR (95% CI)[b]	1.00	1.02 (0.67–1.54)	0.95 (0.62–1.45)	0.97 (0.63–1.48)	0.70 (0.43–1.12)	0.13	
NHS							
No. of cases/person-years	19/151 421	26/226 168	61/343 546	68/451 642	66/585 991		
Multivariate HR (95% CI)[b]	1.00	0.77 (0.43–1.40)	1.22 (0.73–2.05)	1.03 (0.61–1.72)	0.94 (0.55–1.58)	0.82	
HPFS							
No. of cases/person-years	72/163 904	48/123 280	65/116 404	61/119 733	61/140 670		
Multivariate HR (95% CI)[b]	1.00	0.84 (0.58–1.21)	1.17 (0.83–1.65)	1.06 (0.74–1.51)	1.03 (0.72–1.47)	0.61	
Pooled for women (NHS II and NHS)							

	Categories of caffeine intake (mg/d)[a]					*P* for trend	*P* for heterogeneity
	1 (<60)	**2 (60–140)**	**3 (141–246)**	**4 (247–392)**	**5 (≥393)**		
Multivariate HR (95% CI)[b]	1.00	0.93 (0.66–1.31)	1.05 (0.76–1.46)	0.99 (0.71–1.38)	0.80 (0.56–1.13)	0.25	0.33
Pooled for women and men (NHS II, NHS and HPFS)							
Multivariate HR (95% CI)[b]	1.00	0.88 (0.69–1.14)	1.11 (0.87–1.40)	1.02 (0.80–1.30)	0.90 (0.70–1.16)	0.60	0.32

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Quintile cutoffs based on the NHS II.

[b] Multivariate HRs were adjusted for the covariates listed in Table 2 footnote.

Table 4

Hazard Ratios of Incident Melanoma According to Caffeinated and Decaffeinated Coffee Consumption in the NHS II (1991–2009), NHS (1980–2008), and HPFS (1986–2008).

	Serving category				*P* for trend	*P* for heterogeneity
	Never	<1 cup/d	1–2/d	>2/d		
Caffeinated coffee						
NHS II						
No. of cases/person-years	215/480 408	122/298 989	141/317 098	164/446 995		
Age-adjusted HR(95% CI)	1.00	0.87 (0.69–1.08)	0.91 (0.73–1.13)	0.78 (0.63–0.95)	0.04	
Multivariate HR (95% CI)[a]	1.00	0.81 (0.65–1.02)	0.81 (0.65–1.01)	0.72 (0.58–0.89)	0.007	
Multivariate HR (95% CI)[b]	1.00	0.80 (0.63–1.03)	0.79 (0.62–1.01)	0.70 (0.55–0.89)	0.008	
NHS						
No. of cases/person-years	132/285 692	163/284 570	218/402 071	328/786 435		
Age-adjusted HR(95% CI)	1.00	1.05 (0.83–1.33)	1.00 (0.80–1.24)	0.87 (0.71–1.07)	0.07	
Multivariate HR (95% CI)[a]	1.00	0.99 (0.79–1.25)	0.92 (0.73–1.14)	0.84 (0.68–1.03)	0.04	
Multivariate HR (95% CI)[b]	1.00	0.92 (0.72–1.17)	0.86 (0.68–1.08)	0.81 (0.65–1.00)	0.04	
HPFS						
No. of cases/person-years	158/160 151	213/167 908	186/137 937	214/197 995		
Age-adjusted HR(95% CI)	1.00	1.12 (0.91–1.38)	1.13 (0.91–1.40)	1.06 (0.87–1.31)	0.70	
Multivariate HR (95% CI)[a]	1.00	1.10 (0.89–1.35)	1.11 (0.89–1.39)	1.10 (0.89–1.37)	0.47	
Multivariate HR (95% CI)[b]	1.00	1.04 (0.83–1.30)	1.06 (0.84–1.33)	1.07 (0.86–1.34)	0.55	
Pooled for women (NHS II and NHS)						
Multivariate HR (95% CI)[b]	1.00	0.86 (0.72–1.02)	0.83 (0.70–0.98)	0.76 (0.64–0.89)	0.001	0.49
Pooled for women and men (NHS II, NHS and HPFS)						
Multivariate HR (95% CI)[b]	1.00	0.92 (0.80–1.07)	0.90 (0.76–1.07)	0.85 (0.66–1.08)	0.18	0.04
Decaffeinated coffee						
NHS II						
No. of cases/person-years	345/856 121	209/491 087	65/135 975	23/60 308		
Age-adjusted HR(95% CI)	1.00	0.98 (0.83–1.17)	1.08 (0.83–1.41)	0.93 (0.61–1.43)	0.86	
Multivariate HR (95% CI)[a]	1.00	0.88 (0.74–1.05)	0.99 (0.75–1.29)	0.88 (0.58–1.35)	0.59	

	Serving category				*P* for trend	*P* for heterogeneity
	Never	**<1 cup/d**	**1–2/d**	**>2/d**		
Multivariate HR (95% CI)[b]	1.00	0.96 (0.79–1.17)	1.07 (0.80–1.42)	0.93 (0.60–1.44)	0.91	
NHS						
No. of cases/person-years	212/477 068	308/482 160	148/240 643	71/141 564		
Age-adjusted HR(95% CI)	1.00	1.25 (1.04–1.51)	1.19 (0.96–1.49)	1.06 (0.80–1.42)	0.55	
Multivariate HR (95% CI)[a]	1.00	1.17 (0.97–1.41)	1.12 (0.89–1.39)	1.01 (0.75–1.34)	0.91	
Multivariate HR (95% CI)[b]	1.00	1.15 (0.94–1.39)	1.07 (0.84–1.36)	0.98 (0.72–1.32)	0.76	
HPFS						
No. of cases/person-years	256/263 401	321/239 648	137/94 152	57/66 791		
Age-adjusted HR(95% CI)	1.00	1.19 (1.01–1.41)	1.24 (1.00–1.53)	0.89 (0.67–1.19)	0.79	
Multivariate HR (95% CI)[a]	1.00	1.13 (0.95–1.33)	1.16 (0.94–1.44)	0.92 (0.69–1.23)	0.86	
Multivariate HR (95% CI)[b]	1.00	1.10 (0.92–1.32)	1.14 (0.91–1.42)	0.92 (0.68–1.24)	0.98	
Pooled for women (NHS II and NHS)						
Multivariate HR (95% CI)[b]	1.00	1.05 (0.88–1.25)	1.07 (0.89–1.29)	0.96 (0.75–1.23)	0.86	0.77
Pooled for women and men (NHS II, NHS and HPFS)						
Multivariate HR (95% CI)[b]	1.00	1.07 (0.96–1.20)	1.10 (0.95–1.26)	0.94 (0.78–1.14)	0.91	0.96

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Multivariate hazard ratios were adjusted for the covariates listed in Table 2 footnote.

[b]Multivariate hazard ratios were additionally adjusted for consumption of caffeinated tea, decaffeinated tea, caffeinated carbonated beverages, decaffeinated carbonated beverages, caffeine-containing chocolate, and the other coffee (depending on the model) listed in the table.

Table 5

Multivariate Hazard Ratios of Site-Specific Incident Melanoma According to Caffeinated Coffee Consumption in the NHS II (1991–2009), NHS (1980–2008), and HPFS (1986–2008).

	Caffeinated coffee serving category				*P* for trend	*P* for Heterogeneity
	Never	<1 cup/d	1–2 cup/d	>2 cup/d		
Risk of overall melanoma on head, neck, and extremities						
NHS II						
No. of cases/person-years	143/480 408	77/298 989	91/317 098	106/446 995		
Multivariate HR (95% CI)[a]	1.00	0.76 (0.56–1.03)	0.75 (0.55–1.01)	0.68 (0.51–0.91)	0.02	
NHS						
No. of cases/person-years	93/285 692	115/284 570	151/402 071	216/786 435		
Multivariate HR (95% CI)[a]	1.00	0.89 (0.67–1.19)	0.80 (0.61–1.06)	0.72 (0.56–0.93)	0.009	
HPFS						
No. of cases/person-years	93/160 151	109/167 908	95/137 937	105/197 995		
Multivariate HR (95% CI)[a]	1.00	0.86 (0.64–1.17)	0.88 (0.64–1.20)	0.86 (0.63–1.16)	0.48	
Pooled for women (NHS II and NHS)						
Multivariate HR (95% CI)[a]	1.00	0.83 (0.67–1.02)	0.78 (0.63–0.95)	0.70 (0.58–0.85)	<0.001	0.96
Pooled for women and men (NHS II, NHS and HPFS)						
Multivariate HR (95% CI)[a]	1.00	0.84 (0.71–1.00)	0.81 (0.68–0.96)	0.74 (0.63–0.88)	<0.001	0.43
Risk of overall melanoma on trunk						
NHS II						
No. of cases/person-years	69/480 408	43/298 989	47/317 098	58/446 995		
Multivariate HR (95% CI)[a]	1.00	0.89 (0.59–1.36)	0.87 (0.57–1.33)	0.77 (0.51–1.15)	0.23	
NHS						
No. of cases/person-years	32/285 692	44/284 570	67/402 071	97/786 435		
Multivariate HR (95% CI)[a]	1.00	1.05 (0.65–1.69)	1.15 (0.73–1.81)	1.07 (0.70–1.65)	0.71	
HPFS						
No. of cases/person-years	57/160 151	82/167 908	78/137 937	90/197 995		
Multivariate HR (95% CI)[a]	1.00	1.14 (0.79–1.64)	1.26 (0.87–1.82)	1.26 (0.88–1.80)	0.19	
Pooled for women (NHS II and NHS)						

	Caffeinated coffee serving category				*P* for trend	*P* for Heterogeneity
	Never	<1 cup/d	1–2 cup/d	>2 cup/d		
Multivariate HR (95% CI)[a]	1.00	0.96 (0.70–1.31)	0.99 (0.73–1.35)	0.90 (0.65–1.25)	0.62	0.27
Pooled for women and men (NHS II, NHS and HPFS)						
Multivariate HR (95% CI)[a]	1.00	1.03 (0.81–1.31)	1.10 (0.87–1.39)	1.02 (0.76–1.37)	0.80	0.21

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Multivariate hazard ratios were adjusted for the covariates listed in Table 2 footnote and consumption of decaffeinated coffee, caffeinated tea, decaffeinated tea, caffeinated carbonated beverages, decaffeinated carbonated beverages, and caffeine-containing chocolate.