Alcohol Consumption and Melanoma Risk: A Prospective Analysis from the NIH-AARP Diet and Health Study

By

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Thesis

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There is a lack of epidemiological research with cohort study design observing the associations between alcohol consumption and melanoma. Additionally, some observational studies have found significant differences in melanoma risk based on alcoholic beverage type. In this prospective analysis, we investigated the associations of total alcohol consumption and different types of alcoholic beverages with risk of melanoma among 469,828 participants of the NIH-AARP Diet and Health Study. Alcohol consumption in the past year was assessed at baseline by questionnaire and defined as a categorical variable: non-drinker, >0-1 drinks/day, >1-3 drinks/day, and >3 drinks/day. Total melanoma, which includes malignant melanoma and melanoma in situ, was defined according to the ICD-O 3rd edition by anatomic site and histological code. Multivariable-adjusted Cox proportional hazards regressions were used to calculate the hazard ratios (HR) and 95% confidence intervals (CI). We found that the highest risk of melanoma in situ and malignant melanoma was among those who consume >1-3 drinks/day (HR: 1.21, 95% CI: 1.07 - 1.36, $P_{trend} = 0.23$) and >3 drinks/day (HR: 1.19, 95% CI: 1.05 - 1.35, $P_{trend} = 0.21$) respectively compared to non-drinkers. We also observed a significant positive relationship among those who consumed wine and liquor ($P_{trend} < 0.05$). Lastly, we found an increased risk of malignant melanoma and melanoma in situ among participants who consumed >0-1 drinks/day of beer, and significant evidence of an inverse dose-dependent trend among beer consumers. Future investigations are needed to evaluate the association between duration of alcohol consumption on melanoma risk and observe the interactions of alcohol consumption with melanoma risk factors.

Introduction

Skin cancer, one of the most common cancers in the U.S, is a serious public health concern.[1] Although invasive melanoma only accounts for about 1% of incident skin cancers, melanoma constitutes for the majority of skin cancer deaths.[2] Additionally, the incidence of malignant melanoma and melanoma in situ have rapidly increased within the last decade.[3,4] Improvements in treatment have significantly reduced mortalities associated with skin cancer[3], however the number of melanoma deaths is expected to increase by 6.5% in 2022.[2] Melanoma in situ, though not directly associated with mortality,[3] increases the risk of malignant melanoma which leads to poorer prognosis specifically among elderly adults.[5] Multiple non-modifiable factors including family history, melanocytic nevi, genetic phenotypes, such as hair and skin color, and body site are suggested to influence melanoma risk.[6-8] Modifiable and dietary factors, such as UVR exposure, coffee, citrus fruit, alcohol, and fish consumption are also found to be associated with melanoma risk.[7, 9-15]

Experimental studies suggest that alcohol may interfere with the normal genetic, hormonal and immunological functions contributing to an increased risk of cancer.[16-18] In observational studies, investigations have indicated that melanoma risk is elevated after consumption of white wine and liquor.[13,19] Multiple meta-analyses evaluating total alcohol consumption have observed a substantial increase in melanoma risk among alcohol consumers compared to non-drinkers.[20-22, 30] However, these analyses primarily consist of case-control studies which are subject to bias particularly in the matching of case and control participants.[23]

Although these findings are meaningful, there is a lack of epidemiological evidence with cohort study design examining the associations of alcohol consumption and melanoma risk. Additionally, there are no prospective studies based on the US National Institute of Health (NIH)-AARP Diet and Health Study, the largest prospective cohort with dietary data and cancer outcomes in the US, that have evaluated alcohol intake and melanoma risk. Therefore, in this study we aim to examine the associations between total alcohol intake, as well as specific types of alcohol intake, and melanoma risk in the NIH-AARP Diet and Health Cohort Study with extended follow-up.

Methods

Study Population

The NIH-AARP Diet and Health Study is a large prospective cohort study initiated in 1995 and 1996. A baseline questionnaire was mailed to 3.5 million AARP members aged 50 to 71 who resided in one of the six states (California, Florida, Louisiana, New Jersey, North Carolina, or Pennsylvania) or two metropolitan areas (Atlanta, GA or Detroit, MI) with existing population-based cancer registries.[24] The study was approved by the Special Studies Institutional Review Board of the National Cancer Institute. Among the 566,398 participants who completed the questionnaire and provided informed consent, we excluded individuals who reported a history of cancer (n = 50,591) prior to baseline; individuals who were proxy-responders (n =14,487); individuals with extreme calorie intake (n = 3,454) at baseline, defined as more than three standard deviations beyond the mean intake on the log- transformed scale (i.e. calorie: < 426.6 kcal, or > 6,760.8 kcal); individuals who died, moved out of the study area, or were diagnosed with cancer by cancer registry data (not disclosed in self-reported cancer history) before study entry (n = 2,098); and individuals who were identified as having cancer through death reports (n

= 25,940). The resulting analytic cohort consisted of 469,828 participants (279,594 men and 190,234 women).

Cohort Follow-up and Case Ascertainment

Vital status was obtained by linkage to the National Death Index, and cancer diagnoses were updated via linkage to state cancer registries. Participants were followed from baseline until the first date of their first melanoma, the date of death, the end of study (December 31, 2011), or the date the participants moved out of the registry area. Cutaneous melanoma was defined according to the International Classification of Disease for Oncology (ICD-O, 3rd edition) by anatomic site and histological code (C44.0-C44.9 with Histology 8720–8780). This classification includes melanoma in situ and malignant melanoma.

Exposure and covariate assessment

Alcohol consumption and dietary intake were assessed at baseline using a 124-item food frequency questionnaire (FFQ) developed and validated by National Cancer Institute.[25] Participants were asked to report their intake of foods and beverages over the past year in both frequency of consumption and portion size. Line items were linked to the 1994–1996 US Department of Agriculture's Continuing Survey of Food Intakes by Individuals to calculate nutrient and energy intakes.[26] One drink was defined as one 12-fluid-ounce beer, one 5-ounce glass of wine, or one 1.5-ounce shot of liquor, all equaling approximately 13 g of alcohol.[26] In accordance with previous literature, we further categorized total alcohol consumption as non-drinker, up to or including one drinks/day, between one to three drinks/day, and greater than three drinks/day.[27] Beer, wine, and liquor intake were categorized as non-drinker, up to or

including one drinks/day and greater than one drinks/day.[27] We restricted our analysis to alcohol consumed as a beverage and did not include alcohol used in cooking.

The covariates analyzed include age (continuous), sex (male, female), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Other), body mass index (BMI) (continuous), physical activity (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), July erythemal UVR (<=180, >180-188, >188-236, and >236 J/m^2), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), smoking history (never, former, or current smoker), and daily energy intake (continuous). UVR exposure was estimated by noon-time ground-level erythemal dose measured in the month of July between 1978 and 2005, which links Total Ozone Mapping Spectrometer (TOMS) data (http://toms.gsfc.nasa.gov) to the latitude and longitude of census tract of residence at baseline for all cohort members.[28]

Statistical Analysis

We performed bivariate analyses ($\chi 2$ Test and ANOVA) of the baseline results on melanoma type with covariates. Then, we used Cox proportional hazards regression models to estimate hazard ratios (HRs) and two-sided 95% confidence intervals (CIs) for total alcohol intake and the specific types of alcohol intake with risk of total melanoma, malignant melanoma, and melanoma in situ. The age-sex model was adjusted for age and sex while the full multivariate

model was adjusted for age, sex, race, education, and the other covariates previously listed. HRs and 95% CIs were reported for increments of sex-specific, total alcohol and alcohol type cut points of intake (non-drinkers represented the reference category). To evaluate the linear association of alcohol consumption on melanoma risk, we assigned participants the median value of their intake and entered these values as a continuous term in the regression models. We then tested alcohol–covariate interaction terms in relation to melanoma using the likelihood ratio test to identify potential effect modifiers. The factors evaluated were sex, smoking history (never or ever smokers), follow up time (>10 years or <= 10 years), education (college graduates or non-college graduates), UVR exposure (>188 J/m^2 or <=188 J/m^2), and BMI (>25 kg/m^2 or <=25 kg/m^2). Lastly, in our sensitivity analysis, we restricted our data to non-Hispanic White participants and only drinkers. All analyses were conducted using SAS software, version 9.4 (SAS institute, Cary, NC). All statistical tests were 2-sided and considered statistically significant at $P < 0.05$.

Results

During the 6,297,881 person years of follow up with a median of 15.5 years, 8,318 cases of total melanoma (8,183 non-Hispanic White; 15 non-Hispanic Black; 36 Hispanic; 14 Other), 5,034 cases of malignant melanoma (4,949 non-Hispanic White; 13 non-Hispanic Black; 21 Hispanic; 11 Other) and 3,284 cases of melanoma in situ (3,234 non-Hispanic White; 2 non-Hispanic Black; 15 Hispanic, 3 Other) were identified. Table 1 displays the baseline demographics of participants and the health-related risk factors by alcohol intake category. The median age of participants at baseline was 61.5 years old. Within the total cohort most participants self-identified as non-Hispanic White (92.4%) and male (59.5%). Overall, alcohol drinkers were more likely to be non-Hispanic white males, former smokers, have obtained a college and post

graduate education, and be exposed to <=180 J/m2 of UVR. All covariates were statistically associated with total alcohol consumption (Supplemental Table 4). BMI was not statistically associated with malignant melanoma and caffeine intake was not associated with melanoma in situ in age and sex adjusted models (Supplementary Tables 1 and 2).

The results of total alcohol intake in relation to malignant melanoma and melanoma in situ are displayed in Table 2. In the age and sex model, total alcohol consumption was significantly associated with an increased risk of malignant melanoma and melanoma in situ. Participants who consumed >1-3 drinks per day were at the highest risk of malignant melanoma (HR: 1.25, 95% CI: 1.15 - 1.37) and melanoma in situ (HR: 1.45, 95% CI: 1.30 - 1.62) compared to the other categories of alcohol consumption. In the multivariate model, alcohol consumption of >1-3 drinks per day was observed to have the largest association with melanoma in situ risk (HR: 1.21, 95% CI: 1.07 - 1.36). Intakes of >3 drinks per day was found to have the largest relationship with malignant melanoma risk (HR: 1.19, 95% CI: 1.05 - 1.35). There was no evidence of significant linearity when examining the dose-response relationship of total alcohol consumption, malignant melanoma (P_{trend} = 0.21) and melanoma in situ risk (P_{trend} = 0.23) in the multivariate models. Similar results were observed in the sensitivity analysis restricted to non-Hispanic Whites (Supplementary Table 3). In our analysis restricted to only drinkers, we observed a significant increased relationship between those who consume >1-3 drinks per day and risk of melanoma in situ compared to those who drink >0-1 drinks per day. Although there was evidence of a positive risk in malignant melanoma among only drinkers, the hazard ratios and P_{trend} were not statistically significant (Supplementary Table 3).

Table 3 depicts the associations between the 3 specific types of alcohol intake (beer, wine, and liquor) and risk of malignant melanoma and melanoma in situ. Except for the association between wine and malignant melanoma within the multivariate model (P_{trend} = 0.08), there was evidence of a dose-dependent relationship between wine, liquor, and melanoma risk. More specifically, liquor consumption was positively associated with malignant melanoma risk (P_{trend} < 0.001) in both models. In addition, intakes of wine (P_{trend} = 0.001) and liquor (P_{trend} = 0.003) were positively associated with the risk of melanoma in situ. In the multivariate models, there was a similar risk of malignant melanoma (HR: 1.12, 95% CI: 1.05-1.20) and melanoma in situ (HR: 1.12, 95% CI: 1.03-1.21) among those who consumed >0-1 drinks per day of beer, and significant evidence of an inverse dose-dependent trend (P_{trend} <0.05).

Furthermore, the associations between total alcohol intake and malignant melanoma and melanoma in situ were stratified by sex, cigarette smoking status, follow-up time, education, July erythemal UVR, and BMI (Table 4 and Table 5). Among those with melanoma in situ and malignant melanoma, there was evidence of significant interaction between total alcohol consumption and years of follow up time. Participants who consumed >1-3 drinks per day and had <=10 years of follow-up had a 45% increased risk of melanoma in situ (HR: 1.45, 95% CI: 1.23 - 1.70) and a 40% increased risk of malignant melanoma (HR: 1.40, 95% CI: 1.24 - 1.59). However, there was no evidence of interaction between sex, cigarette smoking status, education, July erythemal UVR, or BMI and total alcohol intake on risk of malignant melanoma and melanoma in situ.

Discussion

In this large prospective cohort study, we examined the associations between alcohol intake and risk of incident total melanoma including malignant melanoma and melanoma in situ. Although there was no evidence of significant linearity, we did find a significant increased risk of malignant melanoma and melanoma in situ among those who consumed >3 drinks and >1-3 drinks respectively compared to non-drinkers. Also, liquor intake was positively associated with both malignant melanoma and melanoma in situ, while wine consumption was only positively associated with melanoma in situ. Lastly, we observed similar increased risk of malignant melanoma and melanoma in situ among participants who consumed >0-1 drinks per day of beer compared to non-drinkers, and an inverse dose-dependent trend in both the age-sex and multivariate adjusted models.

Our results on the dose-dependent relationship between melanoma and alcohol consumption are similar to the results of a 2003 large occupational cohort study. In this investigation, the authors did not find a significant dose-dependent association with increasing alcohol consumption and melanoma risk (P_{trend}= 0.08).[29] Comparable results were observed in a pooled meta-analysis, where investigators did not observe a significant linear trend of increasing alcohol intake on malignant melanoma risk.[22] Our results also suggest that there is a slight increase in risk of melanoma comparing the medium intake (>1-3 drinks per day) with the highest intake (>3 drinks per day) of alcohol consumption. The results of a 2016 pooled analysis examined similar findings, where melanoma risk increased by 2% from moderate consumption (10-19.9 grams per day) of alcohol and the highest intake (20+ grams per day) of alcohol.[19]. Although in our study we did not observe significant linearity in our multivariate model, the results of this analysis together with our findings may suggest that there is an exponential relationship between total

alcohol consumption and risk of melanoma. However, further investigations will be needed in the future to evaluate this hypothesis.

We found that the association between alcohol consumption and melanoma risk was significantly higher among men. Specifically, when stratified by sex, the results of our analysis suggest that men who drink between >1-3 drinks per day have an increased risk of melanoma in situ, and men who drink between >1-3 drinks and >3 drinks per day have an increased risk of malignant melanoma. These results contradict those of previous literature that found a higher risk in melanoma among women, which may be based on differences in metabolism and body volume.[19] In general, men typically have a greater volume of blood distribution and higher metabolism which ultimately lead to a lower blood alcohol profile.[31] Similar to our findings, in a 2018 meta-analysis, investigators found that moderate alcohol intake, which was defined as 1-2 drinks per day, significantly increased the risk of malignant melanoma among men.[20] Inconsistencies in melanoma risk by alcohol consumption and gender may be due to confounder adjustments, selection bias or sampling error.

The highest significant risk of melanoma in situ was among those who consume >1-3 drinks per day and received <=188 J/m^2 of UVR exposure. Alternatively, the highest significant risk of malignant melanoma was observed among those who drink >3 drinks per day and received >188 J/m^2 of UVR exposure. There is evidence that alcohol may induce carcinogenesis of melanoma via interaction with UVR.[32-34] More specifically, it has been suggested that acetaldehyde in combination with UVR may trigger the production of oxygen reactive species increasing the likelihood of oxidative DNA damage and ultimately melanoma.[35] In 2006, investigators

observed an increasing risk in melanoma from the interaction of lifetime alcohol consumption and UVR exposure specifically among men who consume hard liquor compared to other alcoholic beverage types.[36] To our knowledge, mechanisms examining the interaction of alcohol intake, UVR exposure and melanoma subtypes are currently unknown indicating a need for supplementary prospective and experimental studies.

Our findings on beer consumption are consistent with results from a previous pooled analysis which focused on alcohol and alcoholic beverage type towards melanoma risk. Their findings based on the results of eight case control studies found an inverse association between increasing beer consumption and melanoma risk among women.[37] In contrast to the results of the same investigation, we did conclude that the inverse association between beer consumption and melanoma risk was statistically significant. However, despite the observed "protective" effects of beer consumption on melanoma risk, it is important to note that chronic alcohol consumption of any type can contribute to detrimental health effects. Therefore, the results of this observation should be interpreted with caution. In addition, we found that consumption of wine and liquor are positively associated with melanoma risk. Both liquor and wine are estimated to have a higher alcohol content percentage compared to beer. According to the U.S. Department of Agriculture, the alcohol content in beer, wine and liquor respectively are 5%, 7% and 12%.[38] Increased levels of acetaldehyde, which is the metabolized by product of alcohol, interferes with cellular replication and has been found to introduce DNA adducts leading to gene mutations.[39,40] Therefore, it can be suggested that an increased content of alcohol can raise the risk of melanoma due to the overwhelming buildup of acetaldehyde.

There were several major strengths of our study including the large sample size, availability of potential confounders, and relatively long follow up period which provided sufficient statistical power to detect associations.[24] The prospective study design reduced the possibility of recall bias and selection bias as well. Lastly, our study examined different types of alcohol intake and melanoma subtypes, which allowed for a more comprehensive understanding of total alcohol, alcoholic beverage types and melanoma risk.

There were also several limitations in our study that should be noted. First, the associations we observed may not justify causality due to unknown confounding biases which are better controlled for in clinical trials. However, it would not be ethical to conduct a clinical trial to evaluate the treatment effects of alcohol intake on melanoma risk. Our study also lacked data on drinking history and duration potentially leading to a skewed effect on the association of melanoma risk and alcohol consumption. There is minimal research observing the effect of alcohol consumption on melanoma risk. Because of this, it may not be possible to conclude an accurate effect of alcohol consumption on our outcome. The results of the mailed FFQ relied on self-reported alcohol consumption. As a result, this study may be subject to recall and reporter bias. Also, the NIH-AARP study population contains predominantly white and well-educated participants limiting generalizability. Lastly, the study lacked information on important risk factors of melanoma such as mole count, hair color, and history of severe sun burn.

In conclusion, we found that alcohol consumption was associated with an increased risk of total melanoma, melanoma in situ and malignant melanoma in comparison to non-drinkers. Future studies should aim to replicate our results and evaluate the association between duration of

alcohol consumption on melanoma risk. Additionally, research is needed to observe if combinations of alcoholic beverage consumption is significantly associated with melanoma risk. The rate of alcohol consumption in the US has significantly increased, especially amidst the COVID-19 pandemic.[41] Based on the results of the analysis, it is critical that we aim to reduce the frequency of alcohol consumption to prevent the development of melanoma and other cancer types.

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Table 1. NIH-AARP Diet and Health Study characteristics by level of total alcohol intake (n = 469,828)*

Characteristic	Total	Total Alcohol Intake (drinks/day)			
		Non-Drinkers	>0-1	>1-3	>3
Total cohort, n (%)	469828	115023 (24.5)	247743 (52.7)	70916 (15.1)	36146 (7.7)
Age, y	61.5 (5.4)	61.9 (5.3)	61.3 (5.4)	61.8 (5.4)	61.6 (5.3)
Sex					
Male	279594 (59.5)	58569 (50.9)	138452 (55.9)	51637 (72.8)	30936 (85.6)
Female	190234 (40.5)	56454 (49.1)	109291 (44.1)	19279 (27.2)	5210 (14.4)
Race/Ethnicity†					
Non-Hispanic white	428413 (92.4)	100291 (88.9)	226854 (92.7)	67073 (95.5)	34195 (95.5)
Non-Hispanic black	18343 (4.0)	7355 (6.5)	8642 (3.5)	1447 (2.1)	899 (2.5)
Hispanic	9045 (2.0)	2164 (1.9)	5257 (2.2)	1126 (1.6)	480 (1.3)
Other	7839 (1.7)	2973 (2.6)	4007 (1.6)	615 (0.9)	244 (0.7)
BMI, kg/m^2†	27.1 (5.1)	27.8 (5.8)	27.1 (5.0)	26.2 (4.3)	26.9 (4.3)
Smoking†					
Never smoker	166542 (36.9)	50119 (45.5)	92430 (38.7)	18135 (26.5)	5858 (16.9)
Former smoker	230601 (51.0)	48223 (43.8)	119455 (50.1)	41560 (60.8)	21363 (61.6)
Current smoker	54831 (12.1)	11929 (10.8)	26788 (11.2)	8635 (12.6)	7479 (21.6)
Education†					
<=11y	119814 (26.3)	40253 (36.5)	59157 (24.3)	12613 (18.2)	7791 (22.1)
High school	46229 (10.1)	11986 (10.9)	24707 (10.3)	6079 (8.8)	3457 (9.8)
Some college	108635 (23.8)	24686 (22.3)	59212 (24.6)	16053 (23.1)	8684 (24.6)
College and beyond	181414 (39.8)	33475 (30.3)	97918 (40.6)	34675 (50.0)	15346 (43.5)
Physical activity†					
Never/rarely	84580 (18.2)	27095 (24.0)	41697 (17.0)	9154 (13.0)	6634 (18.5)
1-3/mo	63431 (13.7)	14655 (13.0)	35050 (14.3)	8673 (12.3)	5053 (14.1)
1-2/wk	101002 (21.7)	22189 (19.6)	55391 (22.6)	15695 (22.3)	7727 (21.6)

3-4/wk	125585 (27.0)	27250 (24.1)	68075 (27.7)	21000 (29.8)	9260 (25.8)
5+/wk	90125 (19.4)	21790 (19.3)	45246 (18.4)	15906 (22.6)	7183 (20.0)
Family history of cancer†					
No	217454 (48.8)	53148 (49.1)	114362 (48.6)	32864 (48.7)	17080 (49.9)
Yes	227952 (51.2)	55100 (50.9)	121080 (51.4)	34631 (51.3)	17141 (50.1)
Marital Status					
No	144169 (30.9)	40263 (35.4)	77901 (31.7)	17345 (24.6)	8660 (24.1)
Yes	321963 (69.1)	73423 (64.6)	168133 (68.3)	53145 (75.4)	27262 (75.9)
July erythemal UVR, J/m^2*					
<=180	204164 (43.5)	50152 (43.6)	109128 (44.1)	29973 (42.3)	14911 (41.3)
>180-188	97509 (20.8)	20705 (18.0)	54647 (22.1)	14469 (20.4)	7688 (21.3)
>188-236	92542 (19.7)	26025 (22.6)	45493 (18.4)	13677 (19.3)	7347 (20.3)
>236	75613 (16.1)	18141 (15.8)	38475 (15.5)	12797 (18.1)	6200 (17.2)
Total fish intake, g/d	19.9 (23.0)	17.7 (23.9)	19.5 (22.0)	22.8 (23.2)	23.3 (25.0)
Caffeinated coffee, g/d	560.8 (664.2)	474.1 (676.0)	552.0 (651.6)	656.0 (652.5)	710.5 (685.5)
Calories, kcal	1849.1 (836.5)	1783.9 (842.3)	1741.8 (752.9)	1927.0 (737.9)	2639.0 (1074.7)

* Mean (SD) for continuous variables and count (percentage) for categorical variables. NIH= National Institutes of Health; UVR = ultraviolet radiation.

† n does not total 469,828 because of missing data.

Table 2. Association of total alcohol intake with total melanoma, malignant melanoma and melanoma in situ in the NIH-AARP Diet and Health Study*

Melanoma Type	Model Estimates	Total Alcohol Intake (drinks/day)				
		Non-Drinkers (Ref.)	>0-1	>1-3	>3	P_{trend}
Total Melanoma‡	No. cases/No. noncases	1622/113401	4348/243395	1602/69314	746/35400	—
	Age & sex-adjusted hazard ratio (95% CI)	1.00	1.16 (1.10-1.23)	1.33 (1.24-1.43)	1.20 (1.10-1.32)	<0.001
	Multivariate (fully) - adjusted hazard ratio (95% CI) †	1.00	1.07 (1.01-1.14)	1.17 (1.08-1.26)	1.19 (1.08-1.31)	0.08
Malignant melanoma	No. cases/No. noncases	999/114024	2651/245092	931/69985	453/35693	—
	Incidence rate per 100,000 person-years	66.2	78.5	96.9	96.5	—
	Age & sex-adjusted hazard ratio (95% CI)	1.00	1.15 (1.07-1.24)	1.25 (1.15-1.37)	1.17 (1.05-1.31)	<0.001
	Multivariate (fully) - adjusted hazard ratio (95% CI) †	1.00	1.08 (0.99-1.16)	1.14 (1.03-1.25)	1.19 (1.05-1.35)	0.21
Melanoma in situ	No. cases/No. noncases	623/114400	1697/246046	671/70245	293/35853	—
	Incidence rate per 100,000 person-years	41.2	50.1	69.7	62.3	—
	Age & sex-adjusted hazard ratio (95% CI)	1.00	1.18 (1.08-1.29)	1.45 (1.30-1.62)	1.26 (1.09-1.45)	<0.001
	Multivariate (fully) - adjusted hazard ratio (95% CI) †	1.00	1.07 (0.97-1.18)	1.21 (1.07-1.36)	1.19 (1.02-1.40)	0.23

* CI = confidence interval; — = not applicable.

† Adjusted for age (continuous), sex (male, female), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Other; categorical), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), July erythemal UVR (<=180, >180-188, >188-236, and >236 J/m2), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake

(continuous), caloric intake (continuous), smoking history (never, former, or current smoker), and marital status (married, not married ; categorical).
‡ Total melanoma includes malignant melanoma and melanoma in situ.

Table 3. Association of other types of alcohol intake with total melanoma, malignant melanoma and melanoma in situ in the NIH-AARP Diet and Health Study*

Alcohol Type	Melanoma Type	Model Estimates	Non-Drinkers	>0-1 Drinks per day	>1 Drinks per day	P_{trend}
Beer Intake						
	Total Melanoma‡	No. cases/No. noncases	3076/212242	4643/217075	599/32193	—
		Age & sex-adjusted hazard ratio (95% CI)	1.00	1.21 (1.15-1.27)	0.98 (0.90-1.08)	<0.001
		Multivariate (fully)-adjusted hazard ratio (95% CI) †	1.00	1.12 (1.07-1.18)	1.04 (0.95-1.15)	0.001
	Malignant Melanoma	No. cases/No. noncases	1873/213445	2810/218908	351/32441	—
		Age & sex-adjusted hazard ratio (95% CI)	1.00	1.19 (1.12-1.27)	0.94 (0.83-1.05)	<0.001
		Multivariate (fully)-adjusted hazard ratio (95% CI) †	1.00	1.12 (1.05-1.20)	1.01 (0.89-1.15)	0.004
	Melanoma in situ	No. cases/No. noncases	1203/214115	1833/219885	248/32544	—
		Age & sex-adjusted hazard ratio (95%CI)	1.00	1.23 (1.14-1.33)	1.06 (0.92-1.22)	<0.001
		Multivariate (fully)-adjusted hazard ratio (95% CI) †	1.00	1.12 (1.03-1.21)	1.09 (0.93-1.27)	0.01
Wine Intake						
	Total Melanoma‡	No. cases/ No. noncases	2733/182994	4874/247752	711/30764	—
		Age & sex-adjusted hazard ratio (95% CI)	1.00	1.25 (1.20-1.31)	1.39 (1.28-1.51)	<0.001
		Multivariate (fully)-adjusted hazard ratio (95% CI) †	1.00	1.10 (1.04-1.15)	1.14 (1.04-1.25)	0.001

	Malignant Melanoma	No. cases/ No. noncases	1719/184008	2914/249712	401/31074	—
		Age & sex-adjusted hazard ratio (95% CI)	1.00	1.19 (1.12-1.27)	1.24 (1.11-1.38)	<0.001
		Multivariate (fully)-adjusted hazard ratio (95% CI) †	1.00	1.06 (0.99-1.13)	1.05 (0.93-1.18)	0.08
	Melanoma in situ	No. cases/ No. noncases	1014/184713	1960/250666	310/31165	—
		Age & sex-adjusted hazard ratio (95% CI)	1.00	1.35 (1.25-1.46)	1.63 (1.43-1.85)	<0.001
		Multivariate (fully)-adjusted hazard ratio (95% CI) †	1.00	1.15 (1.06-1.25)	1.28 (1.12-1.47)	0.001
Liquor Intake						
	Total Melanoma‡	No. cases/No. noncases	3388/217440	3878/200715	1052/43355	—
		Age & sex-adjusted hazard ratio (95% CI)	1.00	1.16 (1.11-1.22)	1.34 (1.25-1.44)	<0.001
		Multivariate (fully)-adjusted hazard ratio (95% CI) †	1.00	1.09 (1.04-1.15)	1.27 (1.18-1.38)	<0.001
	Malignant melanoma	No. cases/No. noncases	2061/218767	2329/202264	644/43763	—
		Age & sex-adjusted hazard ratio (95% CI)	1.00	1.15 (1.08-1.22)	1.34 (1.22-1.46)	<0.001
		Multivariate (fully)-adjusted hazard ratio (95% CI) †	1.00	1.09 (1.02-1.16)	1.29 (1.17-1.42)	0.001
	Melanoma in situ	No. cases/No. noncases	1327/219501	1549/203044	408/43999	—
		Age & sex-adjusted hazard ratio (95% CI)	1.00	1.18 (1.10-1.27)	1.34 (1.19-1.49)	<0.001
		Multivariate (fully)-adjusted hazard ratio (95% CI) †	1.00	1.09 (1.01-1.18)	1.25 (1.10-1.41)	0.003

* CI = confidence interval; — = not applicable.
† Adjusted for age (continuous), sex (male, female), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other; categorical), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), July erythemal UVR (<=180, >180-188, >188-236, and >236 J/m2), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), caloric intake (continuous), smoking history (never, former, or current smoker), and marital status (married, not married ; categorical).
‡ Total melanoma includes malignant melanoma and melanoma in situ.

Table 4. Associations of total alcohol intake and malignant melanoma stratified by different characteristics*

Subgroup	Total Alcohol Intake (drinks/day)	No. Cases	HR (95% CI)*	$P_{heterogeneity}$
Overall*	(Ref)	999	1.00	—
N= 469828	>0-1	2651	1.08 (0.99-1.16)	
	>1-3	931	1.14 (1.03-1.25)	
	>3	453	1.19 (1.05-1.35)	
Sex†				
Males	(Ref)	686	1.00	0.85
n= 279594	>0-1	1892	1.06 (0.97-1.17)	
	>1-3	789	1.15 (1.03-1.28)	
	>3	418	1.19 (1.04-1.36)	
Females	(Ref)	313	1.00	
n= 190234	>0-1	759	1.08 (0.93-1.25)	
	>1-3	142	1.04 (0.83-1.29)	
	>3	35	1.17 (0.80-1.72)	
Smoking history‡				
Never smokers	(Ref)	445	1.00	0.17
n= 166542	>0-1	1068	1.11 (0.99-1.25)	
	>1-3	291	1.26 (1.08-1.48)	
	>3	91	1.21 (0.95-1.54)	
Ever smokers	(Ref)	521	1.00	
n= 285432	>0-1	1487	1.04 (0.93-1.15)	
	>1-3	605	1.05 (0.93-1.20)	
	>3	348	1.15 (0.99-1.34)	
Follow-up time*				
>10 years of follow-up	(Ref)	378	1.00	0.03
n= 381449	>0-1	1012	1.06 (0.93-1.20)	
	>1-3	347	1.06 (0.90-1.24)	
	>3	170	1.16 (0.95-1.41)	
<=10 years of follow-up	(Ref)	621	1.00	
n= 88379	>0-1	1639	1.29 (1.17-1.43)	
	>1-3	584	1.40 (1.24-1.59)	
	>3	283	1.20 (1.03-1.40)	
Education§				
College graduates	(Ref)	357	1.00	0.26
n= 181414	>0-1	1245	1.08 (0.95-1.22)	

	>1-3	543	1.19 (1.03-1.37)	
	>3	245	1.29 (1.07-1.54)	
Non-college graduates	(Ref)	619	1.00	
n= 274678	>0-1	1358	1.10 (0.99-1.22)	
	>1-3	368	1.11 (0.96-1.27)	
	>3	202	1.12 (0.93-1.34)	
July erythemal UVR‖				
UVR>188 J/m^2	(Ref)	399	1.00	0.14
n= 168155	>0-1	980	1.22 (1.07-1.38)	
	>1-3	363	1.20 (1.03-1.41)	
	>3	186	1.30 (1.07-1.58)	
UVR<=188J/m^2	(Ref)	600	1.00	
n= 301673	>0-1	1671	1.01 (0.91-1.11)	
	>1-3	568	1.12 (0.98-1.27)	
	>3	267	1.15 (0.98-1.35)	
BMI¶				
BMI>=25 kg/m^2	(Ref)	693	1.00	0.15
n= 295995	>0-1	1762	1.03 (0.94-1.13)	
	>1-3	575	1.04 (0.93-1.18)	
	>3	331	1.14 (0.99-1.31)	
BMI>=18.5 and <25 kg/m^2	(Ref)	277	1.00	
n= 157786	>0-1	835	1.16 (1.01-1.35)	
	>1-3	341	1.28 (1.08-1.52)	
	>3	111	1.12 (0.88-1.42)	

* Adjusted for age (continuous), sex (male, female), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other ; categorical), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), July erythemal UVR (<=180, >180-188, >188-236, and >236 J/m2), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), caloric intake (continuous), smoking history (never, former, or current smoker), and marital status (married, not married ; categorical).

†Adjusted for age (continuous), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other; categorical), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), July erythemal UVR (<=180, >180-188, >188-236, and >236 J/m2), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), caloric intake (continuous), smoking history (never, former, or current smoker), and marital status (married, not married ; categorical).

‡ Adjusted for age (continuous), sex (male, female), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other; categorical), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), July erythemal UVR (<=180, >180-188, >188-236, and >236 J/m2), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), caloric intake (continuous), and marital status (married, not married ; categorical).

§ Adjusted for age (continuous), sex (male, female), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other; categorical), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), July erythemal UVR (<=180, >180-188, >188-236, and >236 J/m2), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), caloric intake (continuous), smoking history (never, former, or current smoker), and marital status (married, not married ; categorical).

‖ Adjusted for age (continuous), sex (male, female), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other; categorical), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), caloric intake (continuous), smoking history (never, former, or current smoker), and marital status (married, not married ; categorical).

¶ Adjusted for age (continuous), sex (male, female), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other; categorical), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), July erythemal UVR (<=180, >180-188, >188-236, and >236 J/m2), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), caloric intake (continuous), smoking history (never, former, or current smoker), and marital status (married, not married ; categorical).

Table 5. Associations of total alcohol intake and melanoma in situ stratified by different characteristics*

Subgroup	Total Alcohol Intake (drinks/day)	No. Cases	HR (95% CI)*	$P_{heterogeneity}$
Overall*	(Ref)	623	1.00	—
N= 469828	>0-1	1697	1.07 (0.96-1.18)	
	>1-3	671	1.21 (1.07-1.36)	
	>3	293	1.19 (1.02-1.40)	
Sex†				
Males	(Ref)	420	1.00	0.45
n= 279594	>0-1	1196	1.09 (0.97-1.23)	
	>1-3	543	1.20 (1.04-1.38)	
	>3	269	1.19 (1.00-1.42)	
Females	(Ref)	203	1.00	
n= 190234	>0-1	501	1.00 (0.84-1.20)	
	>1-3	128	1.27 (0.99-1.62)	
	>3	24	1.29 (0.83-2.02)	
Smoking history‡				
Never smokers	(Ref)	293	1.00	0.91
n= 166542	>0-1	700	1.07 (0.93-1.24)	
	>1-3	214	1.27 (1.04-1.54)	
	>3	63	1.16 (0.85-1.57)	
Ever smokers	(Ref)	310	1.00	
n= 285432	>0-1	942	1.06 (0.92-1.22)	
	>1-3	431	1.17 (1.00-1.37)	
	>3	219	1.18 (0.98-1.43)	
Follow-up time*				
>10 years of follow-up	(Ref)	280	1.00	0.02
n= 381449	>0-1	759	1.06 (0.91-1.23)	
	>1-3	296	1.18 (0.98-1.41)	
	>3	136	1.25 (1.00-1.57)	
<=10 years of follow-up	(Ref)	343	1.00	
n= 88379	>0-1	938	1.27 (1.11-1.45)	
	>1-3	375	1.45 (1.23-1.70)	
	>3	157	1.12 (0.90-1.38)	
Education§				
College graduates	(Ref)	240	1.00	0.13
n= 181414	>0-1	863	1.10 (0.95-1.28)	

	>1-3	379	1.15 (0.97-1.37)	
	>3	167	1.32 (1.06-1.64)	
Non-college graduates	(Ref)	369	1.00	
n= 274678	>0-1	804	1.07 (0.93-1.22)	
	>1-3	277	1.34 (1.13-1.59)	
	>3	120	1.09 (0.86-1.37)	
July erythemal UVR‖				
UVR>188 J/m^2	(Ref)	281	1.00	0.81
n= 168155	>0-1	627	1.06 (0.91-1.23)	
	>1-3	270	1.15 (0.95-1.38)	
	>3	120	1.20 (0.94-1.52)	
UVR<=188J/m^2	(Ref)	342	1.00	
n= 301673	>0-1	1070	1.09 (0.96-1.25)	
	>1-3	401	1.29 (1.10-1.52)	
	>3	173	1.23 (1.00-1.52)	
BMI¶				
BMI>=25 kg/m^2	(Ref)	413	1.00	0.25
n= 295995	>0-1	1056	1.03 (0.91-1.16)	
	>1-3	406	1.20 (1.04-1.40)	
	>3	185	1.05 (0.87-1.27)	
BMI>=18.5 and <25 kg/m^2	(Ref)	183	1.00	
n= 157786	>0-1	596	1.17 (0.98-1.40)	
	>1-3	249	1.25 (1.01-1.53)	
	>3	104	1.41 (1.08-1.84)	

* Adjusted for age (continuous), sex (male, female), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other; categorical), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), July erythemal UVR (<=180, >180-188, >188-236, and >236 J/m2), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), caloric intake (continuous), smoking history (never, former, or current smoker), and marital status (married, not married ; categorical).

†Adjusted for age (continuous), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other; categorical), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), July erythemal UVR (<=180, >180-188, >188-236, and >236 J/m2), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), caloric intake (continuous), smoking history (never, former, or current smoker), and marital status (married, not married ; categorical).

‡ Adjusted for age (continuous), sex (male, female), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other; categorical), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), July erythemal UVR (<=180, >180-188, >188-236, and >236 J/m2), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), caloric intake (continuous), and marital status (married, not married ; categorical).

§ Adjusted for age (continuous), sex (male, female), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other; categorical), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), July erythemal UVR (<=180, >180-188, >188-236, and >236 J/m2), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), caloric intake (continuous), smoking history (never, former, or current smoker), and marital status (married, not married ; categorical).

‖ Adjusted for age (continuous), sex (male, female), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other; categorical), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), caloric intake (continuous), smoking history (never, former, or current smoker), and marital status (married, not married ; categorical).

¶ Adjusted for age (continuous), sex (male, female), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other; categorical), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), July erythemal UVR (<=180, >180-188, >188-236, and >236 J/m2), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), caloric intake (continuous), smoking history (never, former, or current smoker), and marital status (married, not married ; categorical).

Supplemental Table 1. Associations of NIH-AARP Diet and Health Study Characteristics with Malignant Melanoma Adjusted for Age and Sex (n=469,828)*

Characteristic	HR (95% CI)*	*P*-value§
BMI (kg/m^2)	1.00 (1.00-1.01)	0.60
Age (year)†	1.04 (1.03-1.04)	<0.001
Sex‡		
Male	Ref.	<0.001
Female	0.46 (0.44-0.49)	
Race		
Non-Hispanic White	Ref.	<0.001
Non-Hispanic Black	0.07 (0.04-0.13)	
Hispanic	0.19 (0.13-0.30)	
Other	0.12 (0.07-0.21)	
Smoking		
Never smoker	Ref.	<0.001
Former smoker	0.91 (0.86-0.97)	
Current smoker	0.64 (0.57-0.72)	
Education		
<=11y	Ref.	<0.001
High school graduate	1.03 (0.91-1.15)	
Some college	1.24 (1.14-1.35)	
College and beyond	1.41 (1.31-1.52)	
Physical Activity		
Never/rarely	Ref.	<0.001
1-3/mo	1.18 (1.05-1.32)	
1-2/wk	1.27 (1.15-1.40)	
3-4/wk	1.43 (1.30-1.57)	
5+/wk	1.36 (1.23-1.50)	
Family history of cancer		
No	Ref.	<0.001
Yes	1.14 (1.07-1.24)	
Marital Status		
No	Ref.	0.0005
Yes	1.14 (1.06-1.23)	
July erythemal UVR (J/m^2)		

<=180	Ref.	<0.001
>180-188	1.07 (0.99-1.15)	
>188-236	1.02 (0.94-1.10)	
>236	1.30 (1.20-1.40)	
Total Fish Intake (g/d)		
<=5.62	Ref.	<0.001
<5.62-10.01	1.19 (1.08-1.30)	
<10.01-17.09	1.22 (1.11-1.33)	
<17.09-28.31	1.29 (1.18-1.42)	
>28.31	1.24 (1.13-1.36)	
Caffeinated Coffee (500 g/d)	0.97 (0.95-0.99)	0.005
Calories (500 kcal/d)	0.97 (0.96-0.99)	0.003

* HR = hazard ratio
† Adjusted for sex
‡ Adjusted for age
§Test for significance is the Wald Chi-Square Test

Supplemental Table 2. Associations of NIH-AARP Diet and Health Study Characteristics with Melanoma in Situ Adjusted for Age and Sex (n=469,828)*

Characteristic	HR (95% CI)*	*P*-value§
BMI (kg/m^2)	0.98 (0.97-0.99)	<0.001
Age (year)†	1.03 (1.03-1.04)	<0.001
Sex‡		
Male	Ref.	<0.001
Female	0.50 (0.46-0.54)	
Race		
Non-Hispanic White	Ref.	<0.001
Non-Hispanic Black	0.02 (0.00-0.07)	
Hispanic	0.21 (0.13-0.35)	
Other	0.05 (0.02-0.15)	
Smoking		
Never smoker	Ref.	<0.001
Former smoker	0.91 (0.84-0.98)	
Current smoker	0.55 (0.47-0.64)	
Education		
<=11y	Ref.	<0.001
High school graduate	1.14 (0.98-1.32)	
Some college	1.36 (1.22-1.52)	
College and beyond	1.69 (1.53-1.86)	
Physical Activity		
Never/rarely	Ref.	<0.001
1-3/mo	1.18 (1.02-1.36)	
1-2/wk	1.35 (1.20-1.53)	
3-4/wk	1.53 (1.36-1.72)	
5+/wk	1.52 (1.34-1.72)	
Family history of cancer		
No	Ref.	0.01
Yes	1.10 (1.03-1.18)	
Marital Status		
No	Ref.	<0.001
Yes	1.35 (1.23-1.48)	

July erythemal UVR (J/m^2)		
<=180	Ref.	<0.001
>180-188	0.97 (0.89-1.07)	
>188-236	0.98 (0.89-1.08)	
>236	1.39 (1.27-1.53)	
Total Fish Intake (g/d)		
<=5.62	Ref.	<0.001
<5.62-10.01	1.21 (1.07-1.35)	
<10.01-17.09	1.28 (1.14-1.43)	
<17.09-28.31	1.30 (1.16-1.46)	
>28.31	1.29 (1.15-1.44)	
Caffeinated Coffee (500g/d)	0.98 (0.96-1.01)	0.21
Calories (500 kcal/d)	0.97 (0.95-0.99)	0.007

* HR = hazard ratio
† Adjusted for sex
‡ Adjusted for age
§Test for significance is the Wald Chi-Square Test

Supplemental Table 3. Association of total alcohol intake with total melanoma, malignant melanoma and melanoma in situ restricted to non-Hispanic White participants and only drinkers in the NIH-AARP Diet and Health Study*

Groups	Melanoma Type	Model Estimates	Total Alcohol Intake (drinks/day)				
			Non-Drinkers (Ref.)	>0-1	>1-3	>3	P_{trend}
Non-Hispanic White participants†							
	Total Melanoma§	No. cases/No. noncases	1592/98699	4274/222580	1578/65495	739/33456	—
		Age & sex-adjusted hazard ratio (95% CI)	1.00	1.12 (1.06-1.18)	1.25 (1.17-1.34)	1.14 (1.04-1.24)	<0.001
		Multivariate (fully) - adjusted hazard ratio (95% CI) †	1.00	1.07 (1.01-1.14)	1.16 (1.08-1.26)	1.19 (1.08-1.31)	0.08
	Malignant melanoma	No. cases/No. noncases	979/99312	2606/224248	914/66159	450/33745	—
		Age & sex-adjusted hazard ratio (95% CI)	1.00	1.11 (1.03-1.19)	1.17 (1.07-1.28)	1.11 (0.99-1.24)	0.004
		Multivariate (fully) - adjusted hazard ratio (95% CI) †	1.00	1.08 (0.99-1.16)	1.13 (1.03-1.25)	1.19 (1.05-1.35)	0.22
	Melanoma in situ	No. cases/No. noncases	613/99678	1668/225186	664/66409	289/33906	—
		Age & sex-adjusted hazard ratio (95% CI)	1.00	1.13 (1.03-1.24)	1.37 (1.22-1.53)	1.18 (1.02-1.36)	0.001
		Multivariate (fully) - adjusted hazard ratio (95% CI) †	1.00	1.07 (0.97-1.18)	1.21 (1.07-1.37)	1.19 (1.02-1.40)	0.22
Only Drinkers‡							
	Total Melanoma§	No. cases/No. noncases	—	4348/243395	1602/69314	746/35400	—

	Age & sex-adjusted hazard ratio (95% CI)	—	1.00	1.15 (1.08-1.22)	1.04 (0.96-1.23)	<0.001
	Multivariate (fully) - adjusted hazard ratio (95% CI) ‡	—	1.00	1.09 (1.02-1.16)	1.11 (1.02-1.22)	0.002
Malignant melanoma	No. cases/No. noncases	—	2651/245092	931/69985	453/35693	—
	Age & sex-adjusted hazard ratio (95% CI)	—	1.00	1.09 (1.01-1.18)	1.02 (0.92-1.13)	0.03
	Multivariate (fully) - adjusted hazard ratio (95% CI) ‡	—	1.00	1.06 (0.98-1.15)	1.11 (0.99-1.24)	0.07
Melanoma in situ	No. cases/No. noncases	—	1697/246046	671/70245	293/35853	—
	Age & sex-adjusted hazard ratio (95% CI)	—	1.00	1.24 (1.13-1.35)	1.07 (0.94-1.22)	<0.001
	Multivariate (fully) - adjusted hazard ratio (95% CI) ‡	—	1.00	1.13 (1.02-1.24)	1.12 (0.96-1.29)	0.001

* CI = confidence interval; — = not applicable.

† Adjusted for age (continuous), sex (male, female), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), July erythemal UVR (<=180, >180-188, >188-236, and >236 J/m2), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), caloric intake (continuous), smoking history (never, former, or current smoker), and marital status (married, not married ; categorical)

‡ Adjusted for age (continuous), sex (male, female), education (<=11y, high school, some college, college and beyond), family history of cancer (first-degree relative; yes, no), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other; categorical), BMI (continuous), physical activities (defined as physical activities over the last 12 months lasting 20 minutes or longer that caused increases in breathing or heart rate, or worked up a sweat; never/rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, >=5 times per week), July erythemal UVR (<=180, >180-188, >188-236, and >236 J/m2), total fish intake (defined as average daily fish intake including tuna intake, other fish intake, fried fish intake, and non-fried fish intake; continuous), caffeinated coffee intake (continuous), caloric intake (continuous), smoking history (never, former, or current smoker), and marital status (married, not married; categorical)

§ Total melanoma includes malignant melanoma and melanoma in situ.

Supplemental Table 4. Associations of total alcohol consumption with covariates in the NIH-AARP Diet and Health Study *

Characteristic	***P*-value§†**
BMI (kg/m^2)	<0.001
Age (year)†	<0.001
Sex‡	
Male	<0.001
Female	
Race	
Non-Hispanic White	<0.001
Non-Hispanic Black	
Hispanic	
Other	
Smoking	
Never smoker	<0.001
Former smoker	
Current smoker	
Education	
<=11y	<0.001
High school graduate	
Some college	
College and beyond	
Physical Activity	
Never/rarely	<0.001
1-3/mo	
1-2/wk	
3-4/wk	
5+/wk	
Family history of cancer	
No	<0.001
Yes	
Marital Status	
No	<0.001
Yes	
July erythemal UVR (J/m^2)	

<=180	<0.001
>180-188	
>188-236	
>236	
Total Fish Intake (g/d)	
<=5.62	<0.001
<5.62-10.01	
<10.01-17.09	
<17.09-28.31	
>28.31	
Caffeinated Coffee (500 g/d)	<0.001
Calories (500 kcal/d)	<0.001

§Test for significance is the Wald Chi-Square Test
† Test for significance is the Analysis of Variance (ANOVA) Test