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Coffee and Tea Intake and Risk of Cutaneous Melanoma

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Coffee and Tea Intake and Risk of Cutaneous Melanoma

A Thesis Presented

by

HAOTIAN WU

Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

MASTERS OF SCIENCE

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Epidemiology

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Approved as to style and content by:

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DEDICATION

To anyone and everyone who contributed to my education

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ABSTRACT

COFFEE AND TEA INTAKE AND THE RISK OF CUTANEOUS MELANOMA

MAY 2013

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Cutaneous melanoma accounts for less than 5% of all skin cancers but over 75% of skin cancer related deaths. Prior biologic research suggests caffeine may arrest cancer cell formation and metastasis in vivo. Additionally, certain tea components exhibit anti-inflammatory, anti-oxidant, and other anti-carcinogenic effects. Prior epidemiologic studies show possible protective effect of both coffee and tea on risk of melanoma, but results remain inconsistent. We examined the association between coffee and tea intake and risk of cutaneous melanoma using the Women's Health Initiative Observational Study. Coffee and tea intake were measured through self-administered questionnaires. Melanomas were self-reported and physician adjudicated. Cox proportional hazards models were used to evaluate associations. Of the 66,484 white post-menopausal women with no prior history of cancer (average follow up=7.8 years), 73% reported daily intake of coffee, 26% reported daily tea intake, and 398 cases of melanoma were adjudicated. Daily coffee intake (HR=0.84 95% CI=0.66-1.08) and daily tea intake (HR=1.00, 95% CI=0.78-1.29) were not significantly associated with increased risk of cutaneous melanoma compared to non-daily intake. No significant trend was observed with increased daily coffee (p-trend=0.22) or tea intake (p-trend=0.28). In conclusion, we

observed insignificant inverse associations between coffee intake and cutaneous melanoma among post-menopausal Caucasian women.

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CHAPTER 1

INTRODUCTION

Cutaneous melanoma is the cancer of skin melanocytes (1). It is the most serious skin cancer and its incidence is rising in the United States (1, 2). The overall rate in the U.S. was 19.77 cases per 100,000 White women from 2005 to 2009. During the same period, incidence of melanoma has increased by 2.3% per year (2-4). Older women are at especially high risk. White women ages 50 and above have rates ranging from 29-49 cases per 100,000 per year from 2005 to 2009, compared to women 24 or younger, who have less than 10 cases per 100,000 per year (4). It is estimated that cutaneous melanoma accounts for over 75% of all skin cancer related deaths (5). Cutaneous melanoma is highly resistant to both chemotherapy and radiation (1). A disproportionately large number of deaths due to cutaneous melanoma will be among older women (4).

Environmental factors such as sunlight exposure and ultraviolet radiation exposure are major risk factors for cutaneous melanomas (1). Thus, depletion of the ozone, increased use of indoor UV tanning beds, and changes in behavior are suspected to contribute to the increasing incidence of melanoma (1). Hereditary risk factors include race/skin color, freckles, eye color, hair color, sunburns, and moles (1, 6). Factors such as photosensitive drugs, cosmetics, and artificial ultraviolet radiation exposure are also linked to cutaneous melanoma (1). With the incidence on the rise, it is important to study modifiable potential risk or protective factors aside from environmental or genetic exposures.

While not well understood, it has been theorized that caffeine and tea components may both influence cutaneous melanoma development and metastasis (7-

14). Caffeine has been found to be anti-carcinogenic in non-cutaneous melanoma and non-melanoma skin cancers in mice and *in vitro* (8-11). Tea components are also found to have various anti-carcinogenic effects in melanocytes *in vitro*, including antioxidant, anti-inflammatory, epigenetic changes, DNA repair, and immune system activation effects (12-14).

In earlier epidemiologic studies, higher coffee consumption was linked to a decreased risk for cutaneous melanoma. However, later results found either null associations or evidence suggesting higher coffee intake was linked to higher risk for cutaneous melanoma (14-19). The only prospective epidemiologic study to examine the relationship between tea intake and melanoma risk found null associations, but case control studies suggested both positive and inverse associations (14, 17-19).

Therefore, our study used data from the Women's Health Initiative – Observational Study (WHI-OS), a prospective cohort of post-menopausal women gathered from 40 clinical centers throughout the US, to assess the impact of tea and coffee on the risk of melanoma.

CHAPTER 2

METHODS

2.1 Study Population

The WHI-OS is a large multi-center, ethnically diverse prospective cohort study. WHI-OS recruited 93,676 women at 40 centers in the United States between October 1st, 1993 and December 1st, 1998 (20). Post-menopausal women aged 50-79 who were ineligible or unwilling to participate in the Women's Health Initiative - Controlled Trial (WHI-CT), had expected survival time greater than 3 years, and were not enrolled in another study, were eligible to participate in the WHI-OS (20). We accessed publicly available data with follow up through September 12, 2005.

Of the original 93,676 participants with available data, participants were excluded if they were not self-reported as white (n=15,660) or reported having had a previous cancer (except non-melanoma skin cancer) (n=11,183). Additionally, 349 participants were excluded if they had no follow up information. No women were missing all exposure variables. Our primary analysis included 66,484 participants who contributed a total of 513,650 person-years of follow up. The average follow up among the 66,484 participants was 7.73 years.

2.2 Data Collection

All covariates were collected with structured self-reported questionnaires, interviews, or physical exams. All covariates were collected at baseline screening visits, except sun exposure variables. Sun exposure variables were collected four years after study entry. Participants reported average daily time spent in the sun (<30 minutes, 30-120 minutes, >120 minutes) during the summer and separately for other seasons during the year, in their childhood, teens, thirties, and their current age. Information on regular

sun screen use and skin reaction to sun exposure after 45-60 minutes were also collected. We conducted sensitivity analyses to examine the effect of sun exposure variables within our study.

Information on coffee and tea intake was collected with baseline observational study questionnaire, year 3 follow up questionnaire, and year 6 follow up questionnaire. Participants were asked “Do you usually drink coffee each day?” on the baseline observational study questionnaire. Participants who answered “yes” indicated the number of cups of coffee per day: None, 1 cup/day, 2-3 cups/day, 4-5 cups/day, or 6 or more cups/day. Similar questions were asked for tea and de-caffeinated coffee. At year 3 follow up, participants were asked “during the past 3 months, how often did you drink these beverages” and were given a list including “regular instant coffee”, “regular espresso or latte”, “other regular drip coffee”, “decaf coffee”, “regular tea”, and “herbal tea”. The participants were given the choices, Never or less than once per month, 1-3/month, 1/week, 2-4/week, 5-6/week, 1/day, 2-3/day, 4-5/day, or 6+ per day. Similar questions were asked at year 6. Subdivisions of coffee beverages reported in years 3 and 6 were combined to form categories to match baseline questionnaire. Similarly, regular and herbal tea information were combined. Primary exposures were defined as total coffee intake, caffeinated coffee intake, decaffeinated coffee intake, and total tea intake. For all exposures, both dichotomous and categorical variables were created. For dichotomous variables, participants were classified as either “less than 1 cup per day” or “1 or more cups per day”. For categorical variables of coffee, participants were classified into “less than 1 cup per day”, “1 cup per day”, “2-3 cups per day”, or “4 or more cups per day”. For categorical variables of tea, participants were classified into “less than 1 cup per day”, “1 cup per day”, or “2 or more cups per day”.

Cutaneous melanoma cases were defined as women who had an adjudicated diagnosis of cutaneous melanoma for the duration of follow up (24). Potential cases

were identified through self-reported annual questionnaires on various medical outcomes including melanoma or at a clinic visit at year 3 of follow up (24). Melanoma diagnoses were locally adjudicated until March 31, 2005. After March 31, 2005, all diagnoses were centrally adjudicated at the Clinical Coordinating Center in Seattle, Washington. A total of 398 cases were included in our primary analyses.

2.3 Statistical Analysis

Baseline characteristics of participants were compared by cups of total coffee, caffeinated coffee, decaffeinated coffee, and tea consumption using chi-squared tests. Cox proportional hazards were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). Potential confounders associated with coffee consumption as well as risk factors for cutaneous melanoma were considered, including: age (50-54, 55-59, 60-69, 70-79), body mass index (<25 kg/m², 25-29.99 kg/m², 30+ kg/m²), alcohol (none, <3 drinks/week, 3-7 drinks/week, 7+ drinks/week), recreational physical activity (none, <60 minutes/day, 60-150 minutes/day, >150 minutes/day), height (quartiles), waist-hip ratio (tertiles), education (high school or less, some college, undergraduate degree, graduate degree), income (<\$20,000, \$20,000-\$49,999, \$50,000-\$99,999, >\$100,000), region of residence (Northeast, South, Midwest, West), hormone use (ever, never), smoke (never, past, current), aspirin use (yes/no), sunscreen use (yes/no), skin reaction to sun (no burn/tan, burn/tan, burn/tan slightly, burn/no tan), childhood sun exposure (<=120 minutes/day, >120 minutes/day), teenage sun exposure (<=120 minutes/day, >120 minutes/day), and thirties sun exposure (<=120 minutes/day, >120 minutes/day). To select for covariates, we used the Hosmer-Lemeshow purposeful selection. Covariates were included in the crude multivariate model if they scored $p < 0.25$ in univariate Cox models.

Starting with variables with the highest p-values from the Wald test, a formal log likelihood ratio test was conducted to determine inclusion of variables in the final model. Those with log-likelihood ratio test p-values <0.05 were included. We conducted sensitivity analyses restricting the study population to those who were concordant in their reporting of coffee and tea intake between baseline and year 3 follow up. For this analysis, follow up started at year 3, participants who developed melanoma, dropped out, or died before year 3 were not included. Further analysis restricting to year 4 and beyond to test for effect of post-hoc collection of sun exposure variables was conducted. For this analysis, follow up started at year 4, and participants who developed melanoma, dropped out, or died before year 4 were excluded. The proportional hazards assumption was tested by dividing follow up time to yearly segments (i.e. year 0-1, year 1-2, year 2-3, etc.). For primary analyses, follow up time accrued from enrollment to date of diagnosis, death, or last date of follow up, whichever one was first. For time-period specific analysis, individuals who developed cutaneous melanoma, dropped out, or died prior to start of time period were excluded from analysis.

Two-sided p-values <0.05 were considered statistically significant. All analyses were performed using Stata 12.0 (College Station, Tx) and SAS 9.3 (Cary, NC).

CHAPER 3

RESULTS

After excluding women who were not Caucasian and those who had history of prior cancer(s) (except non-melanoma skin cancers), 66,484 women and 513,650 person-years were available for primary analyses. The average age of the population was 63.6 years old at baseline and average follow up was 7.7 years. A total of 398 cases of cutaneous melanoma were reported, of which 292 occurred in women without a history of non-melanoma skin cancer.

Table 1 shows the consumption of coffee at baseline. 73.23% women reported taking at least one cup of coffee per day, 26.71% reported less than one cup of coffee per day, and 0.06% were missing coffee intake information. Of the 73.23% with at least 1 cup per day, 13.95% reported exactly 1 cup per day, 33.85% reported 2-3 cups per day, and 23.65% reported 4 or more cups per day. The women then further indicated the amount of caffeinated and de-caffeinated coffee consumption. 41.92% women reported less than 1 cup of caffeinated coffee per day, 16.88% reported exactly 1 cup per day, 30.53% reported 2-3 cups per day, and 10.67% reported 4 or more cups per day. 65.08% reported less than 1 cup of decaffeinated coffee per day, 14.88% reported exactly 1 cup per day, 13.97% reported 2-3 cups per day, and 3.55% reported 4 or more cups per day. For overall tea intake, 73.11% reported less than 1 cup per day, 12.36% reported exactly 1 cup, and 13.14% reported 2 or more cups per day.

There were significant differences in distribution of covariates among the coffee exposure groups (Table 2). Those who drank coffee were less likely to be obese ($p<0.001$) and have lower waist-hip ratio ($p<0.001$), though there were no clear differences in exercise. Not surprisingly, those who drank coffee were more likely to drink more alcohol ($p<0.001$), take aspirin ($p<0.001$), and be either past or current

smokers ($p < 0.001$). Women who drank coffee were also slightly more likely to report spending more than 2 hours per day outside during the summer in their thirties ($p < 0.001$), though no clear differences were observed in other sun exposure covariates (sunscreen use, skin reaction to sun, time spent outside during other periods). There were some small differences in distribution of region of residence, as high coffee consumers were less likely to live in the West. Most of the other significant differences in covariates were small and do not follow any patterns (Table 2). Distribution of covariates among tea exposure groups was similar compared to coffee (Appendix A). Table 3 shows the age adjusted hazard ratios of covariates.

Table 4 shows age and multivariate adjusted hazard ratios. Drinking 1 or more cups of coffee per day showed an insignificant 16% lower risk compared to those who drank less than 1 cup of coffee per day (HR=0.84 95% CI=0.66-1.08). There was no dose response observed for overall coffee intake. Those who reported exactly 1 cup of total coffee, 2-3 cups, and 4 or more cups showed 11%, 15%, and 17% decrease in risk of cutaneous melanoma (p-trend=0.22). Daily intake of caffeinated (HR=0.94 95% CI=0.75-1.18) and decaffeinated coffee (HR=0.86 95% CI=0.68-1.09) also showed insignificant decreases in risk of cutaneous melanoma. There were no consistent trends for either caffeinated (p-trend=0.92) or de-caffeinated coffee (p-trend=0.34) intake. Daily tea intake was not associated with risk of cutaneous melanoma (HR=1.00 95% CI=0.78-1.29). There was also no trend observed for tea intake (p-trend=0.28).

Assessment of sunlight exposure and risk of cutaneous melanoma is shown on Table 5. Follow up was restricted to year 4 and beyond and the effects of sunlight variables were tested against the age adjusted model. Coffee and tea intake were updated with year 3 follow up. The inclusion of sun exposure covariates did not appreciably change any hazard ratio estimates between coffee and tea intake and risk of melanoma. The hazard estimate for daily coffee and risk of melanoma remained at 0.73

when region, sunscreen use, skin reaction to sun exposure, and average summer time outdoors in the thirties and last year were added to the model.

Table 6 assessed the hazard ratios for daily coffee intake over time. Follow-up time was divided into yearly segments, with maximum follow-up of 1 year in any given segment, except for year 7 and beyond. Participants were excluded if they had dropped out, died, or had melanoma diagnosis prior to start of segment. Exposure levels during each segment were updated with the most up to date information. For example, people would be included in analysis for time period 3-4 if they had available intake data from year 3 follow up and did not drop out or have event prior to year 3. Hazard ratio estimates changed considerably over time. Higher coffee intake increased risk of melanoma years 1 and 3 of follow up then showed a decreased risk in all other segments.

Table 7 shows results when restricting to only those who were concordant in their reporting of coffee and tea intake between baseline and year 3. When restricted to after year 4, those who reported at least one cup of coffee per day at both baseline and year 3 show a significant 44% decrease in risk of melanoma compared to those who reported less than one cup of coffee per day in both (HR=0.66, 95% CI=0.46-0.96). No downward trend in risk was observed ($p=0.11$) with increased coffee intake. Concordant intake of caffeinated (HR=0.72 95% CI=0.51-1.03) and decaffeinated coffee (HR=0.79 95% CI=0.50-1.24) showed insignificant decreases in risk of cutaneous melanoma. There were also no downward trends in risk observed for either caffeinated (p -trend=0.28) or decaffeinated coffee (p -trend=0.15). Concordant daily tea drinking was not associated with the risk of melanoma (HR=1.05 95% CI=0.66-1.67).

CHAPTER 4

DISCUSSION

In our study of 66,484 post-menopausal women, no evidence of a significant protective effect by either coffee or tea intake with respect to risk of cutaneous melanoma was found. Additionally, no dose-response or threshold was observed for all exposure types and categories.

Two recent prospective cohorts have found similar insignificant relationships between coffee and tea intake and risk of cutaneous melanoma, though they were suggestive of positive relationships (6, 14). Both studies had similar participant demographics compared to the WHI-OS. An 8 year prospective study of post-menopausal women in Iowa by Zheng and colleagues showed an insignificant 11% increase in risk of cutaneous melanoma among high tea consumers (14). Song and colleagues reported a non-significant 31% increase in risk among those in the highest quartile of caffeine consumption (604 mg/day) compared to lowest quartile (31mg/day) in the Nurses' Health Study (6). Case-control study results showed a wide range of results, ranging from strongly protective to positive relationships (17-19). Briefly, Österlind found decreased risk for high coffee consumers and increased risk for high tea consumers in Norwegians (18). Naldi found insignificant decreases in risk for both high coffee and high tea consumers in Italians (17). Fortes found an insignificant decrease in risk for high coffee consumers but a significant decrease in risk for high tea consumers in Italians (19).

Discrepancy in results may be due to several differences. Song and colleagues used caffeine as exposure of interest, which includes not only coffee and tea, but also sodas and increasingly popular energy drinks (6). They were also able to examine a wider range of exposures with the lowest quartile having minimal average caffeine intake

(31 mg/day). It is possible that the threshold for a positive relationship between coffee and tea intake exists at a lower level than we can detect, as our lowest exposure group may still have a high amount of average caffeine intake. The Norwegian cohort and case-control study had very limited amount of melanoma cases and were not able to fully adjust for potential covariates. The Italian case-control studies both used hospital based populations of all ages and both gender. Therefore, they may not be able to generalize to our population of post-menopausal women.

Our studies had several strengths. We had a large prospective cohort of women with a fairly long follow up, totaling over 500,000 person-years under analysis. As a result, we also had a large number of physician adjudicated incident cutaneous melanoma cases. Loss to follow up was minimal, reducing the likelihood of selection bias. We were able to examine the effects of caffeinated and decaffeinated coffee consumption and control for wide range of potential covariates. Study participants were fairly homogenous, with very little differences between groups for most covariates.

There are also several limitations to our study. Coffee and tea intake data were self-reported and not collected consistently with the same questions. Differences in wording may have led to differential reporting of coffee and tea intake. As noted earlier, we could not distinguish between the true non-drinkers and low drinkers. There could be a difference between those who never drink coffee or tea and those who are not daily drinkers. Many potential covariates were adjusted for, but certain information such as family history, history of skin related conditions such as moles, and skin and eye colors was unavailable. Sun exposure data was available, however, it was not collected at baseline, but only at year 4 of follow up. While they demonstrated very little effect on overall hazard ratio estimates, these important covariates may have been potentially biased by recall. Surveillance bias may have been present. There were no significant overall effects but the hazard ratios were suggestive of a positive relationship before

sharply dropping to an inverse relationship. Such non-linear relationships are not expected given the duration of coffee intake among a cohort of older women. It is possible that some cases were diagnosed earlier in women with certain unhealthy lifestyle habits, which includes excessive coffee consumption.

CHAPTER 5

CONCLUSION

In conclusion, we are able to provide further evidence for the elucidation of the true relationship between coffee, tea, and cutaneous melanoma. Coffee and tea intake were not significantly associated with risk of cutaneous melanoma among post-menopausal Caucasian women. However, it is still important to continue to study potential modifiable risk factors of cutaneous melanoma.

Table 1. Frequency of reported coffee and tea intake at baseline

	Number	%
Total Coffee per Day (Cups)		
<1	17505	26.3
1	9275	14.0
2-3	22508	33.9
4+	15724	23.7
<i>Missing</i>	1472	2.2
Caffeinated Coffee per Day (Cups)		
<1	27761	41.9
1	11180	16.9
2-3	20223	30.5
4+	7065	10.7
<i>Missing</i>	255	0.4
Decaf Coffee per Day (Cups)		
<1	43268	65.1
1	9892	14.9
2-3	9291	14.0
4+	2358	3.6
<i>Missing</i>	1675	2.5
Tea per Day (Cups)		
<1	48609	73.1
1	8219	12.4
2+	8741	13.1
<i>Missing</i>	915	1.4

Table 2. Distribution of covariates according to coffee consumption

	<1 cup/day		1 cup/day		2-3 cups/day		4+ cups/day		P	
	N	(%)	N	(%)	N	(%)	N	(%)		
Age										
50-54	2684	15.3	961	10.4	2679	11.9	2063	13.1	<0.001	
55-59	3463	19.8	1587	17.1	4025	17.9	3026	19.2		
60-69	7369	42.1	4073	43.9	10225	45.4	7340	46.7		
70-79	3989	22.8	2654	28.6	5579	24.8	3295	21.0		
Education										
high school or less	3065	17.7	1908	20.7	4631	20.7	3115	19.9	<0.001	
some college	6083	35.0	3360	36.5	8297	37.1	5719	36.6		
bachelors	4493	25.9	2308	25.1	5370	24.0	3752	24.0		
graduate degree	3721	21.4	1630	17.7	4062	18.2	3033	19.4		
Income										
<\$20000	2181	13.4	1108	12.9	2756	13.1	1824	12.4	0.001	
\$20000-49999	6891	42.4	3869	45.1	9226	44.0	6438	43.9		
\$50000-99999	5124	31.6	2605	30.3	6436	30.7	4693	32.0		
>\$100000	2045	12.6	1007	11.7	2549	12.2	1722	11.7		
BMI (kg/m²)										
<25	7660	44.2	4007	43.7	9447	42.4	6601	42.4	<0.001	
25-29.99	5388	31.1	3115	34.0	7843	35.2	5558	35.7		
30+	4267	24.6	2045	22.3	4991	22.4	3408	21.9		
WHR										
<0.75	4455	25.6	2162	23.5	5561	24.8	4292	27.5	<0.001	
0.75-0.85	8724	50.1	4690	50.9	11429	51.1	7981	51.1		
>0.85	4224	24.3	2369	25.7	5397	24.1	3359	21.5		
Height										
<158 (Q1)	4473	25.8	2654	28.9	5812	26.0	3708	23.8	<0.001	
158-162.1 (Q2)	4137	23.8	2251	24.5	5578	25.0	3835	24.6		
162.2-166.3 (Q3)	4381	25.2	2244	24.4	5555	24.9	3967	25.4		
>166.3 (Q4)	4377	25.2	2039	22.2	5396	24.2	4104	26.3		
Alcohol										
Non-Drinkers	8700	49.8	3522	38.0	6906	30.7	5017	31.9	<0.001	
<3 per week	5891	33.7	3355	36.2	8252	36.7	5760	36.7		
3-7 per week	1457	8.3	1152	12.4	3418	15.2	2336	14.9		
>7 per week	1437	8.2	1236	13.3	3911	17.4	2594	16.5		
Exercise per week										
None	2501	14.4	1356	14.7	3051	13.6	2137	13.6	0.003	
<60 minutes	2188	12.6	1201	13.0	2746	12.3	2031	13.0		
60-150 minutes	3919	22.5	2169	23.5	5331	23.8	3657	23.4		
>150 minutes	8823	50.6	4512	48.8	11280	50.3	7840	50.1		
Region										
Northeast	3968	22.7	2576	27.8	5927	26.3	3870	24.6	<0.001	
South	3953	22.6	2414	26.0	5527	24.6	3401	21.6		
Midwest	4191	23.9	1775	19.1	5005	22.2	4312	27.4		
West	5393	30.8	2510	27.1	6049	26.9	4141	26.3		
Hormone Use										
Never	4499	26.1	2431	26.6	6041	27.3	4553	29.5	<0.001	

	<i>Ever</i>	12720	73.9	6704	73.4	16101	72.7	10887	70.5	
Smoke	<i>Never</i>	10540	60.8	5011	54.8	10256	46.2	6245	40.2	<0.001
	<i>Past</i>	6280	36.2	3833	41.9	10637	47.9	7681	49.5	
	<i>Current</i>	507	2.9	308	3.4	1321	6.0	1600	10.3	
Any NSAID use	<i>No</i>	10240	58.5	5268	56.8	12610	56.0	8678	55.2	<0.001
	<i>Yes</i>	7265	41.5	4007	43.2	9897	44.0	7046	44.8	
Aspirin	<i>No</i>	13806	78.9	7198	77.6	17373	77.2	12071	76.8	<0.001
	<i>Yes</i>	3699	21.1	2077	22.4	5134	22.8	3653	23.2	
Sunscreen Use	<i>No</i>	7388	47.3	3890	47.0	9127	45.4	6644	47.2	0.001
	<i>Yes</i>	8236	52.7	4380	53.0	10958	54.6	7419	52.8	
Skin Reaction	<i>no burn/tan</i>	5431	35.1	3065	37.4	7188	36.0	5128	36.5	<0.001
	<i>burn/tan</i>	3906	25.2	2046	24.9	5179	25.9	3594	25.6	
	<i>burn/tan slightly</i>	4226	27.3	2192	26.7	5425	27.2	3777	26.9	
	<i>burn/no tan</i>	1920	12.4	902	11.0	2184	10.9	1565	11.1	
Summer/day during childhood	<i><=120 minutes</i>	4503	28.5	2456	29.4	5721	28.2	4010	28.2	0.201
	<i>>120 minutes</i>	11279	71.5	5901	70.6	14554	71.8	10208	71.8	
Summer/day during Teens	<i><=120 minutes</i>	6502	41.2	3364	40.3	7852	38.8	5497	38.7	<0.001
	<i>>120 minutes</i>	9264	58.8	4980	59.7	12408	61.2	8700	61.3	
Summer/day during thirties	<i><=120 minutes</i>	10931	69.3	5707	68.3	13681	67.4	9566	67.3	<0.001
	<i>>120 minutes</i>	4845	30.7	2644	31.7	6604	32.6	4644	32.7	
Other season/day during childhood	<i><=120 minutes</i>	9966	63.4	5203	62.6	12800	63.4	8934	63.2	0.611
	<i>>120 minutes</i>	5748	36.6	3109	37.4	7404	36.7	5197	36.8	
Other season/day during teens	<i><=120 minutes</i>	11053	70.3	5747	69.1	14077	69.7	9859	69.7	0.255
	<i>>120 minutes</i>	4662	29.7	2568	30.9	6113	30.3	4280	30.3	
Other season/day during thirties	<i><=120 minutes</i>	13144	83.5	6882	82.7	16743	82.9	11733	82.9	0.310
	<i>>120 minutes</i>	2601	16.5	1442	17.3	3465	17.2	2419	17.1	

Table 3. Age adjusted HRs for covariates and risk of melanoma

	Cases	HR	95% CI	p-value
Age				
50-54	51	1	Ref	
55-59	74	1.03	0.72-1.47	0.87
60-69	187	1.14	0.83-1.47	0.42
70-79	86	1.00	0.71-1.42	0.99
Education				
<i>high school or less</i>	42	1	Ref	
<i>some college</i>	124	1.59	1.12-2.26	0.01
<i>bachelors</i>	120	2.27	1.59-3.22	<0.01
<i>graduate degree</i>	106	2.56	1.78-3.66	<0.01
Income				
<20000	24	1	Ref	
20000-49999	135	1.72	1.11-2.66	0.01
50000-99999	149	2.82	1.82-4.37	<0.01
>100000	68	3.43	2.13-5.53	<0.01
BMI				
<25	187	1	Ref	
25-29.99	133	0.91	0.73-1.14	0.40
30+	68	0.70	0.53-0.93	0.01
WHR				
<0.75	122	1	Ref	
0.75-1.00	194	0.80	0.64-1.01	0.06
>1.00	81	0.73	0.55-0.98	0.03
Height				
<158 (Q1)	79	1	Ref	
158-162.1 (Q2)	95	1.27	0.94-1.71	0.12
162.2-166.3 (Q3)	98	1.28	0.95-1.73	0.10
>166.3 (Q4)	118	0.58	1.18-2.12	<0.01
Alcohol				
<i>Non-Drinkers</i>	96	1	Ref	
<3 per week	152	1.62	1.27-2.10	<0.01
3-7 per week	57	1.68	1.21-2.33	<0.01
>7 per week	93	2.53	1.90-3.36	<0.01
Exercise per week				
None	44	1	Ref	
<60 minutes	45	1.11	0.73-1.68	0.62
60-150 minutes	85	1.13	0.78-1.62	0.52
>150 minutes	222	1.36	0.98-1.88	0.06
Region				
<i>Northeast</i>	135	1	Ref	
<i>South</i>	81	0.64	0.49-0.85	<0.01
<i>Midwest</i>	71	0.58	0.43-0.77	<0.01
<i>West</i>	111	0.75	0.58-0.96	0.02
Hormone Use				
<i>Never</i>	101	1	Ref	
<i>Ever</i>	291	1.08	0.86-1.35	0.52
Smoke				

	<i>Never</i>	183	1	Ref	
	<i>Past</i>	194	1.20	0.98-1.47	0.08
	<i>Current</i>	11	0.53	0.29-0.98	0.04
Any NSAID use					
	<i>No</i>	237	1	Ref	
	<i>Yes</i>	161	0.90	0.74-1.10	0.31
Aspirin					
	<i>No</i>	323	1	Ref	
	<i>Yes</i>	75	0.82	0.64-1.06	0.12
Sunscreen Use					
	<i>No</i>	93	1	Ref	
	<i>Yes</i>	273	2.56	2.03-3.25	<0.01
Skin Reaction					
	<i>no burn/tan</i>	84	1	Ref	
	<i>burn/tan</i>	89	1.52	1.12-2.05	0.01
	<i>burn/tan slightly</i>	132	2.12	1.61-2.79	<0.01
	<i>burn/no tan</i>	60	2.28	1.64-3.18	<0.01
Summer/day during childhood					
	<i><=120 minutes</i>	93	1	Ref	
	<i>>120 minutes</i>	279	1.20	0.95-1.52	0.13
Summer/day during teens					
	<i><=120 minutes</i>	133	1	Ref	
	<i>>120 minutes</i>	236	1.17	0.95-1.45	0.14
Summer/day during thirties					
	<i><=120 minutes</i>	216	1	Ref	
	<i>>120 minutes</i>	154	1.53	1.24-1.88	<0.01
Other season/day during childhood					
	<i><=120 minutes</i>	223	1	Ref	
	<i>>120 minutes</i>	147	1.14	0.93-1.40	0.22
Other season/day during teens					
	<i><=120 minutes</i>	2523	1	Ref	
	<i>>120 minutes</i>	116	1.07	0.86-1.33	0.54
Other season/day during thirties					
	<i><=120 minutes</i>	301	1	Ref	
	<i>>120 minutes</i>	69	1.13	0.87-1.46	0.38

Table 4. Adjusted hazards ratios for coffee and tea intake and risk of melanoma

	Age Adjusted					Multivariate Model 1*					Multivariate Model 2†				
	N ^a	Person Years	HR	CI	p	N	Person Years	HR	CI	p	N	Person Years	HR	CI	p
Coffee															
No	105	136846	1	Ref		98	123313	1	Ref		91	109153	1	Ref	
Yes	293	376523	1.01	0.81-1.27	0.91	257	340249	0.89	0.70-1.13	0.34	226	302067	0.84	0.66-1.08	0.18
Coffee (cups)															
<1	102	134955	1	Ref		95	121678	1	Ref		89	107767	1	Ref	
1	54	70871	1.01	0.73-1.41	0.95	47	63521	0.89	0.63-1.26	0.50	44	56200	0.89	0.62-1.28	0.53
2-3	137	173975	1.04	0.81-1.35	0.75	121	157465	0.91	0.69-1.20	0.50	107	139601	0.85	0.64-1.14	0.27
4+	94	122737	1.01	0.77-1.34	0.93	83	111243	0.91	0.67-1.23	0.52	71	99469	0.83	0.60-1.14	0.25
					0.86					0.54					0.22
Regular															
No	164	214256	1	Ref		147	192888	1	Ref		135	171260	1	Ref	
Yes	234	297487	1.03	0.84-1.25	0.79	208	269253	0.98	0.79-1.22	0.88	182	238751	0.94	0.75-1.18	0.60
Regular (cups)															
<1	164	214256	1	Ref		147	192888	1	Ref		135	171260	1	Ref	
1	62	85966	0.94	0.70-1.26	0.69	55	77627	0.87	0.64-1.19	0.39	51	68580	0.87	0.63-1.20	0.40
2-3	129	156568	1.08	0.85-1.36	0.53	116	141887	1.03	0.80-1.32	0.83	100	126167	0.96	0.74-1.26	0.79
4+	43	54954	1.02	0.73-1.43	0.89	37	49740	1.05	0.73-1.51	0.80	31	44004	1.01	0.68-1.50	0.97
					0.62					0.74					0.91
Decaf															
No	252	333588	1	Ref		229	301434	1	Ref		209	267137	1	Ref	
Yes	133	167472	1.05	0.85-1.30	0.64	115	15183	0.93	0.74-1.16	0.52	101	134847	0.86	0.68-1.09	0.22
Decaf (cups)															
<1	252	333588	1	Ref		229	301434	1	Ref		209	267137	1	Ref	
1	57	76832	0.98	0.74-1.31	0.90	48	69209	0.84	0.62-1.15	0.28	43	61632	0.78	0.56-1.09	0.15
2-3	67	72175	1.23	0.94-1.61	0.13	59	65425	1.09	0.82-1.46	0.55	50	58362	0.99	0.72-1.34	0.93
4+	9	18465	0.65	0.33-1.25	0.20	8	16548	0.63	0.31-1.27	0.20	8	14853	0.69	0.34-1.39	0.30
					0.75					0.62					0.34
Tea (cups)															
No	286	375840	1	Ref		257	339406	1	Ref		228	301659	1	Ref	
Yes	108	134044	1.06	0.85-1.32	0.61	95	121002	1.01	0.80-1.28	0.92	87	106931	1.00	0.78-1.29	0.99
Tea															
<1	286	375840	1	Ref		257	339406	1	Ref		228	301659	1	Ref	
1	40	63372	0.83	0.60-1.15	0.27	35	57340	0.76	0.53-1.09	0.13	30	50788	0.72	0.49-1.05	0.09
2+	64	67591	1.24	0.95-1.63	0.11	57	60923	1.24	0.93-1.66	0.14	54	53739	1.31	0.97-1.77	0.08
					0.28					0.39					0.28

a – Number of melanoma diagnoses in each group

* - Adjusted for age, height, waist-hip ratio, education, income, alcohol, smoke, region, aspirin, and history of non-melanoma skin cancer

† - Adjusted for age, height, education, income, alcohol, smoke, region, aspirin, history of non-melanoma skin cancer, sunscreen use, skin reaction, summer sun exposure in thirties

Table 5. Adjusted hazard ratios of coffee and tea intake and risk of melanoma starting from year 4

		Age Adjusted - 4+ year				Age and Sun Adjusted*			
		N ^a	HR	CI	p	N ^a	HR	CI	P
Coffee									
	No	75	1	Ref		70	1	Ref	
	Yes	118	0.73	0.55-0.98	0.04	112	0.73	0.54-0.98	0.04
Coffee (cups)									
	<1	75	1	Ref		70	1	Ref	
	1	30	0.74	0.48-1.13	0.16	30	0.77	0.50-1.19	0.24
	2-3	63	0.76	0.54-1.06	0.11	60	0.75	0.53-1.06	0.1
	4+	25	0.67	0.54-1.03	0.08	22	0.62	0.39-1.01	0.05
					0.05				0.03
Regular									
	No	110	1	Ref		103	1	Ref	
	Yes	84	0.77	0.58-1.02	0.07	80	0.78	0.58-1.04	0.10
Regular (cups)									
	<1	110	1	Ref		103	1	Ref	
	1	25	0.75	0.49-1.17	0.21	25	0.80	0.52-1.24	0.31
	2-3	46	0.81	0.57-1.14	0.23	43	0.80	0.56-1.14	0.21
	4+	13	0.68	0.38-1.21	0.19	12	0.69	0.38-1.26	0.23
					0.09				0.10
Decaf									
	No	151	1	Ref		143	1	Ref	
	Yes	42	0.88	0.62-1.24	0.46	39	0.84	0.59-1.19	0.32
Regular (cups)									
	<1	151	1	Ref		143	1	Ref	
	1	19	0.96	0.60-1.55	0.87	19	0.98	0.60-1.58	0.92
	2-3	21	0.92	0.58-1.45	0.72	18	0.81	0.49-1.32	0.39
	4+	2	0.39	0.10-1.57	0.18	2	0.41	0.10-1.64	0.21
					0.30				0.17
Tea									
	No	136	1	Ref		127	1	Ref	
	Yes	58	1.03	0.76-1.40	0.86	56	1.00	0.73-1.37	0.99
Tea (cups)									
	<1	136	1	Ref		127	1	Ref	
	1	14	0.73	0.42-1.26	0.26	14	0.73	0.42-1.27	0.26
	2-3	44	1.19	0.84-1.66	0.33	42	1.14	0.81-1.62	0.45
					0.49				0.62

a – Number of melanoma diagnoses in each group

*- Adjusted for age, region, skin reaction, sunscreen use, summer sun exposure in thirties and past year

Table 6. Adjusted hazard ratios for coffee in yearly segments

	Daily Coffee*		Cups of Coffee per Day*			
	No	Yes	<1	1	2-3	4+
Year 0-1a	1 (Ref)	1.11	1 (Ref)	0.79	1.62	1.10
Year 1-2a	1 (Ref)	0.86	1 (Ref)	0.79	0.90	0.77
Year 2-3a	1 (Ref)	1.74	1 (Ref)	2.13	1.52	1.69
Year 3-4b	1 (Ref)	0.84	1 (Ref)	0.97	0.84	0.69
Year 4-5b	1 (Ref)	0.69	1 (Ref)	0.33	0.96	0.52
Year 5-6b	1 (Ref)	0.48	1 (Ref)	0.69	0.39	0.41
Year 6-7c	1 (Ref)	0.86	1 (Ref)	1.48	0.66	0.72
Year 7+c	1 (Ref)	0.75	1 (Ref)	0.75	0.53	1.06

*- Adjusted for age, height, whr, education, income, alcohol, smoking, region, aspirin, history of non-melanoma skin cancer

a-baseline intake data
data

b-year 3 intake data

c - year 6 intake data

Table 7. Adjusted Hazards Ratios for coffee and tea intake and risk of melanoma starting from year 4 in concordant intakers

		Multivariate Adjusted*			
		N ^a	HR	CI	p
Coffee					
	No	47	1	ref	
	Yes	91	0.66	0.46-0.96	0.03
Coffee (cups)					
	<1	46	1	ref	
	1	6	0.39	0.17-0.92	0.03
	2-3	28	0.63	0.39-1.04	0.07
	4+	16	0.70	0.39-1.26	0.23
					0.11
Regular Coffee					
	No	70	1	ref	
	Yes	63	0.72	0.51-1.03	0.07
Regular (cups)					
	<1	70	1	ref	
	1	6	0.42	0.18-0.96	0.04
	2-3	29	0.85	0.54-1.32	0.47
	4+	7	0.74	0.33-1.64	0.46
					0.28
Decaf Coffee					
	No	92	1	ref	
	Yes	24	0.79	0.50-1.24	0.31
Decaf (cups)					
	<1	92	1	ref	
	1	3	0.45	0.14-1.40	0.16
	2-3	7	0.71	0.33-1.54	0.39
	4+	1	--	--	--
					0.15
Tea					
	No	110	1	ref	
	Yes	22	1.05	0.66-1.67	0.83
Tea (cups)					
	<1	110	1	ref	
	1	5	0.93	0.38-2.28	0.87
	2+	15	1.48	0.86-2.54	0.16
					0.20

a – Number of melanoma diagnoses in each group

* - Adjusted for age, height, education, income, alcohol, smoke, region, aspirin, history of non-melanoma skin cancer, sunscreen use, skin reaction, and summer sun exposure in thirties

APPENDIX

DISTRIBUTION OF COVARIATES ACCORDING TO TEA

	<1 cup/day		1 cup/day		2+ cups/day		p-value
	Number	(%)	Number	(%)	Number	(%)	
Age							
50-54	6318	13.0	946	11.5	11144	13.1	<0.001
55-59	9147	18.8	1452	17.7	1585	18.1	
60-69	21672	44.6	3696	45.0	3885	44.5	
70-79	11472	23.6	2125	25.9	2127	24.3	
Education							
high school or less	9512	19.7	1522	18.7	1807	20.8	0.008
some college	17480	36.2	3038	37.2	3173	36.6	
bachelors	11956	24.8	2016	24.7	2040	23.5	
graduate degree	9316	19.3	1583	19.4	1652	19.1	
Income							
<\$20000	5874	13.0	1011	13.2	1099	13.5	<0.001
\$20000-49999	19688	43.6	3390	44.2	3590	44.2	
\$50000-99999	14017	31.0	2371	30.9	2573	31.7	
>\$100000	5622	12.4	902	11.8	859	10.6	
BMI (kg/m²)							
<25	20683	43.0	3638	44.7	3635	42.0	<0.001
25-29.99	16288	33.9	2799	34.4	3003	34.7	
30+	11125	23.1	1697	20.9	2011	23.3	
WHR							
<0.75	12329	25.5	2096	25.6	2155	24.8	0.033
0.75-0.85	24463	50.6	4238	51.8	4423	50.8	
>0.85	11517	23.8	1846	22.6	2128	24.4	
Height							
<158 (Q1)	12201	25.3	2280	28.0	2307	26.6	<0.001
158-162.1 (Q2)	11802	24.5	2031	24.9	2123	24.5	
162.2-166.3 (Q3)	12153	25.2	1992	24.4	2130	24.6	
>166.3 (Q4)	12091	25.1	1849	22.7	2103	24.3	
Alcohol							
Non-Drinkers	17969	37.0	2846	34.7	3498	40.1	<0.001
<3 per week	17068	35.2	3200	39.0	3180	36.4	
3-7 per week	6360	13.1	1088	13.3	1002	11.5	
>7 per week	7163	14.8	1072	13.1	1054	12.1	
Exercise per week							
None	6840	14.1	1016	12.4	1264	14.5	<0.001
<60 minutes	6089	12.6	1006	12.3	1141	13.1	
60-150 minutes	11127	23.0	1983	24.2	2121	24.4	
>150 minutes	24358	50.3	4178	51.1	4172	48.0	
Region							
Northeast	11131	22.9	2785	33.9	2531	29.0	<0.001

	<i>South</i>	10885	22.4	2048	24.9	2594	29.7	
	<i>Midwest</i>	12333	25.4	1471	17.9	1533	17.5	
	<i>West</i>	14260	29.3	1915	23.3	2083	23.8	
Hormone Use								
	<i>Never</i>	12888	27.0	2327	28.7	2469	28.7	<0.001
	<i>Ever</i>	34906	73.0	5769	71.3	6137	71.3	
Smoke								
	<i>Never</i>	23378	48.7	4370	53.9	4560	52.9	<0.001
	<i>Past</i>	21725	45.3	3394	41.8	3565	41.3	
	<i>Current</i>	2905	6.1	350	4.3	504	5.8	
Any NSAID use								
	<i>No</i>	27617	56.8	4642	56.5	4859	55.6	0.100
	<i>Yes</i>	20991	43.2	3577	43.5	3882	44.4	
Aspirin								
	<i>No</i>	37797	77.8	6339	77.1	6735	77.1	0.195
	<i>Yes</i>	10811	22.2	1880	22.9	2006	23.0	
Sunscreen Use								
	<i>No</i>	20520	47.3	3131	42.8	3662	47.1	<0.001
	<i>Yes</i>	22913	52.8	4192	57.2	4115	52.9	
Skin Reaction								
	<i>no burn/tan</i>	15686	36.4	2605	35.5	2687	34.8	<0.001
	<i>burn/tan</i>	11204	25397.0	1864	25.4	1803	23.3	
	<i>burn/tan slightly</i>	11540	26.8	2017	27.5	2188	28.3	
	<i>burn/no tan</i>	4710	10.9	846	11.5	1049	13.6	
Summer/day during childhood								
	<i><=120 minutes</i>	12504	28.5	2145	28.9	2197	28.0	0.471
	<i>>120 minutes</i>	31343	71.5	5287	71.1	5654	72.0	
Summer/day during Teens								
	<i><=120 minutes</i>	17354	39.6	3010	40.5	3061	39.1	0.16
	<i>>120 minutes</i>	26439	60.4	4414	59.5	4778	61.0	
Summer/day during thirties								
	<i><=120 minutes</i>	29842	68.1	5068	68.2	5344	68.1	0.976
	<i>>120 minutes</i>	13997	31.9	2364	31.8	2499	31.9	
Other season/day during childhood								
	<i><=120 minutes</i>	27661	63.4	4727	63.9	4829	61.9	0.018
	<i>>120 minutes</i>	15986	36.6	2669	36.1	2975	38.1	
Other season/day during teens								
	<i><=120 minutes</i>	30547	70.0	5232	70.9	5307	67.9	<0.001
	<i>>120 minutes</i>	13096	30.0	2150	29.1	2510	32.1	
Other season/day during thirties								
	<i><=120 minutes</i>	36355	83.2	6161	83.3	6395	81.8	0.008
	<i>>120 minutes</i>	7342	16.8	1239	16.7	1424	18.2	

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