Citrus consumption and risk of cutaneous malignant melanoma
by Wu, et al

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Supplementary Method: justification for the covariates included in the analysis

The present study included a number of known melanoma risk factors and potential confounders in the statistical analysis in order to better estimate the association between citrus consumption and risk of melanoma. It has been documented as early as 1980s that the effects of pigmentary traits (e.g., susceptibility to sunburn), benign nevi (mole count), ethnic origin, and family history as risk factors of melanoma were largely independent of one another.[1] Gandini et al. also conducted a series of meta-analyses which provided evidence for the associations between different risk factors (nevi, sun exposure, and phenotypic factors) and risk of melanoma.[2-4]

In view that the potential photocarcinogenic effect of psoralens requires the presence of UV radiation, sufficient adjustment for sun exposure is critical for the investigation of the association between citrus consumption and melanoma risk. We included three indicators of sun exposure in the analysis. Annual UV flux at residence is an estimate of the amount of UV radiation reaching the earth's surface within one year and has been associated with risk of melanoma.[5] Time spent in direct sunlight is an important variable to denote exposure duration to solar UV in addition to the UV flux. Severe/blistering sunburn is believed to result from high doses of intense UV radiation exposure in short increments of time and is therefore considered as a measure of acute sun exposure, whereas it is also a measure of host cutaneous sensitivity to sun exposure.[6]

Body mass index, smoking status, physical activity, and coffee intake are several lifestyle-related factors that may be associated citrus consumption (e.g., participants with higher physical activity levels were more likely to consume citrus products whereas smokers were less likely to consume citrus products, see Table 1 and Table A1), and thereby may have biased the association between citrus consumption and melanoma risk. A number of previous studies have investigated the potential association between these lifestyle-related factors and risk of melanoma.[7-11] Particularly, caffeine has been shown to prevent UV-induced carcinogenesis[12] and to inhibit growth of melanoma cells in experimental studies,[13] which is supported by epidemiologic studies.[10,11] To exclude potential residual confounding from lifestyle-related factors, it would be necessary to adjust for these variables in the analysis and perform stratified analyses according to these variables in order to demonstrate the independence of the association between citrus consumption and risk of melanoma. These variables have also been commonly adjusted for in previous studies investigating the health risk associated with dietary exposure.[14-17]

It has been suggested that alcohol intake increases sunburn severity,[18] and a recent meta-analysis supports a positive association between alcohol intake and risk of melanoma.[19] Our analyses also revealed a positive association between alcohol intake and melanoma risk among women and men (data unpublished).[20] As we explained in the manuscript introduction, vitamin C has been shown to be preferentially toxic for melanoma cells in experimental studies.[21] In addition, vitamin C supplement was also positively associated with citrus consumption (Table 1 and Table A1) and would also be necessary to adjust for as a potential confounder. Energy intake is also a lifestyle-related variable and has been commonly included as a covariate the assessment of the association between dietary intake and health risk.[14-17]

It has been demonstrated that female hormones (e.g., estrogen) manifest a variety of biological and immunological effects in the skin.[22] Estrogen may also be an underlying reason for the different prognosis of malignant melanoma among women and men.[23] Given that most of the participants in the NHS were postmenopausal

women at baseline, it would be reasonable to include postmenopausal hormone use as a potential confounder to account for potential gender difference in the assessment of citrus consumption and risk of melanoma.

In the statistical analysis, we used the most updated information for time-varying variables (e.g., body mass index) prior to each follow-up interval to take into account potential changes over the follow-up. Missing data during any follow-up period were coded as a missing indicator category for categorical variables (e.g., smoking status) and with carried-forward values for continuous variables.[24]

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Table A1. Characteristics of person-years according to frequency of overall citrus consumption among women and men separately.

	<2/wk	2-4/wk	5-6/wk	1-1.5/d	≥1.6/d
Women					
Age (year)	58.0±9.7†	59.9±9.7	61.1±9.8	60.6±9.9	60.7±9.6
Family history of melanoma (%)	6.5	6.7	7.3	7.3	7.0
Red/blonde hair (%)	14.6	14.8	14.7	15.1	16.3
Arm with moles (%)	35.1	37.0	37.2	37.6	37.6
Painful burn/blisters sun reaction as a child/adolescent (%)	14.9	14.3	13.8	13.2	13.6
Number of lifetime blistering sunburns	8.6±6.9	8.7±6.9	8.7±6.9	8.5±6.9	8.4±6.9
Annual UV flux at residence ($\times 10^{-4}$Robertson-Berger units)‡	125±26	124±26	123±25	121±24	120±24
Average time spent in direct sunlight since high school (hrs/wk)	4.8±2.7	5.0±2.7	5.0±2.7	4.9±2.7	5.0±2.7
Body mass index (kg/m^2)	26.2±5.4	26.6±5.4	26.5±5.3	26.0±5.0	25.7±5.0
Physical activity (metabolic-equivalents/wk)	13.7±19.7	15.8±21.0	17.3±21.8	18.1±22.7	21.1±26.5
Current smoking (%)	21.5	14.7	11.6	11.0	11.5
Postmenopausal status (%)	77.0	77.5	77.5	77.4	77.3
Current postmenopausal hormone use (%)§	34.5	36.6	37.5	36.4	34.7
Dietary intake					
Grapefruit (serving/d)	0.03±0.04	0.07±0.09	0.12±0.14	0.16±0.19	0.31±0.32
Grapefruit juice (serving/d)	0.01±0.03	0.03±0.07	0.07±0.12	0.09±0.18	0.23±0.44
Oranges (serving/d)	0.06±0.05	0.14±0.12	0.21±0.17	0.24±0.23	0.44±0.39
Orange juice (serving/d)	0.06±0.06	0.20±0.14	0.40±0.24	0.72±0.33	1.09±0.69
Total energy (kcal/d)	1574±442	1678±434	1764±435	1839±446	2002±468
Alcohol (g/d)	5.8±11.4	5.3±10.0	5.4±9.5	5.9±9.8	6.3±10.4
Coffee (cup/d)	1.8±1.6	1.7±1.5	1.6±1.4	1.5±1.4	1.5±1.4
Total vitamin C intake (mg/d)	280±328	313±313	348±308	382±321	476±351
Vitamin C from diet (mg/d)	91±44	121±41	151±43	180±47	248±67
Vitamin C from supplement (mg/d)	189±321	192±308	197±303	203±315	228±341
Men					
Age (year)	58.5±9.9	60.1±10.2	61.5±10.4	61.6±10.7	61.9±10.6

Family history of melanoma (%)	4.0	4.3	4.0	4.1	3.9
Red/blonde hair (%)	12.7	12.8	13.0	12.8	12.4
Arm with moles (%)	31.0	31.0	31.7	31.4	31.2
Painful burn/blisters sun reaction as a child/adolescent (%)	23.0	22.1	23.1	22.4	21.7
Number of lifetime blistering sunburns	13.0±12.0	12.8±12.0	13.0±12.1	12.4±11.9	12.5±12.1
Annual UV flux at residence ($\times 10^{-4}$ Robertson-Berger units)‡	133±28	131±27	130±27	127±27	127±27
Average time spent in direct sunlight since high school (hrs/wk)	9.1±5.4	9.2±5.4	9.3±5.5	9.1±5.5	9.1±5.5
Body mass index (kg/m^2)	26.1±4.4	26.2±4.1	26.1±4.1	25.7±4.0	25.7±4.0
Physical activity (metabolic-equivalents/wk)	27.6±37.4	31.6±37.6	34.3±39.9	34.2±39.5	39.5±44.7
Current smoking (%)	9.5	6.5	5.2	4.9	4.2
Dietary intake					
Grapefruit (serving/d)	0.02±0.04	0.07±0.09	0.13±0.15	0.17±0.21	0.35±0.43
Grapefruit juice (serving/d)	0.01±0.03	0.03±0.07	0.06±0.13	0.08±0.19	0.21±0.47
Oranges (serving/d)	0.06±0.05	0.15±0.13	0.22±0.19	0.26±0.26	0.55±0.57
Orange juice (serving/d)	0.06±0.06	0.20±0.15	0.39±0.24	0.69±0.35	1.15±0.87
Total energy (kcal/d)	1810±544	1902±534	1982±547	2046±548	2223±581
Alcohol (g/d)	11.9±17.1	11.3±15.4	11.1±14.7	11.3±14.5	10.5±14.4
Coffee (cup/d)	1.2±1.5	1.0±1.3	0.9±1.2	0.9±1.2	0.8±1.2
Total vitamin C intake (mg/d)	321±396	370±392	406±387	450±405	565±434
Vitamin C from diet (mg/d)	92±46	122±42	153±45	185±49	272±92
Vitamin C from supplement (mg/d)	229±390	248±387	253±382	265±399	293±419

* All variables other than age have been standardized to the age distribution of the cohort.
† Mean±standard deviation (for all such values).
‡ Estimate of the amount of UV radiation reaching the earth's surface of the residence within one year.
§ Percentage among postmenopausal women.

Table A2. Time trends of citrus consumption during the follow-up.

Median consumption (serving/d)	1984	1986	1990	1994	1998	2002	2006
Nurses' Health Study							
Overall citrus	0.78	0.78	0.76	0.76	0.78	0.74	0.70
Grapefruit	0.07	0.07	0.07	0.07	0.07	--	--
Grapefruit juice	0	0	0	0.02	0.01	--	--
Grapefruit and grapefruit juice (combined)	0.07	0.10	0.09	0.10	0.11	0.10	0.09
Oranges	0.07	0.10	0.12	0.12	0.14	0.13	0.13
Orange juice	0.43	0.29	0.31	0.33	0.34	0.34	0.33
Health Professionals Follow-up Study							
Overall citrus		0.86	0.81	0.81	0.83	0.78	0.73
Grapefruit		0.07	0.07	0.07	0.07	--	--
Grapefruit juice		0	0	0	0	--	--
Grapefruit and grapefruit juice (combined)		0.07	0.10	0.10	0.10	0.10	0.08
Oranges		0.07	0.10	0.14	0.14	0.14	0.14
Orange juice		0.43	0.29	0.31	0.34	0.34	0.32

Table A3. Pearson correlation matrix between intakes of citrus products and vitamin C during the follow-up.

Women	Total citrus	Grapefruit	Grapefruit juice	Grapefruit and grapefruit juice (combined)	Oranges	Orange juice	Total vitamin C	Vitamin C from diet	Vitamin C from supplement
Overall citrus	1.00								
Grapefruit	0.47	1.00							
Grapefruit juice	0.39	0.17	1.00						
Grapefruit and grapefruit juice (combined)	0.56	0.74	0.78	1.00					
Oranges	0.49	0.27	0.03	0.20	1.00				
Orange juice	0.77	0.04	0.03	0.04	0.04	1.00			
Total vitamin C	0.19	0.13	0.09	0.15	0.14	0.10	1.00		
Vitamin C from diet	0.75	0.36	0.26	0.40	0.46	0.54	0.27	1.00	
Vitamin C from supplement	0.04	0.06	0.04	0.07	0.05	-0.01	0.98	0.07	1.00
Men	Total citrus	Grapefruit	Grapefruit juice	Grapefruit and grapefruit juice (combined)	Oranges	Orange juice	Total vitamin C	Vitamin C from diet	Vitamin C from supplement
Overall citrus	1.00								
Grapefruit	0.47	1.00							
Grapefruit juice	0.35	0.14	1.00						
Grapefruit and grapefruit juice (combined)	0.55	0.77	0.72	1.00					
Oranges	0.54	0.24	0.03	0.19	1.00				
Orange juice	0.75	0.03	0.03	0.04	0.07	1.00			
Total vitamin C	0.21	0.11	0.09	0.13	0.14	0.13	1.00		
Vitamin C from diet	0.80	0.34	0.24	0.39	0.50	0.59	0.27	1.00	
Vitamin C from supplement	0.05	0.05	0.04	0.06	0.05	0.01	0.98	0.08	1.00

Table A4. Hazard ratios for incident melanoma according to frequency of citrus consumption among women and men separately.

			Serving category		P for trend
Women					
Overall citrus	<2/wk	2-4/wk	5-6/wk	≥1/d	
No. of person-years	258,988	250,413	312,769	468,784	
No. of cases	142	175	296	410	
Age-adjusted hazard ratio (95% CI)	1.00	1.12 (0.90-1.40)	1.47 (1.20-1.79)	1.48 (1.22-1.79)	<0.001
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.05 (0.84-1.31)	1.32 (1.08-1.63)	1.32 (1.08-1.62)	0.001
Grapefruit	Never	<1/wk	1/wk	≥2/wk	
No. of person-years	310,721	422,545	242,981	314,707	
No. of cases	155	331	205	332	
Age-adjusted hazard ratio (95% CI)	1.00	1.32 (1.09-1.60)	1.45 (1.17-1.79)	1.69 (1.39-2.05)	<0.001
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.21 (1.00-1.47)	1.29 (1.04-1.60)	1.44 (1.18-1.76)	<0.001
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.19 (0.98-1.46)	1.26 (1.01-1.58)	1.43 (1.15-1.77)	0.002
Grapefruit juice	Never	<1/wk	1/wk	≥2/wk	
No. of person-years	693,859	316,307	113,348	167,440	
No. of cases	475	296	102	150	
Age-adjusted hazard ratio (95% CI)	1.00	1.16 (1.00-1.35)	1.14 (0.92-1.41)	1.14 (0.95-1.38)	0.12
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.08 (0.93-1.26)	1.06 (0.85-1.31)	1.05 (0.87-1.26)	0.61
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.01 (0.87-1.18)	0.97 (0.77-1.21)	0.96 (0.79-1.16)	0.58
Grapefruit and grapefruit juice (combined)	Never	<1/wk	1/wk	≥2/wk	
No. of person-years	256,197	320,986	235,486	478,285	
No. of cases	114	257	192	460	
Age-adjusted hazard ratio (95% CI)	1.00	1.45 (1.16-1.81)	1.51 (1.20-1.91)	1.74 (1.41-2.14)	<0.001
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.34 (1.07-1.67)	1.36 (1.07-1.72)	1.48 (1.20-1.83)	0.002
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.31 (1.05-1.65)	1.32 (1.04-1.68)	1.44 (1.16-1.80)	0.006
Oranges	Never	≤1/wk	2/wk	≥3/wk	
No. of person-years	140,973	613,659	236,782	299,540	
No. of cases	69	455	241	258	

Age-adjusted hazard ratio (95% CI)	1.00	1.23 (0.95-1.58)	1.43 (1.09-1.87)	1.37 (1.05-1.80)	0.009
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.11 (0.86-1.44)	1.23 (0.93-1.62)	1.18 (0.90-1.56)	0.16
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.04 (0.80-1.35)	1.12 (0.84-1.49)	1.07 (0.81-1.42)	0.44
Orange juice	<1/wk	1-2/wk	3-4/wk	≥5/wk	
No. of person-years	317,865	300,667	261,691	410,731	
No. of cases	200	242	194	387	
Age-adjusted hazard ratio (95% CI)	1.00	1.11 (0.92-1.34)	1.01 (0.83-1.23)	1.34 (1.13-1.59)	0.002
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.07 (0.89-1.30)	0.98 (0.80-1.20)	1.27 (1.06-1.52)	0.02
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.03 (0.85-1.25)	0.94 (0.77-1.15)	1.23 (1.02-1.47)	0.04
Men					
Overall citrus	<2/wk	2-4/wk	5-6/wk	≥1/d	
No. of person-years	145,862	126,063	158,878	280,677	
No. of cases	118	148	200	351	
Age-adjusted hazard ratio (95% CI)	1.00	1.27 (1.00-1.62)	1.29 (1.03-1.62)	1.36 (1.10-1.68)	0.008
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.18 (0.92-1.50)	1.18 (0.93-1.49)	1.28 (1.03-1.59)	0.04
Grapefruit	Never	<1/wk	1/wk	≥2/wk	
No. of person-years	204,442	224,478	111,751	170,807	
No. of cases	162	258	148	249	
Age-adjusted hazard ratio (95% CI)	1.00	1.28 (1.05-1.56)	1.46 (1.17-1.83)	1.44 (1.18-1.76)	<0.001
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.15 (0.95-1.41)	1.34 (1.06-1.68)	1.29 (1.05-1.59)	0.009
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.16 (0.94-1.42)	1.35 (1.06-1.71)	1.30 (1.04-1.63)	0.01
Grapefruit juice	Never	<1/wk	1/wk	≥2/wk	
No. of person-years	413,283	166,236	54,365	77,595	
No. of cases	434	212	70	101	
Age-adjusted hazard ratio (95% CI)	1.00	1.06 (0.90-1.26)	1.11 (0.86-1.43)	1.10 (0.88-1.37)	0.29
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.00 (0.84-1.18)	1.08 (0.84-1.39)	1.11 (0.89-1.38)	0.30
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.94 (0.79-1.11)	0.98 (0.76-1.28)	1.03 (0.82-1.28)	0.86
Grapefruit and grapefruit juice (combined)	Never	<1/wk	1/wk	≥2/wk	

No. of person-years	171,468	165,559	121,501	252,951	
No. of cases	132	189	153	343	
Age-adjusted hazard ratio (95% CI)	1.00	1.24 (0.99-1.55)	1.39 (1.10-1.76)	1.40 (1.15-1.72)	0.001
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.10 (0.88-1.38)	1.24 (0.98-1.58)	1.26 (1.02-1.55)	0.02
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.08 (0.86-1.36)	1.22 (0.96-1.56)	1.24 (1.00-1.54)	0.03
Oranges	Never	≤1/wk	2/wk	≥3/wk	
No. of person-years	90,659	318,142	106,903	195,775	
No. of cases	69	373	131	244	
Age-adjusted hazard ratio (95% CI)	1.00	1.30 (1.00-1.69)	1.07 (0.80-1.45)	1.30 (0.99-1.69)	0.67
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.16 (0.89-1.50)	0.90 (0.66-1.22)	1.16 (0.88-1.52)	0.85
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.09 (0.84-1.43)	0.83 (0.61-1.13)	1.05 (0.79-1.40)	0.40
Orange juice	<1/wk	1-2/wk	3-4/wk	≥5/wk	
No. of person-years	187,642	156,182	139,405	228,249	
No. of cases	159	192	171	295	
Age-adjusted hazard ratio (95% CI)	1.00	1.24 (1.00-1.53)	1.28 (1.03-1.59)	1.34 (1.10-1.63)	0.006
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.16 (0.93-1.43)	1.21 (0.97-1.51)	1.28 (1.05-1.56)	0.02
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.13 (0.91-1.41)	1.18 (0.94-1.47)	1.25 (1.02-1.53)	0.04

* Multivariable analyses were further adjusted for family history of melanoma (yes vs. no), natural hair color (red, blonde, light brown, dark brown, black, or missing), number of arm moles (0, 1-2, 3-9, ≥10, or missing), sunburn susceptibility as a child/adolescent (none/some redness, burn, painful burn/blisters, or missing), number of lifetime blistering sunburns (0, 1-4, 5-9, ≥10, or missing), cumulative UV flux since baseline (quintiles or missing), average time spent in direct sunlight since high school (<2, 2-5, 6-9, ≥10 hrs/wk, or missing), body mass index (<25.0, 25.0-29.9, 30.0-34.9, ≥35.0 kg/m^2), physical activity (quintiles, or missing), smoking status (never, past, current with 1-14, 15-24, or ≥25 cigarettes/d, or missing), intakes of total energy (quintiles or missing), alcohol (0, 0.1-4.9, 5.0-9.9, 10.0-19.9, ≥20.0 g/d, or missing), coffee (0, <1, 1-2, ≥3 cup/d, or missing) and vitamin C from supplement (0, 1-99, 100-299, 300-599, ≥600 mg/d, or missing). Analyses for women were also adjusted for menopausal status and postmenopausal hormone use (premenopausal, postmenopausal never, past, or current use, or missing). CI denotes confidence interval.
† Multivariable analyses were additionally adjusted for consumption of the other individual citrus products listed in the table. Multivariable analyses for the combined grapefruit and grapefruit juice were additionally adjusted for consumption of oranges and orange juice.

Table A5. Sensitivity analyses for the association between citrus consumption and risk of incident melanoma.

	Serving category					P for trend
Adjusting for statin use (yes vs. no)						
Overall citrus	<2/wk	2-4/wk	5-6/wk	1-1.5/d	≥1.6/d	
No. of cases/person-years	260/404,850	323/376,476	496/471,647	488/491,559	273/257,901	
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.10 (0.93-1.30)	1.26 (1.08-1.47)	1.27 (1.09-1.49)	1.37 (1.14-1.64)	<0.001
Grapefruit	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	317/515,163	589/647,023	353/354,732	275/224,690	306/260,825	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.17 (1.01-1.35)	1.30 (1.10-1.53)	1.32 (1.11-1.58)	1.42 (1.10-1.83)	<0.001
Grapefruit juice	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	909/1,107,142	508/482,543	172/167,713	126/111,640	125/133,396	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.98 (0.87-1.10)	0.97 (0.82-1.15)	0.98 (0.81-1.20)	0.98 (0.81-1.19)	0.80
Grapefruit and grapefruit juice (combined)	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	246/427,665	446/486,545	345/356,987	357/303,786	446/427,450	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.19 (0.98-1.43)	1.27 (1.07-1.51)	1.37 (1.15-1.63)	1.32 (1.02-1.70)	0.002
Oranges	Never	≤1/wk	2/wk	3/wk	≥4/wk	
No. of cases/person-years	138/231,632	828/931,801	372/343,685	261/271,097	241/224,218	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.06 (0.88-1.28)	0.96 (0.70-1.32)	1.01 (0.82-1.26)	1.06 (0.85-1.32)	0.83
Orange juice	<1/wk	1-2/wk	3-4/wk	5-6/wk	≥1/d	
No. of cases/person-years	359/505,507	434/456,849	365/401,096	377/314,923	305/324,057	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.07 (0.93-1.23)	1.04 (0.84-1.30)	1.22 (1.05-1.41)	1.26 (1.07-1.47)	<0.001
Adjusting for antiarrhythmic use (yes vs. no)						

Overall citrus	<2/wk	2-4/wk	5-6/wk	1-1.5/d	≥1.6/d	
No. of cases/person-years	260/404,850	323/376,476	496/471,647	488/491,559	273/257,901	
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.10 (0.93-1.30)	1.26 (1.08-1.47)	1.27 (1.09-1.49)	1.37 (1.14-1.63)	<0.001
Grapefruit	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	317/515,163	589/647,023	353/354,732	275/224,690	306/260,825	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.17 (1.01-1.35)	1.30 (1.10-1.53)	1.32 (1.11-1.58)	1.42 (1.09-1.83)	<0.001
Grapefruit juice	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	909/1,107,142	508/482,543	172/167,713	126/111,640	125/133,396	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.98 (0.87-1.10)	0.97 (0.82-1.15)	0.98 (0.81-1.19)	0.98 (0.81-1.19)	0.80
Grapefruit and grapefruit juice (combined)	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	246/427,665	446/486,545	345/356,987	357/303,786	446/427,450	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.19 (0.98-1.44)	1.27 (1.07-1.51)	1.37 (1.15-1.63)	1.32 (1.02-1.70)	0.002
Oranges	Never	≤1/wk	2/wk	3/wk	≥4/wk	
No. of cases/person-years	138/231,632	828/931,801	372/343,685	261/271,097	241/224,218	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.06 (0.88-1.28)	0.96 (0.70-1.31)	1.05 (0.84-1.30)	1.07 (0.86-1.34)	0.83
Orange juice	<1/wk	1-2/wk	3-4/wk	5-6/wk	≥1/d	
No. of cases/person-years	359/505,507	434/456,849	365/401,096	377/314,923	305/324,057	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.07 (0.93-1.23)	1.04 (0.83-1.30)	1.21 (1.04-1.41)	1.25 (1.07-1.47)	<0.001
Adjusting for total vitamin C intake (quintiles)						
Overall citrus	<2/wk	2-4/wk	5-6/wk	1-1.5/d	≥1.6/d	
No. of cases/person-years	260/404,850	323/376,476	496/471,647	488/491,559	273/257,901	

Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.10 (0.93-1.30)	1.25 (1.07-1.47)	1.27 (1.08-1.50)	1.35 (1.12-1.63)	<0.001
Grapefruit	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	317/515,163	589/647,023	353/354,732	275/224,690	306/260,825	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.17 (1.02-1.36)	1.30 (1.10-1.53)	1.33 (1.11-1.59)	1.42 (1.12-1.80)	<0.001
Grapefruit juice	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	909/1,107,142	508/482,543	172/167,713	126/111,640	125/133,396	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.98 (0.87-1.10)	0.97 (0.82-1.15)	0.99 (0.81-1.20)	0.98 (0.81-1.19)	0.79
Grapefruit and grapefruit juice (combined)	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	246/427,665	446/486,545	345/356,987	357/303,786	446/427,450	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.19 (1.00-1.43)	1.27 (1.07-1.51)	1.38 (1.16-1.64)	1.32 (1.04-1.67)	0.002
Oranges	Never	≤1/wk	2/wk	3/wk	≥4/wk	
No. of cases/person-years	138/231,632	828/931,801	372/343,685	261/271,097	241/224,218	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.06 (0.88-1.28)	0.97 (0.72-1.31)	1.05 (0.85-1.31)	1.08 (0.86-1.35)	0.82
Orange juice	<1/wk	1-2/wk	3-4/wk	5-6/wk	≥1/d	
No. of cases/person-years	359/505,507	434/456,849	365/401,096	377/314,923	305/324,057	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.07 (0.93-1.24)	1.04 (0.83-1.31)	1.22 (1.04-1.42)	1.25 (1.06-1.47)	0.002
Adjusting for Alternate Healthy Eating Index-2010 (quintiles)						
Overall citrus	<2/wk	2-4/wk	5-6/wk	1-1.5/d	≥1.6/d	
No. of cases/person-years	260/404,850	323/376,476	496/471,647	488/491,559	273/257,901	
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.08 (0.91-1.27)	1.21 (1.04-1.42)	1.22 (1.04-1.43)	1.29 (1.07-1.54)	0.002

Grapefruit	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	317/515,163	589/647,023	353/354,732	275/224,690	306/260,825	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.15 (1.00-1.33)	1.26 (1.07-1.49)	1.27 (1.06-1.52)	1.35 (1.10-1.66)	0.002
Grapefruit juice	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	909/1,107,142	508/482,543	172/167,713	126/111,640	125/133,396	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.97 (0.86-1.09)	0.96 (0.81-1.14)	0.97 (0.80-1.18)	0.96 (0.79-1.16)	0.63
Grapefruit and grapefruit juice (combined)	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	246/427,665	446/486,545	345/356,987	357/303,786	446/427,450	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.17 (0.98-1.40)	1.23 (1.04-1.46)	1.32 (1.11-1.57)	1.25 (1.01-1.55)	0.02
Oranges	Never	≤1/wk	2/wk	3/wk	≥4/wk	
No. of cases/person-years	138/231,632	828/931,801	372/343,685	261/271,097	241/224,218	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.04 (0.87-1.26)	0.93 (0.71-1.22)	1.00 (0.80-1.24)	1.01 (0.81-1.26)	0.57
Orange juice	<1/wk	1-2/wk	3-4/wk	5-6/wk	≥1/d	
No. of cases/person-years	359/505,507	434/456,849	365/401,096	377/314,923	305/324,057	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.08 (0.93-1.24)	1.05 (0.86-1.29)	1.23 (1.06-1.43)	1.26 (1.07-1.47)	<0.001
Adjusting for sunscreen use (yes vs. no)						
Overall citrus	<2/wk	2-4/wk	5-6/wk	1-1.5/d	≥1.6/d	
No. of cases/person-years	260/404,850	323/376,476	496/471,647	488/491,559	273/257,901	
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.10 (0.93-1.29)	1.24 (1.06-1.45)	1.25 (1.07-1.46)	1.33 (1.11-1.59)	<0.001
Grapefruit	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	317/515,163	589/647,023	353/354,732	275/224,690	306/260,825	
Multivariable-adjusted	1.00	1.17 (1.01-1.35)	1.29 (1.09-1.52)	1.31 (1.09-1.57)	1.39 (1.07-1.81)	0.001

hazard ratio (95% CI)†						
Grapefruit juice	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	909/1,107,142	508/482,543	172/167,713	126/111,640	125/133,396	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.98 (0.87-1.09)	0.97 (0.82-1.15)	0.98 (0.81-1.19)	0.97 (0.80-1.18)	0.71
Grapefruit and grapefruit juice (combined)	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	246/427,665	446/486,545	345/356,987	357/303,786	446/427,450	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.19 (0.98-1.43)	1.26 (1.06-1.49)	1.36 (1.14-1.61)	1.30 (1.00-1.68)	0.004
Oranges	Never	≤1/wk	2/wk	3/wk	≥4/wk	
No. of cases/person-years	138/231,632	828/931,801	372/343,685	261/271,097	241/224,218	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.06 (0.88-1.28)	0.96 (0.71-1.29)	1.04 (0.84-1.29)	1.07 (0.85-1.33)	0.94
Orange juice	<1/wk	1-2/wk	3-4/wk	5-6/wk	≥1/d	
No. of cases/person-years	359/505,507	434/456,849	365/401,096	377/314,923	305/324,057	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.07 (0.93-1.23)	1.04 (0.83-1.29)	1.21 (1.04-1.40)	1.24 (1.06-1.45)	0.002
Adjusting for propensity score (continuous)‡						
Overall citrus	<2/wk	2-4/wk	5-6/wk	1-1.5/d	≥1.6/d	
No. of cases/person-years	260/404,850	323/376,476	496/471,647	488/491,559	273/257,901	
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.09 (0.93-1.29)	1.24 (1.06-1.45)	1.25 (1.07-1.46)	1.34 (1.12-1.60)	<0.001
Grapefruit	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	317/515,163	589/647,023	353/354,732	275/224,690	306/260,825	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.17 (1.01-1.35)	1.28 (1.09-1.51)	1.31 (1.09-1.56)	1.39 (1.10-1.76)	<0.001
Grapefruit juice	Never	<1/wk	1/wk	2/wk	≥3/wk	

No. of cases/person-years	909/1,107,142	508/482,543	172/167,713	126/111,640	125/133,396	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.98 (0.87-1.09)	0.97 (0.82-1.15)	0.98 (0.81-1.19)	0.97 (0.80-1.17)	0.71
Grapefruit and grapefruit juice (combined)	Never	<1/wk	1/wk	2/wk	≥3/wk	
No. of cases/person-years	246/427,665	446/486,545	345/356,987	357/303,786	446/427,450	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.18 (0.99-1.41)	1.25 (1.06-1.49)	1.35 (1.14-1.61)	1.29 (1.02-1.64)	0.004
Oranges	Never	≤1/wk	2/wk	3/wk	≥4/wk	
No. of cases/person-years	138/231,632	828/931,801	372/343,685	261/271,097	241/224,218	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.05 (0.87-1.27)	0.95 (0.71-1.28)	1.03 (0.83-1.29)	1.06 (0.85-1.32)	0.97
Orange juice	<1/wk	1-2/wk	3-4/wk	5-6/wk	≥1/d	
No. of cases/person-years	359/505,507	434/456,849	365/401,096	377/314,923	305/324,057	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.07 (0.93-1.23)	1.04 (0.83-1.30)	1.21 (1.04-1.41)	1.24 (1.06-1.46)	0.001

* Multivariable analyses were adjusted for age, family history of melanoma, natural hair color, number of arm moles, sunburn susceptibility as a child/adolescent, number of lifetime blistering sunburns, cumulative UV flux since baseline, average time spent in direct sunlight since high school, body mass index, physical activity, smoking status, intakes of total energy, alcohol, coffee and vitamin C from supplement. Vitamin C from supplement was not included in the models with adjustment for total vitamin C. Analyses for women were also adjusted for menopausal status and postmenopausal hormone use. For further details of these variables, see the Table A4 footnote. Results among women and men were pooled using the random-effects model. CI denotes confidence interval.

† Multivariable analyses were additionally adjusted for consumption of the other individual citrus products listed in the table. Multivariable analyses for the combined grapefruit and grapefruit juice were additionally adjusted for consumption of oranges and orange juice.

‡ A propensity score was generated from a logistic model for each intake and adjusted in the multivariable analyses for that intake.

Table A6. Lag analyses for the association between citrus consumption and risk of incident melanoma.

	Serving category				P for trend
2-year lag (exclude the first 2 years of follow-up)					
Overall citrus	<2/wk	2-4/wk	5-6/wk	≥1/d	
No. of cases/person-years	245/369,250	305/335,855	471/417,971	735/676,085	
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.15 (0.92-1.42)	1.32 (1.12-1.54)	1.35 (1.16-1.57)	<0.001
Grapefruit	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	315/472,261	563/579,218	322/318,282	556/429,398	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.17 (1.01-1.35)	1.23 (1.04-1.45)	1.37 (1.17-1.61)	<0.001
Grapefruit juice	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	890/1,005,207	470/427,281	158/149,101	238/217,571	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.95 (0.84-1.07)	0.94 (0.79-1.12)	0.97 (0.83-1.13)	0.54
Grapefruit and grapefruit juice (combined)	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	250/394,556	428/431,634	307/319,409	771/653,559	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.19 (1.01-1.40)	1.15 (0.97-1.37)	1.30 (1.12-1.52)	0.004
Oranges	Never	≤1/wk	2/wk	≥3/wk	
No. of cases/person-years	137/215,442	801/839,863	330/298,658	488/445,197	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.10 (0.92-1.33)	0.95 (0.65-1.39)	1.11 (0.91-1.36)	0.99
Orange juice	<1/wk	1-2/wk	3-4/wk	≥5/wk	
No. of cases/person-years	352/463,385	408/405,826	345/356,997	651/572,953	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.09 (0.94-1.26)	1.06 (0.91-1.24)	1.26 (1.10-1.44)	0.002
4-year lag (exclude the first 4 years of follow-up)					

Overall citrus	<2/wk	2-4/wk	5-6/wk	≥1/d	
No. of cases/person-years	241/331,635	283/295,032	449/365,323	700/602,383	
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.14 (0.88-1.47)	1.34 (1.14-1.58)	1.34 (1.15-1.56)	<0.001
Grapefruit	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	317/426,762	524/511,402	308/281,741	524/374,466	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.11 (0.95-1.28)	1.21 (1.02-1.44)	1.36 (1.14-1.63)	<0.001
Grapefruit juice	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	860/900,223	443/372,799	141/130,744	229/190,605	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.97 (0.86-1.09)	0.91 (0.75-1.09)	1.01 (0.81-1.25)	0.76
Grapefruit and grapefruit juice (combined)	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	254/358,592	395/377,472	291/281,830	733/576,478	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.15 (0.98-1.35)	1.14 (0.93-1.38)	1.29 (1.11-1.51)	0.003
Oranges	Never	≤1/wk	2/wk	≥3/wk	
No. of cases/person-years	133/197,179	787/746,609	302/255,641	451/394,942	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.22 (1.01-1.47)	1.04 (0.77-1.40)	1.15 (0.93-1.41)	0.73
Orange juice	<1/wk	1-2/wk	3-4/wk	≥5/wk	
No. of cases/person-years	361/418,332	360/355,562	336/313,054	616/507,423	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.98 (0.85-1.14)	1.07 (0.84-1.36)	1.20 (1.05-1.38)	0.002
6-year lag (exclude the first 6 years of follow-up)					
Overall citrus	<2/wk	2-4/wk	5-6/wk	≥1/d	
No. of cases/person-years	243/295,986	258/257,431	405/315,905	672/530,748	
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.06 (0.89-1.27)	1.26 (1.07-1.48)	1.30 (1.12-1.52)	<0.001

Grapefruit	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	305/382,964	483/446,958	308/247,250	482/322,897	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.11 (0.96-1.30)	1.32 (1.11-1.58)	1.40 (1.19-1.65)	<0.001
Grapefruit juice	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	826/800,166	412/321,386	130/113,342	210/165,174	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.97 (0.85-1.09)	0.88 (0.73-1.07)	0.99 (0.71-1.37)	0.65
Grapefruit and grapefruit juice (combined)	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	251/323,520	346/328,097	302/246,934	679/501,517	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.09 (0.91-1.31)	1.27 (1.07-1.52)	1.29 (1.10-1.51)	<0.001
Oranges	Never	≤1/wk	2/wk	≥3/wk	
No. of cases/person-years	139/178,999	744/658,213	267/215,754	428/347,102	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.15 (0.95-1.39)	0.96 (0.76-1.21)	1.10 (0.89-1.34)	0.58
Orange juice	<1/wk	1-2/wk	3-4/wk	≥5/wk	
No. of cases/person-years	342/374,658	339/308,965	318/271,981	579/444,464	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.03 (0.88-1.20)	1.12 (0.95-1.31)	1.24 (1.08-1.43)	<0.001
8-year lag (exclude the first 8 years of follow-up)					
Overall citrus	<2/wk	2-4/wk	5-6/wk	≥1/d	
No. of cases/person-years	238/262,202	238/221,913	367/269,093	636/462,143	
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.05 (0.87-1.25)	1.24 (1.05-1.46)	1.30 (1.11-1.52)	<0.001
Grapefruit	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	296/341,367	452/385,513	290/214,457	441/274,013	

Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.11 (0.95-1.30)	1.30 (1.09-1.56)	1.37 (1.15-1.65)	<0.001
Grapefruit juice	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	791/705,206	369/272,324	123/97,053	196/140,765	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.96 (0.84-1.09)	0.91 (0.75-1.11)	1.01 (0.70-1.46)	0.85
Grapefruit and grapefruit juice (combined)	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	245/289,953	329/281,906	286/213,738	619/429,754	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.12 (0.91-1.37)	1.28 (1.07-1.53)	1.26 (1.07-1.48)	0.003
Oranges	Never	≤1/wk	2/wk	≥3/wk	
No. of cases/person-years	127/161,932	706/574,257	245/177,914	401/301,247	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.29 (1.06-1.56)	1.13 (0.90-1.42)	1.23 (1.00-1.52)	0.86
Orange juice	<1/wk	1-2/wk	3-4/wk	≥5/wk	
No. of cases/person-years	337/332,863	314/264,677	302/233,231	526/384,579	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.02 (0.88-1.20)	1.14 (0.97-1.34)	1.20 (1.04-1.39)	0.004
10-year lag (exclude the first 10 years of follow-up)					
Overall citrus	<2/wk	2-4/wk	5-6/wk	≥1/d	
No. of cases/person-years	231/228,630	228/188,325	335/225,224	566/393,022	
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.08 (0.90-1.30)	1.23 (1.02-1.48)	1.25 (1.06-1.46)	0.003
Grapefruit	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	290/299,911	424/325,401	248/182,451	398/227,439	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.15 (0.98-1.35)	1.22 (1.02-1.47)	1.42 (1.19-1.68)	<0.001
Grapefruit juice	Never	<1/wk	1/wk	≥2/wk	

No. of cases/person-years	754/611,472	332/225,014	98/81,277	176/117,438	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.98 (0.86-1.13)	0.82 (0.66-1.02)	1.01 (0.74-1.46)	0.63
Grapefruit and grapefruit juice (combined)	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	246/255,617	306/238,270	252/181,925	556/359,390	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.13 (0.95-1.34)	1.21 (1.01-1.45)	1.25 (1.06-1.46)	0.01
Oranges	Never	≤1/wk	2/wk	≥3/wk	
No. of cases/person-years	133/143,746	647/493,172	229/143,586	351/254,698	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.22 (0.94-1.59)	1.20 (0.95-1.51)	1.15 (0.93-1.42)	0.80
Orange juice	<1/wk	1-2/wk	3-4/wk	≥5/wk	
No. of cases/person-years	333/290,022	283/222,904	279/196,328	465/325,949	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.99 (0.84-1.17)	1.14 (0.97-1.34)	1.13 (0.98-1.31)	0.03
12-year lag (exclude the first 12 years of follow-up)					
Overall citrus	<2/wk	2-4/wk	5-6/wk	≥1/d	
No. of cases/person-years	223/196,266	202/156,566	296/184,040	508/327,979	
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.05 (0.84-1.31)	1.26 (1.06-1.51)	1.22 (1.03-1.44)	0.006
Grapefruit	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	286/259,675	363/268,981	229/152,147	351/184,046	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.06 (0.90-1.25)	1.18 (0.98-1.43)	1.40 (1.16-1.70)	0.001
Grapefruit juice	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	695/521,633	284/181,317	103/66,532	147/95,367	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.02 (0.88-1.18)	1.01 (0.81-1.25)	1.01 (0.71-1.41)	0.98

Grapefruit and grapefruit juice (combined)	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	246/222,071	257/197,605	215/151,769	511/293,404	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.02 (0.85-1.22)	1.11 (0.91-1.35)	1.28 (1.08-1.51)	<0.001
Oranges	Never	≤1/wk	2/wk	≥3/wk	
No. of cases/person-years	129/126,009	609/415,785	181/111,555	310/211,501	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.29 (1.06-1.57)	1.21 (0.95-1.54)	1.14 (0.92-1.42)	0.69
Orange juice	<1/wk	1-2/wk	3-4/wk	≥5/wk	
No. of cases/person-years	317/248,817	244/183,161	243/161,680	425/271,194	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.97 (0.81-1.15)	1.13 (0.84-1.51)	1.16 (0.99-1.35)	0.02
14-year lag (exclude the first 14 years of follow-up)					
Overall citrus	<2/wk	2-4/wk	5-6/wk	≥1/d	
No. of cases/person-years	210/163,645	173/126,158	242/,145,980	440/267,177	
Multivariable-adjusted hazard ratio (95% CI)*	1.00	1.01 (0.83-1.24)	1.18 (0.98-1.42)	1.15 (0.97-1.37)	0.05
Grapefruit	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	259/219,234	313/215,761	207/123,974	286/143,991	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.12 (0.94-1.33)	1.27 (1.04-1.56)	1.43 (1.13-1.81)	0.004
Grapefruit juice	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	623/433,662	234/141,120	87/53,365	121/74,813	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.03 (0.88-1.21)	0.99 (0.79-1.26)	1.03 (0.67-1.60)	0.94
Grapefruit and grapefruit juice (combined)	Never	<1/wk	1/wk	≥2/wk	
No. of cases/person-years	222/188,342	228/158,937	194/123,545	421/232,136	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.11 (0.92-1.34)	1.20 (0.98-1.47)	1.32 (1.11-1.58)	0.001

Oranges	Never	≤1/wk	2/wk	≥3/wk	
No. of cases/person-years	129/107,773	536/341,113	145/82,089	255/171,986	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	1.22 (1.00-1.49)	1.23 (0.95-1.59)	1.03 (0.82-1.29)	0.39
Orange juice	<1/wk	1-2/wk	3-4/wk	≥5/wk	
No. of cases/person-years	301/206,976	206/145,746	181/129,604	377/220,633	
Multivariable-adjusted hazard ratio (95% CI)†	1.00	0.92 (0.76-1.10)	0.94 (0.65-1.35)	1.11 (0.95-1.30)	0.16

* Multivariable analyses were adjusted for age, family history of melanoma, natural hair color, number of arm moles, sunburn susceptibility as a child/adolescent, number of lifetime blistering sunburns, cumulative UV flux since baseline, average time spent in direct sunlight since high school, body mass index, physical activity, smoking status, intakes of total energy, alcohol, coffee and vitamin C from supplement. Analyses for women were also adjusted for menopausal status and postmenopausal hormone use. For further details of these variables, see the Table A4 footnote. Results among women and men were pooled using the random-effects model. CI denotes confidence interval.

† Multivariable analyses were additionally adjusted for consumption of the other individual citrus products listed in the table. Multivariable analyses for the combined grapefruit and grapefruit juice were additionally adjusted for consumption of oranges and orange juice.

Table A7. Pooled multivariable-adjusted hazard ratios for incident melanoma according to frequency of grapefruit consumption in subgroups of host risk factors and sun exposure related factors.*

		Grapefruit serving category				P for trend	P for interaction†
		Never	<1/wk	1/wk	≥2/wk		
Family history of melanoma							
No	No. of person-years	486,419	607,699	332,555	456,182		
	No. of cases	277	523	315	508		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.19 (1.02-1.39)	1.34 (1.12-1.59)	1.38 (1.17-1.62)	<0.001	0.84
Yes	No. of person-years	28,743	39,325	22,177	29,332		
	No. of cases	40	66	38	73		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.07 (0.63-1.79)	1.09 (0.64-1.87)	1.22 (0.45-3.28)	0.61	
Natural hair color							
Red/blonde	No. of person-years	59,904	81,714	45,324	63,012		
	No. of cases	54	105	64	97		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.12 (0.79-1.58)	1.15 (0.63-2.10)	1.19 (0.81-1.74)	0.60	
Light brown	No. of person-years	155,068	211,996	120,569	157,572		0.24
	No. of cases	101	201	129	208		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.18 (0.92-1.53)	1.41 (1.05-1.91)	1.55 (1.18-2.03)	<0.001	
Dark brown/black	No. of person-years	215,514	277,513	150,947	211,992		
	No. of cases	114	211	124	211		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.11 (0.87-1.42)	1.19 (0.90-1.57)	1.19 (0.92-1.54)	0.21	
Presence of arm moles							
No	No. of person-years	246,854	332,379	185,213	255,007		
	No. of cases	119	253	152	230		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.32 (1.05-1.66)	1.41 (1.08-1.83)	1.33 (1.03-1.70)	0.10	0.84

Yes	No. of person-years	128,379	184,283	103,126	140,905		
	No. of cases	114	234	137	225		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.15 (0.90-1.46)	1.24 (0.95-1.62)	1.29 (0.88-1.90)	0.21	
Sunburn susceptibility as a child/adolescent							
None/some redness	No. of person-years	226,984	313,249	180,145	238,507		
	No. of cases	109	213	121	203		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.13 (0.88-1.44)	1.07 (0.80-1.42)	1.26 (0.97-1.65)	0.17	0.40
Burn or painful burn/blisters	No. of person-years	208,665	266,593	140,584	199,342		
	No. of cases	170	319	207	321		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.14 (0.94-1.39)	1.43 (1.15-1.78)	1.33 (1.04-1.71)	0.002	
Number of lifetime blistering sunburns							
Low (<5)	No. of person-years	171,907	225,683	126,436	178,800		
	No. of cases	94	152	93	155		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	0.97 (0.74-1.28)	1.06 (0.52-2.16)	1.00 (0.72-1.39)	0.86	0.14
High (≥5)	No. of person-years	264,259	354,657	194,437	259,784		
	No. of cases	185	380	237	373		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.23 (1.02-1.48)	1.45 (1.18-1.79)	1.50 (1.13-1.98)	<0.001	
Average time spent in direct sunlight since high school							
Below median	No. of person-years	161,074	221,403	117,171	159,892		
	No. of cases	111	216	113	186		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.15 (0.90-1.46)	1.18 (0.88-1.57)	1.18 (0.71-1.97)	0.59	0.41
Above median	No. of person-years	170,667	249,167	144,447	183,309		
	No. of cases	107	253	152	260		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.30 (1.02-1.65)	1.36 (1.04-1.78)	1.54 (1.19-1.99)	0.004	

Annual UV flux at residence							
Low (<113)	No. of person-years	165,113	224,449	127,351	177,065		
	No. of cases	115	196	119	199		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	0.99 (0.77-1.26)	1.09 (0.74-1.61)	1.13 (0.87-1.47)	0.21	0.22
High (≥113)	No. of person-years	350,050	422,575	227,380	308,449		
	No. of cases	202	393	234	382		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.28 (1.07-1.53)	1.43 (1.17-1.76)	1.50 (1.22-1.85)	<0.001	

* Multivariable analyses were adjusted for age, family history of melanoma, natural hair color, number of arm moles, sunburn susceptibility as a child/adolescent, number of lifetime blistering sunburns, cumulative UV flux since baseline, average time spent in direct sunlight since high school, body mass index, physical activity, smoking status, intakes of total energy, alcohol, coffee, vitamin C from supplement and the other individual citrus products (grapefruit juice, oranges and orange juice). Analyses for women were also adjusted for menopausal status and postmenopausal hormone use. For each stratified analysis, the stratifying variable was omitted from the model. Results among women and men were pooled using the random-effects model. CI denotes confidence interval.

† For the pooled analysis, P values for interactions were calculated using the Q statistic comparing the subgroup-specific pooled multivariable-adjusted hazard ratios for grapefruit consumption as a median trend variable.

Table A8. Pooled multivariable-adjusted hazard ratios for incident melanoma according to frequency of grapefruit consumption in subgroups of additional potential confounders.*

		Grapefruit serving category				P for trend	P for interaction†
		Never	<1/wk	1/wk	≥2/wk		
Total other fruit and juice (13 items, except citrus products) intake							
Low (<1.6/d)	No. of person-years	415,413	454,529	193,860	135,399		
	No. of cases	248	396	178	150		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.16 (0.95-1.43)	1.26 (1.02-1.56)	1.29 (1.04-1.61)	0.02	0.77
High (≥1.6/d)	No. of person-years	99,749	192,494	160,872	350,116		
	No. of cases	69	193	175	431		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.18 (0.71-1.97)	1.33 (0.84-2.13)	1.36 (1.01-1.84)	0.01	
Total vegetable (26 items) intake							
Low (<3.5/d)	No. of person-years	379,383	422,919	194,670	210,894		
	No. of cases	241	360	203	256		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.04 (0.87-1.24)	1.29 (1.05-1.58)	1.29 (1.06-1.57)	0.001	0.51
High (≥3.5/d)	No. of person-years	135,780	224,104	160,063	274,619		
	No. of cases	76	229	150	325		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.47 (1.09-2.00)	1.35 (1.00-1.81)	1.52 (1.15-2.00)	0.06	
Physical screening during the previous two years‡							
No	No. of person-years	183,531	208,884	107,834	145,727		
	No. of cases	106	167	93	156		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.20 (0.93-1.55)	1.36 (1.00-1.84)	1.55 (1.17-2.05)	0.002	0.24
Yes	No. of person-years	213,879	345,796	188,157	279,878		
	No. of cases	175	392	231	392		
	Multivariable-adjusted hazard ratio (95% CI)	1.00	1.22 (1.01-1.48)	1.30 (1.05-1.61)	1.32 (1.08-1.61)	0.045	

* Multivariable analyses were adjusted for age, family history of melanoma, natural hair color, number of arm moles, sunburn susceptibility as a child/adolescent, number of lifetime blistering sunburns, cumulative UV flux since baseline, average time spent in direct sunlight since high school, body mass index, physical activity, smoking status, intakes of total energy, alcohol, coffee, vitamin C from supplement and the other individual citrus products (grapefruit juice, oranges and orange juice). Analyses for women were also adjusted for menopausal status and postmenopausal hormone use. Results among women and men were pooled using the random-effects model. CI denotes confidence interval.
† For the pooled analysis, P values for interactions were calculated using the Q statistic comparing the subgroup-specific pooled multivariable-adjusted hazard ratios for grapefruit consumption as a median trend variable.
‡ Physical screening during the previous two years was asked biennially since 1988 among both women and men.