

Daily coffee consumption and prevalence of nonmelanoma skin cancer in Caucasian women

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The purpose of this study was to assess the relationship between daily coffee consumption and nonmelanoma skin cancer. This study was a cross-sectional analysis of women enrolled in the Women's Health Initiative Observational Study ($n=93\ 676$). As nearly all cases of self-reported nonmelanoma skin cancer occurred among Caucasian women (97.8%), we focused our analyses on this group. Compared with nondrinkers, women drinking only caffeinated coffee on a daily basis had a 10.8% lower prevalence of nonmelanoma skin cancer. Consumption of six or more cups of caffeinated coffee per day was associated with a 36% reduction in nonmelanoma skin cancer. After adjusting for various demographic and life style variables, daily consumption of six or more cups was associated with a 30% reduced prevalence of nonmelanoma skin cancer. In contrast to caffeinated coffee, daily consumption of decaffeinated coffee was not associated with a significant change in self-reported nonmelanoma skin cancer for Caucasian women. Daily caffeinated coffee consumption was associated with a

dose-related decreased prevalence of nonmelanoma skin cancer in Caucasian women. *European Journal of Cancer Prevention* 16:446–452 © 2007 Lippincott Williams & Wilkins.

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Introduction

Most epidemiological studies examining associations between coffee drinking and cancer have focused primarily on cancers of the bladder, pancreas, colorectum and breast. While some of these studies have reported an increased association for these cancers among coffee drinkers compared with nondrinkers, results have been inconsistent. The absence of a dose or duration-related association in studies reporting statistically significant associations also precludes concluding that a strong relationship exists between coffee consumption and nonmelanoma skin cancer (NMSC) (e.g. Tavani and LaVecchia, 2000; Michels *et al.*, 2002).

Nonmelanoma skin cancer is one of the most common types of cancer in the United States (Strom and Yamamura, 1997). Lifetime probability of developing this form of cancer in the United States is one in five (Tavani and LaVecchia, 2000). About 1.3 million new cases are diagnosed each year (Tavani and LaVecchia, 2000). While mortality is low (about 0.1%) owing to low metastasis (Von Domarus and Stevens, 1984), morbidity and treatment costs are considerable (Johnson *et al.*, 1984). Although studies in animals have reported

strong evidence that caffeine inhibits skin cancers and other tumors (Wang *et al.*, 1991, 1992, 1994; Huang *et al.*, 1997), we are unaware of epidemiological studies examining the relationship between caffeine and NMSC, with the exception of two small studies that found a decrease in NMSC among coffee drinkers (Jacobsen *et al.*, 1986; Corona *et al.*, 2001).

The current study examined the relationship between caffeinated and decaffeinated coffee consumption and NMSC among more than 90 000 postmenopausal women participating in the Women's Health Initiative (WHI) Observational Study, taking into account confounding factors previously found to be associated with NMSC (Schottenfeld, 1996; Rosenberg *et al.*, 2004).

Methods

Study population

Postmenopausal women, 50–79 years of age, enrolled in the WHI Observational Study between 1993 and 1998, at 40 clinical centers throughout the United States who were either ineligible for the WHI clinical trial or declined to participate in it, were studied. Detailed

eligibility criteria and study methods have been previously described in detail [The Women's Health Initiative (WHI) Study Group, 1998], as well as baseline characteristics of participants (Langer *et al.*, 2003). Briefly, women of diverse ethnic backgrounds, representing the major ethnic groups in the United States, who volunteered to participate, were eligible if postmenopausal at time of enrollment. At time of enrollment, women completed screening and enrollment questionnaires that included questions about demographic and lifestyle variables, coffee consumption and history of skin cancer. The questionnaire categorized coffee and tea consumption each day, as none, one, two to three, four to five, or six or more cups per day. Respondents were also asked whether they consumed caffeinated coffee, decaffeinated coffee, or tea for the past 3 months.

Data analysis

Data analyses were based on information obtained at the baseline visit. Previous history of NMSC was based on self-report. *A priori* variables included in the analyses were those known or suspected as being associated with NMSC (Schottenfeld, 1996; Rosenberg *et al.*, 2004) using the same criteria or cut points as Rosenberg *et al.* (2004). These included age at screening, ethnicity (native American, Asian, Black/African-American, Hispanic, White/Caucasian, other), latitude of the clinic where patients were enrolled (Southern < 35°N, Middle 35–40°N; Northern > 40°N); body mass index (BMI) (< 25 or ≥ 25 kg/m²), history of smoking (current, past, nonsmoker), alcohol use (nondrinker, past drinker, < 7 or ≥ 7 drinks per week), menopausal hormone therapy (current users, past users, defined as those receiving therapy for > 3 months but not receiving therapy at time of interview and nonusers), education (highest grade completed: < 12 years, high school, some college, college degree or postgraduate school), household income (< \$20 000, \$20 000–49 000, > \$50 000), percentage daily calories from fat (< 30.0, 30.0–35.0, 35.1–40.0, > 40.0), physical activity (METs/week) and β-carotene intake (μg); the latter two were categorized into four levels based on the 25th percentile cut-points (0–25, 26–50, 51–75, > 75), having a current healthcare provider and marital status (never married, divorced or separated, presently married). As in the Rosenberg *et al.* (2004) study, we considered women reporting daily energy intakes of < 600 or > 5000 kcal/day as unreliable and excluded them from our analyses. Demographic and lifestyle variables, including daily coffee (regular and decaffeinated) and tea consumption, were evaluated for their association with NMSC by χ^2 tests. Sample size for each analysis differed because of missing data values. Other sources of caffeine intake (e.g. colas) were not included in the regression model because relevant information was not available. Stepwise logistic regression analysis was used to construct a dose–response model for caffeinated

coffee's association with NMSC. In order to avoid the spurious choice of variables in the model as a consequence of the large sample size, we used a criteria of a significant F value to enter and another F value to remove from the analyses of 0.01 and 0.05, respectively. The data were analyzed using the SPSS (version 11.0) statistical package for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 93 676 women of diverse ethnic backgrounds, 16.4% of whom were minority, provided baseline data. Overall prevalence of self-reported NMSC among all women in the study was 8.3% ($n = 7775$). As the majority of women in this study were Caucasian (83.6%), and nearly all cases (97.8%) of self-reported NMSC occurred among these women, and because ethnicity was significantly related to the occurrence of NMSC ($\chi^2 = 1265.3$, d.f. = 5, $P < 0.001$), we focused on this subgroup of 78 013 women. Of these 78 013 women, information with respect to self-reported NMSC was missing for 638 women. A further 467 (0.6%) had missing data with respect to daily coffee drinking. Daily coffee consumption for the remaining 77 373 women is shown in Table 1; 40.1% ($n = 31 048$) of these women only drank caffeinated coffee, 15.0% ($n = 11 597$) only drank decaffeinated coffee, 16.5% ($n = 12 759$) drank both caffeinated and decaffeinated coffee, and 28.4% ($n = 21 969$) reported drinking no coffee.

The relationship between demographic/life style variables and NMSC is shown in Table 2.

Latitude of residence was significantly associated with NMSC; the highest prevalence occurred among women living in the southernmost latitude (12.6%) and the lowest in the northernmost latitude (7.6%). Higher BMI (≥ 25) was also significantly associated with NMSC. The higher the education and income levels, the higher the prevalence of NMSC. Smoking and alcohol consumption were both significantly associated with NMSC. Past or current users of menopausal hormone replacement therapy had a higher prevalence of NMSC than nonusers, but only the differences between past users or current users, and never users were significant ($P < 0.001$ for each). Physical activity was positively associated with the prevalence of NMSC whereas percentage of daily dietary calories from fat was negatively related. Beta-carotene intake was significantly related to NMSC but the association with NMSC was not linear.

The relationship between daily caffeinated coffee consumption and NMSC is shown in Table 3. Drinking caffeinated coffee was associated with a decreased prevalence of self-reported NMSC compared with non-drinkers (9.1 vs. 10.2%, respectively). This association

Table 1 Demographic characteristics of Caucasian women with and without skin cancer^a

Variable	Levels	Noncases (n=69 893)		Cases (n=7482)		χ^2 (d.f.) P
		n	Percentage	n	Percentage	
Age group at screening (years)	50–59	21 907	31.3	1515	20.2	535.5 (2) <0.001
	60–69	30 995	44.3	3413	45.6	
	70–79	16 991	24.3	2554	34.1	
	Missing	0		0		
Education	<12 years	23 49	3.4	168	2.3	177.0 (3) <0.001
	HS/GED	11 736	16.9	946	7.5	
	School after HS	25 467	36.7	2606	35.1	
	College degree or higher	29 828	43.0	3714	50.0	
	Missing	513	0.7	48	0.6	
Income category	<\$20 000	8936	12.8	838	11.2	15.2 (2) <0.001
	\$20 000–49 999	28 535	40.8	3073	41.1	
	\$50 000	27 576	39.5	3026	40.4	
	Missing	4846	6.9	545	7.3	
Body mass index	<25	29 252	41.9	3516	47.0	71.9 (1) <0.001
	>25	39 822	57.0	3889	52.0	
	Missing	819	1.2	77	1.0	
Menopausal hormone therapy	Never used	27 091	38.8	2767	37.0	27.3 (2) <0.001
	Past user	10 435	14.9	1281	17.1	
	Current user	32 317	46.2	3426	45.8	
	Missing	50	0.1	8	0.1	
Region by latitude	Southern <35°N	19 215	27.5	2763	36.9	372.5 (2) <0.001
	Middle 35–40°N	19 600	28.0	2150	28.7	
	Northern >40°N	31 078	44.5	2569	34.3	
	Missing	0		0		
Smoking status	Never	34 318	49.1	3609	48.2	7.5 (2) <0.001
	Past	30 666	43.9	3391	45.3	
	Current	4075	5.8	397	5.3	
	Missing	834	1.2	85	1.1	
Alcohol	Nondrinker	6282	9.0	623	8.3	17.4 (3) <0.001
	Past drinker	11 868	17.0	1214	16.2	
	<7 drinks per week	41 686	59.6	4452	59.5	
	7+ drinks per week	9723	13.9	1158	15.5	
	Missing	334	0.5	35	0.5	
Total calories from fat (%)	<30	31 969	45.7	3560	47.6	22.1 (3) <0.001
	30–35	14 161	20.3	1578	21.1	
	35–40	10 889	15.6	1143	15.3	
	>40	10 776	15.4	1016	13.6	
	Missing	20 78	3.0	187	2.5	
Beta carotene (log μ g as percentiles)	25% (<2296)	17 144	24.5	1590	21.3	68.6 (3) <0.001
	50% (2296–3479)	16 866	24.1	1739	23.2	
	75% (3480–5275)	16 876	24.1	1866	25.2	
	100% (>5275)	16 854	24.1	2085	27.6	
	Missing	21 53	3.1	202	2.7	
Physical activity total METs per week	25% (<3.67)	17 518	25.1	1642	21.9	41.4 (3) <0.001
	50% (3.68–10.5)	18 219	26.1	1970	26.3	
	75% (10.51–20.5)	16 517	23.6	1844	24.6	
	100% (>20.5)	17 034	24.4	1979	26.5	
	Missing	605	0.9	47	0.6	
Current healthcare provider	Yes	66 204	94.7	7154	95.6	15.7 (1) <0.001
	No	3130	4.5	261	3.5	
	Missing	559	0.8	67	0.9	
Marital status	Never married	3110	4.4	336	4.5	7.23 (2) <0.03
	Divorced/separated	21 555	30.8	2417	32.3	
	Presently married	44 959	64.3	4697	62.6	
	Missing	269	0.4	32	0.4	
Daily coffee drinking	None	19 723	28.2	2246	30.0	31.3 (3) <0.001
	Caffeinated only	28 243	40.4	2805	37.5	
	Decaffeinated only	10 372	14.8	1225	16.4	
Daily tea drinking	Both	11 553	16.5	1206	16.4	2.6 (1) NS
	Yes	18 360	26.8	2029	27.1	
	No	50 999	72.4	5392	72.1	
	Missing	534	0.8	61	0.8	

^aChi-squared did not include 'missing' data categories. METs, metabolic equivalent tasks.

was systematically related to the level of consumption. For those drinking six or more cups of caffeinated coffee per day, prevalence decreased from 10.3 to 6.7%, compared with nondrinkers, a 35% decrease in prevalence.

After adjusting for covariates, drinking caffeinated coffee was associated with a dose-related decreased prevalence of self-reported NMSC among Caucasian women in the regression model. A polynomial contrast analysis indicated that the linear trend for the relationship between

Table 2 Demographic/lifestyle variables and risk of nonmelanoma skin cancer

Variable	Category	Crude OR		Unadjusted OR	
		OR	95% CI	OR	95% CI
Age (years)	50–59	–	–	–	–
	60–69	1.05	(1.01–1.10)	1.05	(1.02–1.09)
	70–79	1.45	(1.38–1.52)	1.44	(1.39–1.49)
Alcohol	Nondrinker				
	Past drinker	1.09	(0.94–1.27)	1.03	(0.93–1.14)
	<7 drinks per week	1.24	(1.09–1.42)	1.08	(0.99–1.18)
	>7 drinks per week	1.38	(1.19–1.60)	1.20	(1.08–1.33)
Education	<12 years				
	High school degree	1.31	(1.03–1.65)	1.13	(0.95–1.34)
	After high school	1.59	(1.27–2.00)	1.43	(1.22–1.68)
	College degree	1.90	(1.52–2.39)	1.74	(1.48–2.04)
Hormone replacement therapy status	Never used				
	Past user	1.17	(1.07–1.28)	1.20	(1.12–1.29)
	Current user	1.04	(0.97–1.11)	1.04	(0.99–1.09)
Region	Southern				
	Middle	0.99	(0.95–1.04)	1.00	(0.97–1.04)
	Northern	0.76	(0.73–0.80)	0.76	(0.73–0.78)
Body mass index	<25				
	≥25	0.89	(0.83–0.94)	0.81	(0.77–0.85)
Calories from fat (%)	<30				
	30–35	1.03	(0.94–1.13)	1.00	(0.94–1.06)
	35.1–40	1.05	(0.96–1.15)	0.94	(0.88–1.01)
	>40	1.19	(1.08–1.30)	0.85	(0.79–0.91)

OR, odds ratio; CI, confidence interval.

Table 3 Daily caffeinated coffee drinking and risk of nonmelanoma skin cancer among Caucasian women (77 373)

Cups	<i>n</i>	Percentage	Percentage with skin cancer	Odds ratio ^a	95% Confidence interval	Unadjusted odds ratio ^b
0 ^c	33 568	43.4	10.3	1.0	–	–
1	12 584	16.3	10.2	0.96	(0.89–1.03)	0.99 (0.92–1.05)
2–3	23 133	29.9	9.1	0.87	(0.81–0.92)	0.87 (0.82–0.92)
4–5	6352	8.2	8.1	0.83	(0.75–0.92)	0.76 (0.69–0.84)
6 or more	1738	2.2	6.7	0.70	(0.60–0.88)	0.63 (0.52–0.76)
Total	77 375		9.7			

^aOdds ratio variables included in stepwise regression model: age at screening, alcohol consumption, smoking, income, region of residence by latitude, education, menopausal hormone therapy, body mass index, and β-carotene intake.

^bUnadjusted odds ratio based on cups of regular coffee as the only predictor in the model.

^cDrinks either no coffee or decaffeinated coffee only.

Table 4 Daily intake of decaffeinated coffee and tea and unadjusted odds ratio (OR) of nonmelanoma skin cancer (NMSC) risk

Cups	<i>n</i>	Decaffeinated coffee				Tea					
		Percentage	Percentage NMSC	OR	95% CI	Cups	<i>n</i>	Percentage	Percentage NMSC	OR	95% CI
0	29 777	54.3	9.1	–	–	0	56 391	73.9	9.6	–	–
1	11 537	21.0	10.0	1.12	1.04–1.20	1	9653	12.6	10.1	1.06	0.99–1.14
2–3	10 803	19.7	10.1	1.13	1.05–1.22	2–3	8105	10.6	11.0	1.05	0.97–1.14
4–5	2246	4.1	8.8	0.96	0.83–1.12	4–5	1683	2.2	9.1	0.95	0.80–1.12
>6	483	0.9	9.7	1.08	0.80–1.46	>6	488	0.6	8.2	0.84	0.61–1.17
Total	54 846		9.5			Total	76 320		9.7		

CI, confidence interval.

caffeinated coffee consumption and the risk of NMSC was statistically significant ($P < 0.001$).

As chronic cumulative exposure to solar ultraviolet radiation is the most important factor associated with NMSC (Taylor and Sober, 1996), we also tested for an interaction between cups of caffeinated coffee and latitude, for risk of NMSC. The interaction was not statistically significant.

We also conducted a subgroup analysis of the relationship between coffee consumption and NMSC stratifying for histories of other cancers. The relationship between caffeinated coffee consumption and NMSC was not significant for women with a history of cancer other than NMSC. A significant dose–response relationship, however, was still evident for those women without a history of other cancers. The odds ratio for six or more for the latter cups was 0.70 (confidence interval: 0.56–0.89, $P < 0.001$).

Although statistically significant as a sole factor, consumption of decaffeinated coffee or tea was not significantly associated with NMSC for Caucasian women in the logistic regression (see Table 4).

Discussion

Nonmelanoma skin cancer is the most common type of skin cancer among Caucasians in the United States (Strom and Yamamura, 1997). We focused on caffeinated coffee consumption in this study, because experiments in animals have found that caffeine reduced the occurrence of skin cancers in mice exposed to relatively large amounts of ultraviolet radiation (Wang *et al.*, 1991, 1992, 1994; Huang *et al.*, 1997), and because of corroborative reports from small-scale epidemiological studies that coffee had a small but significant protective association with NMSC in humans (Jacobsen *et al.*, 1986; Corona *et al.*, 2001). Although cola and tea drinks are another source of caffeine intake, the questionnaire did not distinguish between different sodas or teas, which differ in the amounts of caffeine they contain, or assess patterns of soda intake. A recent study also indicated that daily caffeine intake from soft drinks for women 55–64 years old is less than 10% and for women 65 years of age and older, less than 4% (Frary *et al.*, 2005).

Our cross-sectional epidemiological study examined the association between daily coffee consumption and NMSC in a relatively large sample of postmenopausal women, 50 years of age or older, using baseline data at time of initial entry to the WHI Observational Study, and took into account many of the potentially confounding variables previously found to be associated with cancer (Schottenfeld, 1996; Rosenberg *et al.*, 2004). As nearly all the instances of NMSC occurred in Caucasian women, we focused on this group. While basal cell carcinomas are the primary type of NMSCs among Caucasians in the United States (Tavani and LaVecchia, 2000), the other common condition included in this type of skin cancer is cutaneous squamous cell carcinoma (Marks, 1996). Unfortunately, the data available for our study did not include information with respect to the different types of NMSCs. No reason, however, exists to suspect that the women in this study differed from the general population in typology.

As previously reported, we found that residential sunlight exposure was related to the prevalence of NMSC (Webb *et al.*, 1988; Taylor and Sober, 1996; Strom and Yamamura, 1997). Prevalence was highest for women living in the southernmost latitudes and lowest for those in the northernmost latitudes. Greater body weight (BMI > 25 kg/m²) and decreased physical activity, on the other hand, were significantly associated with a reduced prevalence of NMSC. One likely explanation is that women who are overweight and are less active do not

spend as much time outdoors and therefore have less exposure to ultraviolet radiation. We did not, however, find a significant interaction between coffee consumption and latitude on NMSC. Higher income and education were also both related to a higher prevalence of NMSC, possibly because they may be associated with more outdoor leisure activity and vacationing in sunny climates for those individuals. Menopausal hormone therapy was also associated with a higher prevalence of NMSC. Prevalence of NMSC was higher for women with current healthcare providers, suggesting that the overall prevalence of NMSC is underestimated.

Diet and body weight are known to influence the occurrence of cancers (Black, 1998; Riboli, 2001; Kaaks *et al.*, 2002), but we did not find such an association with NMSC. We did, however, corroborate a previous report of the association between increased alcohol consumption and past smoking with a higher prevalence of NMSC (Aubry and MacGibbon, 1985; Grodstein *et al.*, 1995; Veierod *et al.*, 1997; De Hertog *et al.*, 2001). We also found that past smoking was associated with an increased prevalence of NMSC, although current smokers had the lowest rate of NMSC.

Daily consumption of caffeinated coffee was associated with a dose-related decreased prevalence on NMSC of nearly 5% for each cup. Daily consumption of six or more cups of caffeinated coffee was associated with a decreased prevalence of 31%. Daily consumption of decaffeinated coffee or tea, on the other hand, was not related to a significantly altered prevalence of NMSC.

One of the strengths of this study was that it included a relatively large population, enabling us to evaluate daily coffee consumption while controlling for other potentially confounding variables. This, however, was also a cross-sectional study, and therefore the temporal relationship between coffee consumption and NMSC could not be elucidated from these data. It is unlikely, however, that women began drinking coffee only after a diagnosis of NMSC. Several limitations are also associated with this study. One is the potential recruitment bias associated with any volunteer study. It is possible, for instance, that women with cancer or concerned about cancer were over-represented. On the other hand, healthy women, concerned about cancer, may be over-represented.

Recall bias is another concern. Although the current study relied on self-report for a history of NMSC, recent studies suggest that self-reported NMSC has a high degree of accuracy (Ming *et al.*, 2004). Recall bias also has to be considered with respect to the amount of coffee and tea consumption. Assessment error is inherent in questionnaire-based dietary information, so that estimated relationships are not objective. As diet likely changed for

many women in the years prior to assessment, the dietary information recorded at enrollment may not reflect general patterns of diet over the lifespan. Denial and under-reporting also has to be considered in the context of smoking and alcohol use (Abel, 1998). We, however, are not aware of any data suggesting differential under-reporting of either smoking or alcohol use in women with and without NMSC. Information about coffee and tea use may also be problematic as women were asked to recall their levels of daily consumption at the time of enrollment and consumption levels may have not been similar at the time women were diagnosed with skin cancer.

Despite these caveats, the decreased prevalence in NMSC associated with consumption of daily consumption of caffeinated coffee that we observed was dose-related and consistent with other studies. Among the possible explanations for caffeine's protective effect on NMSC that have been suggested is an antioxidant effect (Kuo, 1997; Trevisanato and Kim, 2000) and/or inhibition of DNA synthesis and cell division, making cells less susceptible to carcinogenesis (Timson, 1997).

We conclude that daily caffeinated coffee consumption is associated with a dose-related decreased prevalence of NMSC in Caucasian women. Ideally, the observations reported here and our conclusion should be explored in future prospective studies.

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Appendix

Short list of Women's Health Initiative investigators

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