THE ASSOCIATION BETWEEN CITRUS CONSUMPTION AND SKIN CANCER: AN ANALYSIS OF RISK AND NUTRIENT-GENE INTERACTION

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DEDICATION

To my family for their overwhelming support. To my wife, Blayre, for being my rock, my support, my cheerleader, and my confidant. For the times you've needed to shoulder a load on your own, for the sacrifices you have made to support my academic pursuits, for your patience and encouragement when I've been working late into the night and every spare moment of the weekend, for the times you've gone to sleep alone and woken up to find me already working, for supporting my goals and dreams, and for the countless times you have given of yourself to support me, I offer my most heartfelt and sincere "thank you". I could not have done this without you, and I could not ask for a better partner with which to share this achievement.

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Purpose. In the US, melanoma and non-melanoma skin cancer (NMSC) rates have increased substantially in recent decades. While many skin cancer risk factors have been established, the impact of dietary citrus, which is naturally abundant in photocarcinogenic psoralens, remains enigmatic. The purpose of this research was to investigate associations between citrus consumption and risks of melanoma and NMSC, and to conduct a genome-wide study to identify genetic variants that may modify this association.

Methods. Participants from the UK Biobank were leveraged for these analyses. Citrus consumption was collected via five rounds of 24-hour recall questionnaires, with complete citrus data available for n=210,126 participants. Ascertainment of melanoma and NMSC cases were identified by international classification of disease codes via linkage with national registries. Logistic regression was used to estimate odds ratios and 95% confidence intervals for the associations between citrus consumption and skin cancer outcomes. Individual citrus products were assessed for independent associations with skin cancer risk, and established skin cancer risk factors were tested for interaction. Joint 2-degree-of-freedom (df) and 1-df tests were used to assess interaction between total citrus consumption and genetic variants.

Results. After controlling for covariates, high total citrus consumption was significantly associated with increased melanoma risk, an association primarily driven by orange and orange juice consumption. Skin color was found to be a significant effect modifier for the

association between total citrus consumption and melanoma risk, but only before adjusting for multiple comparisons. No significant associations were observed for high total citrus consumption or consumption of any individual citrus products and NMSC risk. Significant associations for half a serving of citrus consumption and NMSC risk were likely due to chance or confounding. Index SNPs on chromosomes 3, 9, and 16 were significant according to the joint 2-df test, and 7 SNPs on chromosome 16 displayed evidence of a citrus-gene interaction.

Conclusion. My analyses provide evidence in support of high citrus consumption significantly increasing risk of melanoma, but not NMSC. I also identified SNPs on *AFG3L1P* that may modify this association. Future research should further explore these associations, particularly for NMSC and to confirm my genetic findings.

Jiali Han, PhD, co-chair

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UKBB: UK Biobank

NMSC: non-melanoma skin cancer

UV: ultraviolet

NHS: Nurses' Health Study

HPFS: Health Professionals Follow-up Study

WHI: Women's Health Initiative

ICD: International Classification of Diseases

EPIC: European Prospective Investigation into Cancer and Nutrition

GWAS: genome-wide association study

G-E: gene-environment

OR: odds ratio

HR: hazard ratio

CI: confidence Intervals

df: degrees-of-freedom

CHAPTER I: CITRUS CONSUMPTION AND MELANOMA RISK

Introduction

Over the last several decades, there has been a dramatic increase in melanoma incidence in the United States and worldwide.[1,2] In the U.S., melanoma incidence has been increasing by an average of more than 3% per year,[3] and it is expected to be the 5th and 6th most common cancer among U.S. men and women, respectively, in 2020.[4] Globally, melanoma incidence is increasing by 3-7% per year,[5] a rate faster than any other cancer,[2,5] suggesting a doubling in incidence approximately every 10-20 years.[6] This increase in incidence is not an artifactual result of increased screening,[7] and it is predicted to continue for the foreseeable future.[3,8] Melanoma is also the second most diagnosed cancer among young adults,[9] thus having the highest individual cost of cancer death regarding years of productive life lost.[10] Because of this rapid increase in melanoma rates, primary prevention research is necessary and urgent.

Several melanoma risk factors have been established, including exposure to ultraviolet (UV) radiation from the sun;[11,12] having fair skin, fair hair, light-colored eyes, or the inability to tan;[12-17] the use of solariums or sunlamps;[18,19] and a history of sunburn during adolescence.[17,20] Psoralen, a type of furocoumarin used in photochemotherapy using oral psoralen and ultraviolet-A radiation (PUVA), is also known to be photocarcinogenic.[21] Abundantly found in nature as part of a plant's natural defense against pathogens,[22] citrus products are naturally rich sources of psoralens,[22-24] leading to the hypothesis that citrus consumption may increase melanoma risk due to psoralen photocarcinogenicity.

This fairly new hypothesis has yielded inconsistent results. Research from the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) found

that high total citrus consumption was significantly associated with an increased risk of melanoma,[25] and research from the European Prospective investigation into Cancer and Nutrition cohort (EPIC) found high citrus fruit consumption (but not total citrus consumption) to increase melanoma risk.[26] Conversely, an analysis of the Women's Health Initiative (WHI) found no association between citrus consumption and melanoma risk, save for among those with the highest consumption of citrus juice and spent the most time outdoors.[27] The only other research to investigate this association is an Italian case-control study of the Mediterranean diet, which found high citrus consumption to be a protective factor.[13] This sparse, conflicting evidence represents a critical gap in the melanoma knowledge base and highlights the need for further investigation of citrus as a potential melanoma risk factor. Furthermore, these previous studies were limited by samples of health care professionals,[25] postmenopausal women,[27] hospital patients,[13] or with possible inter-country heterogeneity,[26] limiting the generalizability.

The purpose of the current study is to address these gaps in knowledge by performing the following analyses in the UK Biobank (UKBB), a large, population-based, prospective cohort: 1) investigate the association between total citrus consumption and melanoma risk, 2) investigate the association between individual citrus products and melanoma risk, and 3) test for interactions between total citrus intake and established melanoma risk factors. This information will be particularly useful to cancer researchers, clinicians, interventionists, and anyone interested in the primary prevention of melanoma. I believe the results of the current study will increase current knowledge and understanding of skin cancer risk factors, and, upon further validation, can serve as an empirical basis for future primary prevention interventions.

Methods

Study Population

As described in greater detail elsewhere,[28-30] the UKBB is a major health resource founded in the United Kingdom with the goal of improving the diagnosis, treatment, and prevention of a variety of serious illness, including cancer, heart disease, stroke, diabetes, and depression, among others. For this large, prospective cohort, a sample of 500,000 participant volunteers aged 40-69 years old were recruited from 2006-2010. At baseline, all 500,000 UKBB participants were assessed at 22 assessment centers throughout the UK to provide physical measures, samples of blood, urine, and saliva, and detailed personal information. Follow-up took place via linkage of participants' past and future medical records, and by the completion of online questionnaires every few years.

Assessment of Citrus Consumption

In the UKBB, citrus consumption data were collected via five 'rounds' of 24-hour recall questionnaires. The first 'round' took place in the assessment center between April 2009-September 2010. The next four 'rounds' were administered electronically via email invitations to complete the online questionnaire. For the first two online 'rounds', participants were given until 3 days after the invitation date to complete the questionnaire; for the latter two online 'rounds', participants were given up to 14 days after the invite to complete the questionnaire. The four online 'rounds' were sent to participants during: February-April, 2011; June-September, 2011; October-December 2011; and April-June, 2012, respectively. A total of n=210,126 participants completed at least one 24-hour dietary recall assessment over the course of these 5 'rounds' and

provided complete citrus consumption data for the current analysis. Compared with an interviewer-administered 24-hour recall, the web-based 24-hour recall used by the UKBB has yielded Spearman's correlation coefficients of 0.5-0.9 (mean of 0.6).[31] Additionally, between the first and last dietary assessments, at least 70% of UKBB participants reported nutrient intake in the same or adjacent intake category (82% reported the same or adjacent category for fresh fruit intake).[32]

To measure orange consumption, participants were asked: "How may oranges (fresh, frozen, canned) did you have?". For grapefruit consumption, participants were asked: "How many whole/servings of grapefruit (fresh, frozen, canned) did you have?", and for satsuma consumption, participants were asked: "How many whole/servings of orange-like small fruits e.g. satsuma, clementine, mandarin (fresh, frozen, canned) did you have?". For each of these measures, participants had the option to select: "half", "1", "2", "3", or "4+". For orange juice and grapefruit juice intake, participants were asked: "How many glasses/cartons/250ml of pure orange (grapefruit) juice did you drink yesterday?", with possible responses of: "half", "1", "2", "3", "4", "5", and "6+". A cumulative average of participants' citrus consumption over the 5 'rounds' of nutritional data collection was used to assess consumption of each citrus product.

Ascertainment of Melanoma Cases

International Classification of Diseases (ICD) codes were used to identify melanoma outcome data, which are acquired via linkage with national registries. These registries acquire cancer diagnosis data from various sources dating back to the registries' inception in the early 1970s. These sources include hospitals, treatment centers, nursing homes, hospices, general practices, screening programs, death certificates, and others. For

participants residing in England and Wales, cancers diagnosed from 1971-1978, 1979-1994, and 1995-present are coded according to the ICD 8,9, and 10, respectively. For those residing in Scotland, cancer diagnoses through the end of 1996 and from the start of 1997 are coded according to ICD 9 and 10 classifications, respectively. ICD codes C43.0-9 were used to identify melanoma cases.

Statistical Analysis

As done in previous studies,[25,27] only White/Caucasian participants were included in the analyses due to low melanoma incidence in ethnic minorities.[33-36] This resulted in *n*=11,162 (5.3%) of the 210,126 participants with complete citrus data being excluded, leaving *n*=198,964 to be included in the analyses. To estimate the effect of total citrus consumption, we combined intake of all citrus products into a single composite variable with five groups: 0, half, >half-1, >1-2, and > 2 servings, with 0 servings as the reference group. Consumption of each citrus product was categorized into four groups: 0, half, >half-1, and >1 serving, with 0 servings as the reference group. Chi-square tests and one-way ANOVA were used to test for participant differences in categorical and continuous variables of interest, respectively, according to levels of total citrus consumption. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between citrus consumption and melanoma risk. Three models were constructed for these analyses, one age adjusted model and two multivariable adjusted models. For the analysis of total citrus, we controlled for sex, education, income, physical activity, body mass index (BMI), smoking status, alcohol intake, and total energy intake in the first multivariable adjusted model (controlling for demographic variables) and additionally for coffee intake, tanning ability, childhood sunburn

occasions, natural hair color, skin color, average time spent outdoors in summer, solarium/sunlamp use, use of UV protection, and ICD-confirmed history of non-melanoma skin cancer (NMSC) in the second multivariable adjusted model (controlling for demographic and sun-exposure variables). For analyses of individual citrus products, the first multivariable adjusted model controlled for all variables in the first and second models for total citrus, and the second model additionally adjusted for consumption of the other individual citrus products. Trend tests across groups were performed by assigning median values to each category then treating them as continuous variables.

Likelihood ratio tests comparing the model with and without product terms were used to test for potential interactions between reported skin cancer risk factors and total citrus consumption. When evidence of interaction existed, odds ratios and confidence intervals were calculated for each stratum. SAS software version 9.4 (SAS Institute, Cary, NC) was used for all statistical tests, all tests were 2-tailed, with $p<.05$ indicating statistical significance. All data was stored using Karst, a high-performance computing cluster, at Indiana University.

Results

In the UKBB population, total citrus intake significantly varied by several demographic and sun exposure variables (Table 1.1). Relative to those with no total citrus consumption, participants with higher intakes of total citrus were more likely to be older, male, have a higher education and income, less likely to smoke, and more physically active. A number of sun-exposure variables also varied by citrus intake. Relative to those with no citrus consumption, participants who consumed more citrus were less likely to use sunlamps or solariums, more likely to report sunburns during childhood, and less likely to describe themselves as olive skinned.

There were a total of 1,592 melanoma cases among the 198,964 participants included in this analysis. Total citrus consumption was significantly associated with melanoma risk, as participants consuming the most total citrus were at a significantly increased risk for melanoma (Table 1.2). In the fully adjusted model, the ORs (95% CIs) were 0.98 (0.82-1.16) for ½ a serving, 1.07 (0.91-1.25) for >½ to 1 serving, 1.13 (0.93-1.36) for >1 to 2 servings, and 1.63 (1.24-2.12) for >2 servings of total citrus per day relative to our reference group of no citrus consumption (*p*-trend = 0.0051).

Of the individual citrus products analyzed, consumption of oranges and orange juice were independently associated with melanoma risk (Table 1.3). In the fully adjusted models, participants in the highest category of orange and orange juice consumption (>1 serving per day) had a significantly increased risk of melanoma relative to those with no consumption. Relative to no consumption, ORs (95% CIs) were 1.79 (1.07-2.78) and 1.54 (1.10-2.10) for the highest consumption of oranges and orange juice, respectively (*p*-trend = 0.043 and 0.021). No other orange or orange juice serving categories were

significant in either of the multivariable-adjusted models, and no significant results were seen for any other citrus product.

I tested for interactions between total citrus consumption and other melanoma risk factors, including coffee intake, tanning ability, childhood sunburn occasions, natural hair color, skin color, average time outdoors in summer, solarium/sunlamp use, and sun/UV protection use. Before adjustment for multiple comparisons, I found statistical evidence of interaction only for skin color (p for interaction = 0.019) and then conducted stratified analyses to evaluate this potential interaction (Table 1.4). A linear relationship between citrus consumption and melanoma risk was observed among participants with a fair or very fair skin complexion, with a significantly increased melanoma risk associated with those in the highest category of total citrus consumption. Relative to no citrus consumption, ORs (95% CIs) of 1.05 (0.87-1.26), 1.10 (0.93-1.30), 1.17 (0.96-1.42), and 1.75 (1.31-2.29) were observed among fair/very fair participants with total citrus consumptions of ½, >½ to 1, >1 to 2, and >2 daily servings, respectively (p-trend = 0.0015). A decreased melanoma risk was observed among olive-skinned participants consuming half a serving of citrus per day (OR [95% CI] = 0.48 [0.23-0.89]).

Discussion

In the current study, I found a significant association between total citrus consumption and melanoma risk after adjusting for potential confounders. This result is consistent with findings from the NHS and HPFS,[25] but not with those from EPIC[26] or the WHI.[27] In the NHS and HPFS study, participants with the highest total citrus consumption had a 36% increased risk of melanoma. The greater effect size in the current analysis (63% increased risk) may reflect the fact that the NHS and HPFS is comprised of health care professionals who may be more likely to work indoors and/or have greater knowledge of UV protection compared with our UKBB sample drawn from the general population. The greater effect size in the current analysis could also be a reflection of differences in the assessment of citrus consumption. In the current analysis, our reference group for total citrus was zero intake and the highest intake category was >2 servings per day. In the NHS/HPFS, the reference group for total citrus was <twice/week and the highest intake category was $\geq$1.6 times/day. As our evaluation of the effect of total citrus was based on a wider range of citrus intake with zero consumption as the referent, our larger effect size is plausible.

In the WHI, there was no significant association between total citrus and melanoma risk. The null finding from the WHI could potentially be explained by the fact that the WHI cohort is comprised of postmenopausal women. Not only does an older, all-female sample detract from generalizability, but since men have a greater risk of melanoma,[37,38] and older women are less likely than younger women to engage in certain melanoma-risk behaviors, such as indoor tanning, solarium use, and sunbathing,[39-42] it is plausible to see lower risk estimates in this sample. In EPIC, there was also no significant

association between melanoma risk and total citrus intake (hazard ratio [HR] [95% CI] = 0.98 [0.83-1.15]), but there was a significant association between citrus fruit intake and melanoma risk (HR [95% CI] = 1.23 [1.02-1.48]).[26] These results respectively oppose and support our current hypothesis/findings. The inconsistency for total citrus consumption between the current analysis and the EPIC study could possibly be due to study population differences. While the current study utilizes an all-British sample, EPIC combined data from several different European countries with differing levels of citrus intake (highest = 115.8 grams/day in Spain, lowest = 64.5 grams/day in Denmark), as well as other possible physical or behavioral characteristics. In addition to differences in citrus consumption, differing countries may have different food processing or agricultural regulations that could possibly influence furocoumarin concentrations in citrus products from country to country and therefore impact study results.

Results of all four of these studies (the current analysis, NHS/HPFS, WHI, and EPIC) are in contrast with the findings of Fortes. et al., who reported a protective effect of citrus for melanoma risk for high citrus fruit consumption (>5 times/week) relative to low citrus fruit consumption (up to twice/week) (OR [95% CI] = 0.51 [0.32-0.80]).[13] However, this small, Italian case-control study was based on a total of 304 melanoma cases and utilized hospital patients for cases and controls. Furthermore, this study did not control for several key dietary or sun-exposure variables, such as total energy intake, other nutritional variables in the analysis, time spent outdoors, tanning ability, solarium/sunlamp use, or use of sun/UV protection, increasing the possibility that any of these factors could have contributed to the observed outcome. Because of these limitations, I believe that the results of the current study, and of the NHS/HPFS and WHI

analyses, provide a more reliable estimation of the association between citrus consumption and melanoma risk.

I also found that orange and orange juice consumption were independently associated with melanoma risk. These findings are consistent with results from the NHS and HPFS, which found a significant increased risk associated with orange consumption (age-adjusted model only) and a 25% increased risk associated with orange juice consumption. Unlike NHS/HPFS findings, the current study found no significant results associated with grapefruit consumption. Although grapefruits are rich sources of psoralens,[24] and have a higher furocoumarin concentrations than oranges,[23] our UKBB sample had low grapefruit consumption (5.7% of our UKBB cases reported grapefruit consumption vs. 83% of cases in the NHS/HPFS), limiting power for statistical evaluation.

In subgroup analyses, skin color was found to play a significant role in the relationship between total citrus consumption and melanoma risk, but only before adjustment for multiple comparisons. Participants with fair to very fair skin complexion also had a citrus-associated melanoma risk that was greater than participants with olive complexions. This result is biologically plausible as fairer skin is a known melanoma risk factors[12,15] due to the lack of melanin, which helps protect the skin against UV radiation.[43] As psoralens and furocoumarins are known photocarcinogens in mice[44,45] and humans,[46-49] due to their photosensitizing properties,[44] it is reasonable to speculate that the potential photocarcinogenic effect of psoralen-rich foods on melanoma could be magnified among people with fairer skin who are particularly susceptible to sun/UV damage.

As with all studies, the current analysis has limitations. Dietary data were self-reported, likely resulting in nondifferential misclassification. However, I calculated a cumulative average intake over several timepoints to minimize random error, and 82% of participants reported the same or adjacent intake category across timepoints.[32] Another potential limitation of this study could be the difficulty of generalizing results from United Kingdom-based data to the U.S. population. Average citrus consumption between these two nations represents a particular challenge to this; however, estimates reveal that the U.S. and the U.K. consume roughly the same amount fruit per day,[50-52] making it plausible that citrus consumption is also approximately equal. Differences in climate could be another challenge to generalizability, as there are much fewer hours of sunshine in the U.K. relative to the U.S.[53,54] However, this could mean that the current analysis may be biased towards the null, and implications for the U.S. population could be even greater due to the greater sunshine exposure. Finally, these analyses are limited by the inability to control for family history of melanoma. Melanoma can be heritable,[55,56] so residual confounding from the inability to adjust for this factor is a limitation.

In conclusion, our current analysis, based on a large, prospective, population-based cohort, found that high citrus consumption was associated with a significantly increased risk of melanoma. Of the citrus products examined, consumption of oranges and orange juice were independently associated with melanoma risk. These findings support previous evidence of the photosensitivity and photocarcinogenicity of psoralens and support the hypothesis that high consumption of psoralen-rich foods may increase melanoma risk. Although biologically plausible, further investigations are needed to confirm our findings, particularly those which support a potential effect modification by

skin color. Further investigation and confirmation of these findings could lead to updated sun-exposure guidance and improved melanoma risk-reduction strategies.

Table 1.1. Demographic and sun-exposure characteristics of UK Biobank study participants according to daily total citrus intake.

		Total citrus intake					
	Total	None	½ serving	>½-1 serving	>1-2 servings	>2 servings	*p*-value
***N* (%)**	198,964	82,297 (41.4%)	36,828 (18.5%)	45,829 (23.0%)	26,740 (13.4%)	7,270 (3.7%)	
Age at recruitment	56.2 (7.9)	55.8 (8.1)	56.3 (7.9)	56.6 (7.8)	56.8 (7.6)	56.9 (7.6)	<.0001
Years (mean/SD)							
Sex							<.0001
Male	89,022 (44.7%)	36,104 (43.9%)	16,139 (43.8%)	20,814 (45.4%)	12,382 (46.3%)	3,583 (49.3%)	
Female	109,942 (55.3%)	46,193 (56.1%)	20,689 (56.2%)	25,015 (54.6%)	14,358 (53.7%)	3,687 (50.7%)	
Education							<.0001
College or university degree	84,279 (42.4%)	29,702 (36.1%)	16,404 (44.5%)	21,087 (46.0%)	13,178 (49.3%)	3,908 (53.8%)	
A level/AS level	26,312 (13.2%)	10,772 (13.1%)	5,027 (13.7%)	6,185 (13.5%)	3,446 (12.9%)	882 (12.1%)	
O level/GCSE	41,543 (20.9%)	19,095(23.2%)	7,564 (20.5%)	8,877 (19.4%)	4,823 (18.0%)	1,184 (16.3%)	
CSE	8,391 (4.2%)	4,428 (5.4%)	1,390 (3.8%)	1,563 (3.4%)	831 (3.1%)	179 (2.5%)	
NVQ, HND, or HNC	10,786 (5.4%)	5,061 (6.2%)	1,789 (4.9%)	2,319 (5.1%)	1,299 (4.9%)	318 (4.4%)	
Other professional degree	9,816 (4.9%)	3,976 (4.8%)	1,850 (5.0%)	2,294 (5.0%)	1,349 (5.0%)	347 (4.8%)	
Missing	17,837 (9.0%)	9,263 (11.3%)	2,804 (7.6%)	3,504 (7.7%)	1,814 (6.8%)	452 (6.2%)	
Income							<.0001
Less than £30,999	70,866 (35.6%)	31,524 (38.3%)	12,648 (34.3%)	15,654 (34.2%)	8,782 (32.8%)	2,258 (31.1%)	
£31,000 - £51,999	51,176 (25.7%)	20,522 (24.9%)	9,709 (26.4%)	11,977 (26.1%)	7,120 (26.6%)	1,848 (25.4%)	
£52,000 and up	57,037 (28.7%)	21,344 (25.9%)	10,953 (29.7%)	13,782 (30.1%)	8,408 (31.4%)	2,550 (35.1%)	
Missing	19,885 (10.0%)	8,907 (10.8%)	3,518 (9.6%)	4,416 (9.6%)	2,430 (9.1%)	614 (8.5%)	
Tanning ability							<.0001
Never tan, only burn	34,027 (17.4%)	14,349 (17.7%)	6,108 (16.9%)	7,749 (17.2%)	4,561 (17.4%)	1,260 (17.7%)	
Mildly/occasionally tanned	43,003 (22.0%)	17,562 (21.7%)	8,079 (22.3%)	10,110 (22.4%)	5,764 (21.9%)	1,488 (20.9%)	
Moderately tanned	80,326 (41.0%)	32,647 (40.3%)	15,011 (41.4%)	18,711 (41.5%)	11,025 (41.9%)	2,932 (41.1%)	
Very tanned	38,381 (19.6%)	16,391 (20.3%)	7,041 (19.4%)	8,559 (19.0%)	4,939 (18.8%)	1,451 (20.4%)	

Solarium/sunlamp use	0.45 (4.1)	0.54 (4.7)	0.41 (3.5)	0.40 (3.3)	0.37 (4.0)	0.31 (4.1)	<.0001
Times per year (mean/SD)							
Childhood sunburn occasions	1.95 (6.2)	1.89 (5.7)	2.03 (7.9)	1.93 (5.1)	1.95 (3.6)	2.28 (13.3)	<.0001
Before age 15 (mean/SD)							
Natural hair color							0.0003
Red/blonde	30,898 (15.6%)	12,989 (15.8%)	5,605 (15.2%)	7,121 (15.6%)	4,023 (15.1%)	1,160 (16.0%)	
Light brown	80,795 (40.7%)	33,279 (40.5%)	15,053(40.9%)	18,648 (40.7%)	10,967 (41.1%)	2,848 (39.2%)	
Dark brown/black	85,366 (43.0%)	35,142 (42.8%)	15,837 (43.0%)	19,688 (43.0%)	11,502 (43.1%)	3,197 (44.0%)	
Other	1,702 (0.9%)	777 (1.0%)	312 (0.9%)	334 (0.7%)	222 (0.8%)	57 (0.8%)	
Skin color							0.0004
Dark/light olive	40,134 (20.2%)	16,820 (20.4%)	7,419 (20.2%)	9,160 (20.0%)	5,312 (19.9%)	1,423 (18.1%)	
Fair	142,125 (71.4%)	58,381 (70.9%)	26,343 (71.5%)	32,886 (71.8%)	19,302 (72.2%)	5,213 (71.7%)	
Very fair	16,705 (8.4%)	7,096 (8.6%)	3,066 (8.3%)	3,783 (8.3%)	2,126 (8.0%)	634 (8.7%)	
Time spent outdoors in summer	3.52 (2.2)	3.57 (2.3)	3.43 (2.1)	3.49 (2.2)	3.48 (2.2)	3.51 (2.2)	<.0001
Hours per day (mean/SD)							
Use of sun/ultraviolet protection							<.0001
Always	40,618 (20.5%)	16,705 (20.4%)	7,285 (19.9%)	9,462 (20.7%)	5,601 (21.0%)	1,565 (21.6%)	
Most of the time	78,033 (39.4%)	31,378 (38.3%)	14,715 (40.1%)	18,326 (40.1%)	10,753 (40.4%)	2,861 (39.5%)	
Sometimes	65,769 (33.2%)	27,397 (33.5%)	12,323 (33.6%)	15,122 (33.1%)	8,581 (32.2%)	2,346 (32.4%)	
Never/rarely	13,651 (6.9%)	6,368 (7.7%)	2,366 (6.5%)	2,744 (6.0%)	1,701 (6.4%)	472 (6.5%)	
History of NMSC							<.0001
Yes	9,873 (5.0%)	3,790 (4.6%)	1,928 (5.2%)	2,396 (5.2%)	1,427 (5.3%)	359 (4.9%)	
No	189,091 (95.0%)	78,507 (95.4%)	34,900 (94.8%)	43,460 (94.8%)	25,313 (94.7%)	6,911 (95.1%)	

Coffee consumption	0.76 (0.8)	0.63 (0.8)	0.89 (0.9)	0.81 (0.9)	0.87 (0.9)	0.89 (0.9)	<.0001
Cups per day (mean/SD)							
BMI	26.9 (4.6)	27.3 (4.8)	26.7 (4.5)	26.7 (4.5)	26.6 (4.4)	26.7 (4.7)	<.0001
kg/m^2 (mean/SD)							
Smoking status							<.0001
Never	111,289 (56.1%)	43,761 (53.3%)	20,992 (57.1%)	26,396 (57.7%)	15,789 (59.2%)	4,351 (60.0%)	
Previous	71,890 (36.2%)	30,245 (36.8%)	13,283 (36.1%)	16,462 (36.0%)	9,406 (35.2%)	2,494 (34.4%)	
Current	15,369 (7.7%)	8,104 (9.9%)	2,497 (6.8%)	2,867 (6.3%)	1,491 (5.6%)	410 (5.7%)	
Alcohol intake							<.0001
Never/special occasions only	29,496 (14.8%)	13,865 (16.9%)	4,852 (13.2%)	6,077 (13.3%)	3,639 (13.6%)	1,063 (14.6%)	
Less than 3 times/week	71,764 (36.1%)	30,391 (36.9%)	13,211 (35.9%)	16,224 (35.4%)	9,389 (35.1%)	2,549 (35.1%)	
Three times/week or more	97,650 (49.1%)	38,011 (46.2%)	18,759 (51.0%)	23,513 (51.3%)	13,709 (51.3%)	3,658 (50.3%)	
Physical activity							<.0001
Low	30,922 (15.5%)	13,685 (16.6%)	5,858 (15.9%)	6,731 (14.7%)	3,694 (13.8%)	954 (13.1%)	
Moderate	71,727 (36.1%)	28,601 (34.8%)	13,631 (37.0%)	16,986 (37.1%)	9,944 (37.2%)	2,565 (35.3%)	
High	66,478 (33.4%)	26,537 (32.3%)	12,110 (32.9%)	15,549 (33.9%)	9,433 (35.3%)	2,849 (39.2%)	
Missing	29,837 (15.0%)	13,474 (16.4%)	5,229 (14.2%)	6,563 (14.3%)	3,669 (13.7%)	902 (12.4%)	

Data shown are mean (SD) for continuous variables or N (%) for categorical variables

Some percentages do not add up to 100% due to rounding

Abbreviation: NMSC, non-melanoma skin cancer

Table 1.2. Melanoma risk according to frequency of total citrus consumption among study participants in the UK Biobank.

Citrus type	Serving category					
	None	½ serving	>½-1 serving	>1-2 servings	>2 servings	*p*-trend
Total citrus						
N (number of cases)	82,297 (606)	36,828 (277)	45,829 (398)	26,740 (229)	7,270 (82)	
Age-adjusted OR (95% CI)	1.00	1.01 (0.87-1.16)	**1.15 (1.01-1.31)**	1.13 (0.97-1.31)	**1.49 (1.17-1.86)**	0.0009
Multivariable-adjusted OR1 (95% CI)[1]	1.00	0.98 (0.85-1.13)	1.12 (0.98-1.27)	1.10 (0.94-1.28)	**1.44 (1.14-1.81)**	0.0047
Multivariable-adjusted OR2 (95% CI)[2]	1.00	0.98 (0.82-1.16)	1.07 (0.91-1.25)	1.13 (0.93-1.36)	**1.63 (1.24-2.12)**	0.0051

Note: bold font indicates statistical significance

[1]Further adjusted for: sex (male, female), education (categorical – college or university degree; A level/AS level; O level/GCSE, CSE; NVQ, HND, or HNC; other professional degree; none of the preceding), income (categorical – less than £30,999, £31,000 - £51,999, £52,000 and up, missing), physical activity (categorical – low, moderate, high, missing), BMI (continuous), smoking status (categorical – never, previous, current), alcohol intake (categorical – never/special occasions only, <3 times/week, $\geq$ 3 times/week), and total energy intake (quartiles – KJ).

[2]Additionally adjusted for: coffee intake (continuous – mean cups/day), tanning ability (categorical – never tan, mildly/occasionally tan, moderately tan, very tanned), childhood sunburn occasions (continuous), natural hair color (categorical – red/blonde, light brown, dark brown/ black, other), skin color (categorical – dark/light olive, fair, very fair), average time spent outdoors in summer (continuous – hours/day), sunlamp/solarium use (continuous – times/year), sun/UV protection use (categorical – always, most of the time, sometimes, never/rarely), and history of non-melanoma skin cancer (yes, no).

Abbreviation: OR, odds ratio; CI, confidence interval

Table 1.3. Melanoma risk according to frequency of individual citrus product consumption among study participants in the UK Biobank.

Citrus type	Serving category				
	None	½ serving	>½-1 serving	>1 serving	*p*-trend
Grapefruit					
N (number of cases)	188,932 (1,502)	8,240 (70)	1,724 (19)	68 (1)	
Age-adjusted OR (95% CI)	1.00	0.99 (0.78-1.26)	1.29 (0.79-1.98)	1.81 (0.10-8.22)	0.30
Multivariable-adjusted OR1 (95% CI)[1]	1.00	1.04 (0.78-1.37)	1.56 (0.90-2.48)	2.49 (0.14-11.63)	0.075
Multivariable-adjusted OR2 (95% CI)[2]	1.00	1.04 (0.77-1.37)	1.54 (0.89-2.45)	2.41 (0.14-11.25)	0.089
Grapefruit juice					
N (number of cases)	190,053 (1,521)	6,117 (40)	2,479 (28)	315 (3)	
Age-adjusted OR (95% CI)	1.00	0.81 (0.58-1.09)	1.42 (0.95-2.02)	1.23 (0.30-3.21)	0.30
Multivariable-adjusted OR1 (95% CI)[1]	1.00	0.72 (0.47-1.05)	1.23 (0.73-1.92)	2.07 (0.51-5.94)	0.52
Multivariable-adjusted OR2 (95% CI)[2]	1.00	0.71 (0.46-1.03)	1.20 (0.71-1.89)	1.96 (0.48-5.23)	0.60
Orange					
N (number of cases)	162,721 (1,263)	21,102 (195)	13,302 (111)	1,839 (23)	
Age-adjusted OR (95% CI)	1.00	1.14 (0.97-1.32)	1.00 (0.82-1.21)	1.55 (0.99-2.29)	0.15
Multivariable-adjusted OR1 (95% CI)[1]	1.00	1.02 (0.83-1.23)	1.12 (0.89-1.39)	**1.83 (1.10-2.85)**	0.030
Multivariable-adjusted OR2 (95% CI)[2]	1.00	1.00 (0.82-1.21)	1.11 (0.88-1.38)	**1.79 (1.07-2.78)**	0.043
Orange Juice					
N (number of cases)	126,576 (968)	38,782 (312)	28,976 (260)	4,630 (52)	
Age-adjusted OR (95% CI)	1.00	1.04 (0.92-1.19)	**1.17 (1.02-1.34)**	**1.51 (1.13-1.98)**	0.0007
Multivariable-adjusted OR1 (95% CI)[1]	1.00	0.96 (0.82-1.13)	1.10 (0.92-1.30)	**1.57 (1.12-2.14)**	0.016
Multivariable-adjusted OR2 (95% CI)[2]	1.00	0.96 (0.82-1.13)	1.09 (0.92-1.29)	**1.54 (1.10-2.10)**	0.021
Satsuma					
N (number of cases)	157,266 (1,228)	20,989 (187)	14,592 (122)	6,117 (55)	
Age-adjusted OR (95% CI)	1.00	1.14 (0.97-1.32)	1.06 (0.88-1.27)	1.16 (0.88-1.51)	0.17
Multivariable-adjusted OR1 (95% CI)[1]	1.00	1.19 (0.98-1.43)	1.04 (0.82-1.30)	1.29 (0.92-1.74)	0.11

Multivariable-adjusted OR2 (95% CI)[2]	1.00	1.20 (0.99-1.45)	1.03 (0.82-1.31)	1.29 (0.92-1.74)	0.11

Note: bold font indicates statistical significance. Four levels of citrus intake were used for consumption of grapefruit, grapefruit juice, and oranges due to a lack of observations above the >1 serving category.

[1]Multivariable analyses were further adjusted for: sex (male, female), education (categorical – college or university degree; A level/AS level; O level/GCSE, CSE; NVQ, HND, or HNC; other professional degree; none of the preceding), income (less than £30,999, £31,000 - £51,999, £52,000 and up, missing), physical activity (low, moderate, high, missing), BMI (continuous), smoking status (never, previous, current), alcohol intake (never/special occasions only, < 3 times/week, $\geq$ 3 times/week), coffee intake (continuous – mean cups/day), tanning ability (never tan, mildly/occasionally tan, moderately tan, very tanned), childhood sunburn occasions (continuous), natural hair color (red/blonde, light brown, dark brown/black, other), skin color (dark/light olive, fair, very fair), average time spent outdoors in summer (continuous – hours/day), sunlamp/solarium use (continuous – times/year), sun/UV protection use (always, most of the time, sometimes, never/rarely), total energy intake (quartiles – KJ), and history of non-melanoma skin cancer (yes, no).

[2]Additionally adjusted for consumption of other individual citrus products listed in table

Abbreviation: OR, odds ratio; CI, confidence interval

Table 1.4. Melanoma risk according to frequency of total citrus consumption according to melanoma risk factor variables with evidence of interaction with citrus consumption among study participants in the UK Biobank.

Melanoma risk factor	Total citrus serving category					
	None	½ serving	>½-1 serving	>1-2 servings	>2 servings	*p*-trend
Skin color						
Dark/light olive						
N (number of cases)	16,820 (69)	7,419 (20)	9,160 (37)	5,312 (23)	1,423 (5)	
Age-adjusted OR (95% CI)	1.00	0.64 (0.38-1.03)	0.93 (0.62-1.39)	1.00 (0.61-1.58)	0.81 (0.52-2.30)	0.85
Multivariable-adjusted OR1 (95% CI)[1]	1.00	0.64 (0.38-1.03)	0.95 (0.63-1.41)	1.02 (0.62-1.62)	0.84 (0.29-1.89)	0.95
Multivariable-adjusted OR2 (95% CI)[2]	1.00	**0.48 (0.23-0.89)**	0.84 (0.50-1.36)	0.84 (0.44-1.50)	0.68 (0.17-1.89)	0.45
Fair/very fair						
N (number of cases)	65,477 (537)	29,409 (257)	36,669 (361)	21,428 (206)	5,847 (77)	
Age-adjusted OR (95% CI)	1.00	1.05 (0.90-1.22)	**1.18 (1.03-1.34)**	1.14 (0.97-1.34)	**1.56 (1.22-1.98)**	0.0005
Multivariable-adjusted OR1 (95% CI)[1]	1.00	1.03 (0.88-1.19)	1.14 (0.99-1.30)	1.11 (0.94-1.30)	**1.51 (1.18-1.92)**	0.0029
Multivariable-adjusted OR2 (95% CI)[2]	1.00	1.05 (0.87-1.26)	1.10 (0.93-1.30)	1.17 (0.96-1.42)	**1.75 (1.31-2.29)**	0.0015

Note: bold font indicates statistical significance

[1]Further adjusted for: sex (male, female), education (categorical – college or university degree; A level/AS level; O level/GCSE, CSE; NVQ, HND, or HNC; other professional degree; none of the preceding), income (categorical – less than £30,999, £31,000 - £51,999, £52,000 and up, missing), physical activity (categorical – low, moderate, high, missing), BMI (continuous), smoking status (categorical – never, previous, current), alcohol intake (categorical – never/special occasions only, < 3 times/week, ≥ 3 times/week), and total energy intake (quartiles – KJ).

[2]Additionally adjusted for: coffee intake (continuous – mean cups/day), tanning ability (categorical – never tan, mildly/occasionally tan, moderately tan, very tanned), childhood sunburn occasions (continuous), natural hair color (categorical – red/blonde, light brown, dark brown/black, other), skin color (categorical – dark/light olive, fair, very fair), average time spent outdoors in summer (continuous – hours/day), sunlamp/solarium use (continuous – times/year), sun/UV protection use (categorical – always, most of the time, sometimes, never/rarely), and history of non-melanoma skin cancer (yes, no).

Abbreviation: OR, odds ratio; CI, confidence interval

CHAPTER II: CITRUS CONSUMPTION AND RISK OF NON-MELANOMA SKIN CANCER

Introduction

Incidence of non-melanoma skin cancer (NMSC), of which about 99% of cases are keratinocyte carcinomas[57] (basal cell carcinoma [BCC] and squamous cell carcinoma [SCC]), has been drastically increasing in the U.S. and around the world.[1,58] NMSC is the most common malignancy in the U.S.,[59] representing a tremendous public health burden, particularly among Caucasian populations.[60] With over 5.5 million new estimated cases per year, U.S. NMSC incidence is roughly three times greater than all other human malignancies combined.[61] Although not associated with low mortality,[3] NMSC is still a tremendous economic burden, ranking as the 5th costliest carcinoma in the U.S.,[60] (costing a total of $4.8 billion per year[62]) and accounting for roughly 4.5% of all Medicare cancer spending.[58] As incidence of this burdensome and costly group of cancers is projected to continue increasing for the foreseeable future,[3] research for improved primary prevention is paramount.

Psoralen, a type of furocoumarin used in photochemotherapy using oral psoralen and ultraviolet-A radiation (PUVA), is a known photocarcinogen.[21] Citrus products are naturally abundant in psoralens,[22-24] it has been hypothesized that high citrus consumption may elevate NMSC risk due to psoralen photocarcinogenicity. Epidemiological support of this hypothesis has been published, as research from the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)[63] as well as in the European Prospective Investigation into Cancer and Nutrition cohort (EPIC)[26] found significantly increased risks of BCC and SCC associated with high total citrus intake. Evidence in contrary to this hypothesis has also been published, as a case-control

study in Arizona found no association between citrus consumption and risk of SCC.[64] This limited, inconsistent evidence highlights the need for further investigation, particularly in a population-based sample.

The purpose of the current study is to address this inconsistent evidence and address these gaps in NMSC knowledge by: 1) investigating the association between total citrus intake and risk of NMSC, 2) investigating the association between individual citrus products and NMSC risk, and 3) testing for interactions between intake of total citrus and established NMSC risk factors. These analyses will be performed in the UK Biobank (UKBB), a large, population-based, prospective cohort. Results of the current study will improve our understanding of photocarcinogenesis and modifiable NMSC risk factors, and will be of interest to cancer researchers, clinicians, and those involved in NMSC primary prevention.

Methods

Study Population

As further described elsewhere,[28-30] the UKBB is a major United Kingdom-based health resource with the goal of diagnosing, treating, and preventing of a variety of adverse health conditions, including cancer, heart disease, stroke, diabetes, and depression, among others. For this large, prospective cohort, a sample of 500,000 participant volunteers were recruited from 2006-2010. All participants were aged 40-69 years old at recruitment. At baseline, all 500,000 UKBB participants attended one of 22 assessment centers throughout the UK to provide physical measures, blood samples, urine, saliva, and detailed personal information. Follow-up took place via linkage of participants' past and future medical records, in addition to the completion of online questionnaires every few years.

Assessment of Citrus Consumption

For UKBB participants, citrus consumption data were collected via five 'rounds' of 24-hour recall questionnaires. The first 'round' took place in the assessment center between April 2009-September 2010. The next four 'rounds' were completed online via email invitation. For the first two online 'rounds', participants were given three days post-invitation to complete the questionnaire; for the latter two online 'rounds', participants had up to 14 days to complete the questionnaire. The dates that these four online 'rounds' were sent to participants are as follows: February-April, 2011; June-September, 2011; October-December 2011; and April-June, 2012, respectively. Over the course of these 5 'rounds', a total of n=210,126 participants completed at least one 24-hour dietary recall assessment and provided complete citrus consumption data for the

current study. The web-based 24-hour recall utilized by the UKBB has Spearman's correlation coefficients of 0.5-0.9 (mean of 0.6)[31] compared with an interviewer-administered 24-hour recall. Additionally, between the first and last dietary assessments, over 70% of UKBB participants reported nutrient intake in the same or adjacent intake category, with that number increasing to 82% for fresh fruit intake.[32]

To measure orange consumption, participants were asked: "How may oranges (fresh, frozen, canned) did you have?". For grapefruit consumption, participants were asked: "How many whole/servings of grapefruit (fresh, frozen, canned) did you have?", and for satsuma consumption, participants were asked: "How many whole/servings of orange-like small fruits e.g. satsuma, clementine, mandarin (fresh, frozen, canned) did you have?". For each of these measures, participants were to select: "half", "1", "2", "3", or "4+". For orange juice and grapefruit juice intake, participants were asked: "How many glasses/cartons/250ml of pure orange (grapefruit) juice did you drink yesterday?", with possible responses of: "half", "1", "2", "3", "4", "5", and "6+". A cumulative average of participants' citrus consumption over the 5 'rounds' of nutritional data collection was used to assess consumption of each citrus product.

Ascertainment of NMSC Cases

International Classification of Diseases (ICD) codes, acquired via linkage with national registries, were used to identify NMSC outcomes. These registries acquire cancer diagnosis data from various sources, (including hospitals, treatment centers, nursing homes, hospices, general practices, screening programs, death certificates and others) dating back to the registries' inception in the early 1970s. For English and Welch residents, cancers diagnosed from 1971-1978, 1979-1994, and 1995-present are coded

according to the ICD 8,9, and 10, respectively. For Scottish residents, cancer diagnoses through the end of 1996 and from the start of 1997 are coded according to ICD 9 and 10 classifications, respectively. ICD codes C44.0-9 were used to identify NMSC cases.

Statistical Analysis

As done in previous studies,[63] I only included White/Caucasian participants in the analyses due to low NMSC incidence in ethnic minorities,[33-35] resulting in *n*=11,162 (5.3%) of the 210,126 participants with complete citrus data being excluded. To avoid potential confounding, I also excluded *n*=1,592 (0.76%) participants with a history of melanoma, leaving *n*=197,372 participants to be included in the analyses. To estimate the effect of total citrus consumption, I combined consumption of all citrus products into a single composite variable with five intake groups: 0, half, >half-1, >1-2, and > 2 servings. Participants with 0 servings served as the reference group. Consumption of each citrus product was categorized into four groups: 0, half, >half-1, and >1 serving, with 0 servings as the reference group. Chi-square tests and one-way ANOVA were used to respectively assess participant differences in categorical and continuous variables of interest according to levels of total citrus consumption. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between citrus consumption and NMSC risk. I constructed three models for these analyses, one age-adjusted model and two multivariable-adjusted models. For the total citrus analyses, I controlled for sex, education, income, physical activity, body mass index (BMI), smoking status, alcohol intake, and total energy intake in the first multivariable-adjusted model (controlling for demographic variables). To control for demographic and sun-exposure variables, I additionally adjusted for coffee intake,

tanning ability, childhood sunburn occasions, natural hair color, skin color, average time spent outdoors in summer, solarium/sunlamp use, and use of UV protection in the second multivariable-adjusted model. For analyses of individual citrus products, the first multivariable-adjusted model controlled for all variables in the first and second total citrus models, and the second model additionally adjusted for consumption of the other individual citrus products. Trend tests across groups were performed by assigning median values to each category then treating them as continuous variables.

To test for potential interactions between NMSC risk factors and total citrus consumption, likelihood ratio tests comparing the model with and without product terms were used. Odds ratios and confidence intervals were calculated for each stratum when evidence of interaction existed. SAS software version 9.4 (SAS Institute, Cary, NC) was used for all statistical tests, all tests were 2-tailed, with $p<.05$ indicating statistical significance. All data was stored using Karst, a high-performance computing cluster, at Indiana University.

Results

As seen in Table 2.1, total citrus intake significantly varied by several demographic and sun exposure variables in our UKBB sample. Participants with higher intakes of total citrus were more likely to be older, male, have a higher education and income, less likely to smoke, and more physically active relative to those with no total citrus consumption. Additionally, participants with high citrus consumption were less likely to use sunlamps or solariums, more likely to report sunburns during childhood, and less likely to describe themselves as olive skinned relative to those with no citrus consumption.

There were a total of 9,613 NMSC cases among the 197,372 participants included in this analysis. I found no association between high citrus consumption and NMSC risk. A slightly increased risk of NMSC was associated with total citrus, but only among those consuming half a serving of citrus per day, with no significant results being observed in other intake groups (Table 2.2). In the fully adjusted model, the ORs (95% CIs) were 1.08 (1.01-1.16) for ½ a serving, 1.00 (0.93-1.06) for >½ to 1 serving, 1.03 (0.95-1.12) for >1 to 2 servings, and 0.91 (0.79-1.05) for >2 servings of total citrus per day relative to no citrus consumption (*p*-trend = 0.65). I also analyzed intake of each individual citrus product (grapefruit, grapefruit juice, orange, orange juice, and satsuma) with respect to NMSC risk, but no significant associations were observed in any of the multivariable-adjusted models (Table 2.3).

I tested for interactions between total citrus consumption and other NMSC risk factors, including coffee intake, tanning ability, childhood sunburn occasions, natural hair color, skin color, average time outdoors in summer, solarium/sunlamp use, and sun/UV

protection use. I found evidence of interaction for childhood sunburns (p=0.031) and skin color (p=0.00061), although only the p-value for skin color would remain significant after adjusting for multiple comparisons. I conducted stratified analyses to evaluate these potential interactions (Table 2.4). In the fully adjusted models, olive skin complexion was positively associated with melanoma risk, but only among participants consuming half a serving of citrus per day and no significant associations were observed for any of the greater citrus consumption categories (ORs [95% CIs] of 1.20 [1.01-1.43], 0.92 [0.78-1.09], 1.00 [0.82-1.22], and 0.74 [0.49-1.08)] for half, >half-1, >1-2, and >2 servings of total citrus per day, respectively). There were no significant associations in the fully adjusted model for either stratum of childhood sunburn occasions.

Discussion

In the current study, there was no association between high total citrus consumption and NMSC risk. This result is inconsistent with previous findings from the NHS/HPFS, and EPIC. In the NHS and HPFS, participants with the greatest total citrus intake had a 16% and 21% increased risk of BCC and SCC, respectively, relative to those with the lowest intake (hazard ratios [HRs] [95% CIs] = 1.16 [1.09-1.23] and 1.21 [1.06-1.38], respectively).[63] In EPIC, HRs (95% CIs) of 1.11 (1.02-1.20) and 1.23 (1.04-1.47) were associated with BCC and SCC, respectively, among those in the highest quartile of citrus intake relative to those in the lowest quartile.[26] The inconsistency between these findings and results of these previous analyses could be due, in part, to differences in study design. Unlike the prospective nature of the NHS/HPFS and EPIC studies, the current analysis is retrospective, possibly allowing for greater confounding that may have influenced the outcome.

Our null result for the association between high citrus consumption and NMSC risk is consistent with an Arizona-based case-control study in which ORs (95% CIs) of 0.99 (0.73-1.32) and 0.97 (0.71-1.31) were found for the association between SCC and consumption of citrus fruit and citrus juice, respectively.[64] However, this retrospective study included a relatively small sample (242 cases and 228 controls) from a single state, it did not investigate BCC, and it did not control for several key NMSC risk factors such as childhood sunburns, hair color, time spent outdoors, or skin complexion. Therefore, evidence presented in this analysis may not be as strong as published evidence from the NHS/HPFS and EPIC.

I also reported a slightly increased risk of NMSC associated with half a serving of total citrus per day, with no significant results in other serving categories. This result was not observed in the aforementioned previously published results,[26,63] and, to our knowledge, there is no biologically plausible rationale for this finding. This result was still observed after removing personal history of melanoma from the exclusion criteria, thus including participants with a history of melanoma in the analysis (Appendix A), and after creating and controlling for a composite phenotypic susceptibility variable (described below) to reduce multicollinearity (Appendix B). Therefore, this result may be due to chance or to residual confounding. Similarly, I also report a greater risk of NMSC associated with half a serving of total citrus among those with darker (olive) skin. This result is in direct contradiction to well-established, consistent literature that has long contributed to our knowledge of pigmentation and NMSC risk.[12,16,65] Therefore, based on previously published research,[66,67] I used data for skin complexion, hair color, and tanning ability to create a single variable to represent phenotypic susceptibility to NMSC (see Appendix C), testing it for interaction using the methodology previously described for other NMSC risk factors. As no evidence of interaction existed for this composite variable ($p=0.11$), I suggest that the significant interaction associated with skin color is probably driven by sample size, and results of our subgroup analyses (Table 2.4), are likely due to chance or residual confounding.

The current study is subject to limitations. As dietary data were self-reported, nondifferential misclassification is likely; however, I calculated a cumulative average intake over several timepoints to minimize random error, and 82% of participants reported the same or adjacent intake category across timepoints.[32] Another potential

limitation of this study could be the difficulty of generalizing results from United Kingdom-based data to the U.S. population, with average citrus consumption between these two countries representing a particular challenge. However, it is estimated that the U.S. and the U.K. consume roughly the same amount fruit per day,[50-52] making it plausible that citrus consumption is also approximately equal. As described above, differences in climate could be another challenge to generalizability, as there are much fewer hours of sunshine in the U.K. relative to the U.S.,[53,54] possibly contributing to our null results. If true, these null findings could signify greater implications for regions with greater sun exposure. As NMSC can be heritable,[68,69] this analysis is limited by the inability to control for NMSC family history. Finally, this analysis was limited by the inability to distinguish BCC and SCC as they are grouped together under the umbrella of NMSC. As BCC and SCC are two distinct diseases with distinguishable clinical and epidemiological characteristics, the inability to separate the two detracts from our analyses.[70]

In conclusion, our current analysis of UKBB participants found no association between high intake of total citrus and NMSC risk. I also found no association between individual citrus products and NMSC risk. Our reported findings of a slightly increased risk among participants with half a serving of citrus intake are likely due to residual confounding or chance. Unlike previous results, our findings do not support the biologically plausible hypothesis of high citrus consumption increasing NMSC risk due to the phototoxicity and photocarcinogenicity of psoralen. Additional studies are needed to further our understanding of citrus and risk of NMSC.

Table 2.1. Demographic and sun-exposure characteristics of UK Biobank study participants according to daily total citrus intake.

		Total citrus intake					
	Total	None	½ serving	>½-1 serving	>1-2 servings	>2 servings	*p*-value
***N* (%)**	197,372	81,691 (41.4%)	36,551 (18.5%)	45,431 (23.0%)	26,511 (13.4%)	7,188 (3.6%)	
Age at recruitment	56.2 (7.9)	55.7 (8.1)	56.3 (7.9)	56.6 (7.8)	56.8 (7.6)	56.9 (7.6)	<.0001
Years (mean/SD)							
Sex							<.0001
Male	88,353 (44.8%)	35,867 (43.9%)	16,016 (43.8%)	20,645 (45.4%)	12,278 (46.3%)	3,547 (49.4%)	
Female	109,019 (55.2%)	45,824 (56.1%)	20,535 (56.2%)	24,786 (54.6%)	14,233 (53.7%)	3,641 (50.7%)	
Education							<.0001
College or university degree	83,594 (42.4%)	29,488 (36.1%)	16,275 (44.5%)	20,908 (46.0%)	13,065 (49.3%)	3,858 (53.7%)	
A level/AS level	26,121 (13.2%)	10,699 (13.1%)	5,000 (13.7%)	6,137 (13.5%)	3,409 (12.9%)	876 (12.2%)	
O level/GCSE	41,201 (20.9%)	18,941(23.2%)	7,499 (20.5%)	8,803 (19.4%)	4,785 (18.1%)	1,173 (16.3%)	
CSE	8,335 (4.2%)	4,401 (5.4%)	1,382 (3.8%)	1,553 (3.4%)	825 (3.1%)	174 (2.4%)	
NVQ, HND, or HNC	10,717 (5.4%)	5,029 (6.2%)	1,782 (4.9%)	2,296 (5.1%)	1,293 (4.9%)	317 (4.4%)	
Other professional degree	9,722 (4.9%)	3,935 (4.8%)	1,836 (5.0%)	2,296 (5.0%)	1,339 (5.1%)	343 (4.8%)	
Missing	17,682 (9.0%)	9,198 (11.3%)	2,777 (7.6%)	3,465 (7.6%)	1,795 (6.8%)	447 (6.2%)	
Income							<.0001
Less than £30,999	70,297 (35.6%)	31,280 (38.3%)	12,557 (34.4%)	15,523 (34.2%)	8,702 (32.8%)	2,235 (31.1%)	
£31,000 - £51,999	50,796 (25.7%)	20,389 (25.0%)	9,642 (26.4%)	11,874 (26.1%)	7,061 (26.6%)	1,830 (25.5%)	
£52,000 and up	56,587 (28.7%)	21,193 (25.9%)	10,877 (29.8%)	13,666 (30.1%)	8,338 (31.5%)	2,513 (35.0%)	
Missing	19,692 (10.0%)	8,829 (10.8%)	3,475 (9.5%)	4,368 (9.6%)	2,410 (9.1%)	610 (8.5%)	
Tanning ability							<.0001
Never tan, only burn	33,652 (17.3%)	14,210 (17.7%)	6,041 (16.8%)	7,657 (17.1%)	4,503 (17.3%)	1,241 (17.6%)	
Mildly/occasionally tanned	42,571 (21.9%)	17,412 (21.7%)	8,003 (22.3%)	9,996 (22.3%)	5,691 (21.8%)	1,469 (20.8%)	
Moderately tanned	79,768 (41.1%)	32,423 (40.4%)	14,904 (41.4%)	18,586 (41.5%)	10,955 (42.0%)	2,900 (41.1%)	
Very tanned	38,174 (19.7%)	16,306 (20.3%)	7,017 (19.5%)	8,499 (19.0%)	4,913 (18.9%)	1,439 (20.4%)	

Solarium/sunlamp use	0.45 (4.0)	0.54 (4.7)	0.40 (3.5)	0.40 (3.3)	0.36 (3.3)	0.31 (4.2)	<.0001
Times per year (mean/SD)							
Childhood sunburn occasions	1.94 (6.3)	1.88 (5.7)	2.02 (7.9)	1.92 (5.1)	1.95 (3.6)	2.26 (13.3)	<.0001
Before age 15 (mean/SD)							
Natural hair color							0.0005
Red/blonde	30,475 (15.5%)	12,820 (15.7%)	5,532 (15.1%)	7,018 (15.5%)	3,968 (15.0%)	1,137 (15.8%)	
Light brown	80,125 (40.6%)	33,024 (40.5%)	14,942 (40.9%)	18,486 (40.7%)	10,858 (41.0%)	2,815 (39.2%)	
Dark brown/black	84,885 (43.1%)	34,969 (42.9%)	15,746 (43.1%)	19,559 (43.1%)	11,440 (43.2%)	3,171 (44.2%)	
Other	1,686 (0.9%)	768 (0.9%)	310 (0.9%)	331 (0.7%)	222 (0.8%)	57 (0.8%)	
Skin color							0.0003
Dark/light olive	39,980 (20.3%)	16,751 (20.5%)	7,399 (20.2%)	9,123 (20.1%)	5,289 (20.0%)	1,418 (19.7%)	
Fair	140,903 (71.4%)	57,916 (70.9%)	26,129 (71.5%)	32,584 (71.7%)	19,128 (72.2%)	5,146 (71.6%)	
Very fair	16,489 (8.4%)	7,024 (8.6%)	3,023 (8.3%)	3,724 (8.2%)	2,094 (7.9%)	624 (8.7%)	
Time spent outdoors in summer	3.51 (2.2)	3.57 (2.3)	3.43 (2.1)	3.49 (2.2)	3.47 (2.2)	3.51 (2.2)	<.0001
Hours per day (mean/SD)							
Use of sun/ultraviolet protection							<.0001
Always	40,066 (20.4%)	16,506 (20.3%)	7,186 (19.7%)	9,314 (20.6%)	5,521 (20.9%)	1,539 (21.5%)	
Most of the time	77,387 (39.4%)	31,130 (38.3%)	14,606 (40.1%)	18,175 (40.2%)	10,651 (40.3%)	2,825 (39.4%)	
Sometimes	65,448 (33.3%)	27,264 (33.6%)	12,267 (33.7%)	15,044 (33.2%)	8,545 (32.4%)	2,328 (32.5%)	
Never/rarely	13,588 (6.9%)	6,345 (7.8%)	2,354 (6.5%)	2,727 (6.0%)	1,692 (6.4%)	470 (6.6%)	
Coffee consumption	0.76 (0.8)	0.63 (0.7)	0.89 (0.9)	0.81 (0.9)	0.87 (0.9)	0.89 (0.9)	<.0001
Cups per day (mean/SD)							
BMI	26.9 (4.6)	27.3 (4.8)	26.7 (4.5)	26.7 (4.5)	26.6 (4.4)	26.7 (4.7)	<.0001
kg/m^2 (mean/SD)							
Smoking status							<.0001
Never	110,351 (56.0%)	43,417 (53.3%)	20,830 (57.1%)	26,170 (57.7%)	15,633 (59.1%)	4,301 (60.0%)	

Previous	71,325 (36.2%)	30,029 (36.8%)	13,187 (36.1%)	16,302 (36.0%)	9,341 (35.3%)	2,466 (34.4%)	
Current	15,284 (7.8%)	8,060 (9.9%)	2,479 (6.8%)	2,855 (6.3%)	1,483 (5.6%)	407 (5.7%)	
Alcohol intake							<.0001
Never/special occasions only	29,287 (14.8%)	13,773 (16.9%)	4,825 (13.2%)	6,027 (13.3%)	3,609 (13.6%)	1,053 (14.7%)	
< 3 times per week	71,221 (36.1%)	30,181 (37.0%)	13,101 (35.9%)	16,098 (35.5%)	9,319 (35.2%)	2,522 (35.1%)	
≥ Three times per week	96,810 (49.1%)	37,707 (46.2%)	18,619 (51.0%)	23,291 (51.3%)	13,580 (51.2%)	3,613 (50.3%)	
Physical activity							<.0001
Low	30,696 (15.6%)	13,583 (16.6%)	5,826 (15.9%)	6,680 (14.7%)	3,642 (13.8%)	943 (13.1%)	
Moderate	71,151 (36.1%)	28,388 (34.8%)	13,529 (37.0%)	16,829 (37.0%)	9,867 (37.2%)	2,538 (35.3%)	
High	65,927 (33.4%)	26,337 (32.2%)	12,017 (32.9%)	15,424 (34.0%)	9,338 (35.2%)	2,811 (39.1%)	
Missing	29,598 (15.0%)	13,383 (16.4%)	5,179 (14.2%)	6,498 (14.3%)	3,642 (13.7%)	896 (12.5%)	

Data shown are mean (SD) for continuous variables or N (%) for categorical variables

Some percentages do not add up to 100% due to rounding

Table 2.2. Risk of non-melanoma skin cancer according to frequency of total citrus consumption in the UK Biobank.

Citrus type	Serving category					
	None	½ serving	>½-1 serving	>1-2 servings	>2 servings	*p*-trend
Total citrus						
N (number of cases)	81,691 (3,699)	36,551 (1,884)	45,431 (2,305)	26,511 (1,381)	7,188 (344)	
Age-adjusted OR (95% CI)	1.00	**1.11 (1.05-1.18)**	**1.07 (1.01-1.13)**	**1.09 (1.02-1.16)**	0.99 (0.88-1.11)	0.040
Multivariable-adjusted OR1 (95% CI)[1]	1.00	**1.08 (1.02-1.14)**	1.04 (0.98-1.09)	1.05 (0.98-1.12)	0.95 (0.84-1.06)	0.55
Multivariable-adjusted OR2 (95% CI)[2]	1.00	**1.08 (1.01-1.16)**	1.00 (0.93-1.06)	1.03 (0.95-1.12)	0.91 (0.79-1.05)	0.65

Note: bold font indicates statistical significance

Abbreviation: OR, odds ratio; CI, confidence interval

[1]Further adjusted for: sex (male, female), education (categorical – college or university degree; A level/AS level; O level/GCSE, CSE; NVQ, HND, or HNC; other professional degree; none of the preceding), income (categorical – less than £30,999; £31,000 - £51,999; £52,000 and up; missing), physical activity (categorical – low, moderate, high, missing), BMI (continuous), smoking status (categorical – never, previous, current), alcohol intake (categorical – never/special occasions only, <3 times/week, ≥3 times/week), and total energy intake (quartiles – KJ).

[2]Additionally adjusted for: coffee intake (continuous – mean cups/day), ease of tanning (categorical – never tan, mildly/occasionally tan, moderately tan, very tanned), childhood sunburn occasions (continuous), natural hair color (categorical – red/blonde, light brown, dark brown/black, other), skin color (categorical – dark/light olive, fair, very fair), average time spent outdoors in summer (continuous – hours/day), sunlamp/solarium use (continuous – times/year), and sun/UV protection use (categorical – always, most of the time, sometimes, never/rarely).

Table 2.3. Risk of non-melanoma skin cancer according to frequency of individual citrus product consumption in the UK Biobank.

Citrus type	Serving category				
	None	½ serving	>½-1 serving	>1 serving	*p*-trend
Grapefruit					
N (number of cases)	187,430 (9,023)	8,170 (484)	1,705 (104)	67 (2)	
Age-adjusted OR (95% CI)	1.00	1.08 (0.98-1.19)	1.10 (0.90-1.34)	0.58 (0.10-1.88)	0.16
Multivariable-adjusted OR (95% CI)[1]	1.00	0.99 (0.88-1.12)	1.05 (0.81-1.34)	0.43 (0.02-1.98)	0.98
Multivariable-adjusted OR (95% CI)[2]	1.00	0.99 (0.88-1.12)	1.07 (0.82-1.36)	0.44 (0.03-2.02)	0.94
Grapefruit juice					
N (number of cases)	188,532 (9,203)	6,077 (291)	2,451 (108)	312 (11)	
Age-adjusted OR (95% CI)	1.00	0.96 (0.85-1.08)	0.90 (0.74-1.09)	0.76 (0.39-1.32)	0.13
Multivariable-adjusted OR (95% CI)[1]	1.00	0.93 (0.80-1.07)	0.87 (0.69-1.10)	0.94 (0.45-1.75)	0.19
Multivariable-adjusted OR (95% CI)[2]	1.00	0.92 (0.80-1.07)	0.88 (0.69-1.10)	0.94 (0.44-1.75)	0.18
Orange					
N (number of cases)	161,458 (7,649)	20,907 (1,113)	13,191 (764)	1,816 (87)	
Age-adjusted OR (95% CI)	1.00	1.02 (0.96-1.09)	1.05 (0.97-1.13)	0.92 (0.73-1.13)	0.55
Multivariable-adjusted OR (95% CI)[1]	1.00	1.01 (0.94-1.10)	1.07 (0.97-1.17)	0.82 (0.61-1.07)	0.73
Multivariable-adjusted OR (95% CI)[2]	1.00	1.01 (0.93-1.09)	1.07 (0.97-1.17)	0.82 (0.61-1.07)	0.78
Orange Juice					
N (number of cases)	125,608 (5,940)	38,470 (1,988)	28,716 (1,461)	4,578 (224)	
Age-adjusted OR (95% CI)	1.00	**1.08 (1.03-1.14)**	**1.07 (1.01-1.14)**	1.10 (0.95-1.26)	0.0059
Multivariable-adjusted OR (95% CI)[1]	1.00	1.03 (0.97-1.10)	0.98 (0.91-1.06)	1.06 (0.90-1.24)	0.87
Multivariable-adjusted OR (95% CI)[2]	1.00	1.03 (0.97-1.10)	0.98 (0.91-1.05)	1.06 (0.90-1.24)	0.91
Satsuma					

N (number of cases)	157,038 (7,572)	20,802 (1,058)	14,470 (718)	6,062 (265)	
Age-adjusted OR (95% CI)	1.00	1.05 (0.98-1.12)	1.01 (0.93-1.09)	0.92 (0.81-1.04)	0.48
Multivariable-adjusted OR (95% CI)[1]	1.00	1.04 (0.95-1.12)	0.99 (0.90-1.09)	0.88 (0.78-1.03)	0.22
Multivariable-adjusted OR (95% CI)[2]	1.00	1.04 (0.95-1.12)	0.99 (0.90-1.09)	0.88 (0.75-1.03)	0.23

Note: bold font indicates statistical significance. Four levels of citrus intake were used for consumption of grapefruit, grapefruit juice, and oranges due to a lack of observations above the >1 serving category.

Abbreviation: OR, odds ratio; CI, confidence interval

[1]Multivariable analyses were further adjusted for: sex (male, female), education (categorical – college or university degree; A level/AS level; O level/GCSE, CSE; NVQ, HND, or HNC; other professional degree; none of the preceding), income (less than £30,999; £31,000 - £51,999; £52,000 and up; missing), physical activity (low, moderate, high, missing), BMI (continuous), smoking status (never, previous, current), alcohol intake (categorical – never/special occasions only, <3 times/week, $\geq$ 3 times/week), coffee intake (continuous – mean cups/day), ease of tanning (never tan, mildly/occasionally tan, moderately tan, very tanned), childhood sunburn occasions (continuous), natural hair color (red/blonde, light brown, dark brown/black, other), skin color (dark olive/light olive, fair, very fair), average time spent outdoors in summer (continuous – hours/day), sunlamp/solarium use (continuous – times/year), sun/UV protection use (always, most of the time, sometimes, never/rarely), and total energy intake (quartiles – KJ).

[2]Additionally adjusted for consumption of other individual citrus products listed in table

Table 2.4. Non-melanoma skin cancer (NMSC) risk according to frequency of total citrus consumption according to NMSC risk factor variables with evidence of interaction with citrus consumption among study participants in the UK Biobank.

NMSC risk factor	Total citrus serving category					
	None	½ serving	>½-1 serving	>1-2 servings	>2 servings	*p*-trend
Childhood sunburn occasions						
Above median						
N (number of cases)	22,030 (1,141)	10,463 (625)	12,461 (729)	7,424 (448)	2,052 (112)	
Age-adjusted OR (95% CI)	1.00	1.09 (0.99-1.21)	1.06 (0.97-1.17)	1.09 (0.97-1.22)	0.93 (0.76-1.12)	0.41
Multivariable-adjusted OR1 (95% CI)[1]	1.00	1.06 (0.96-1.18)	1.03 (0.94-1.14)	1.05 (0.94-1.18)	0.89 (0.74-1.08)	0.98
Multivariable-adjusted OR2 (95% CI)[2]	1.00	1.07 (0.97-1.19)	1.03 (0.93-1.14)	1.06 (0.94-1.19)	0.88 (0.72-1.06)	0.97
Below median						
N (number of cases)	59,661 (2,558)	26,088 (1,259)	32,970 (1,576)	19,087 (933)	5,136 (232)	
Age-adjusted OR (95% CI)	1.00	**1.10 (1.03-1.18)**	1.06 (1.00-1.13)	**1.09 (1.01-1.18)**	1.01 (0.88-1.15)	0.057
Multivariable-adjusted OR1 (95% CI)[1]	1.00	**1.08 (1.01-1.16)**	1.04 (0.97-1.11)	1.07 (0.98-1.15)	0.99 (0.87-1.13)	0.27
Multivariable-adjusted OR2 (95% CI)[2]	1.00	1.08 (0.99-1.19)	0.97 (0.89-1.06)	1.05 (0.94-1.16)	0.93 (0.77-1.10)	0.77
Skin color						
Dark/light olive						
N (number of cases)	16,751 (559)	7,399 (278)	9,123 (324)	5,289 (191)	1,418 (42)	
Age-adjusted OR (95% CI)	1.00	1.09 (0.94-1.26)	1.00 (0.86-1.14)	1.02 (0.86-1.20)	0.83 (0.59-1.12)	0.58
Multivariable-adjusted OR1 (95% CI)[1]	1.00	1.06 (0.91-1.23)	0.96 (0.83-1.11)	0.99 (0.83-1.17)	0.80 (0.57-1.09)	0.31
Multivariable-adjusted OR2 (95% CI)[2]	1.00	**1.20 (1.01-1.43)**	0.92 (0.78-1.09)	1.00 (0.82-1.22)	0.74 (0.49-1.08)	0.21
Fair/very fair						
N (number of cases)	64,940 (3,140)	29,152 (1,606)	36,308 (1,981)	21,222 (1,190)	5,770 (302)	
Age-adjusted OR (95% CI)	1.00	**1.12 (1.05-1.19)**	**1.08 (1.02-1.15)**	**1.10 (1.02-1.18)**	1.02 (0.90-1.15)	0.016
Multivariable-adjusted OR1 (95% CI)[1]	1.00	**1.09 (1.02-1.16)**	1.05 (0.99-1.12)	1.06 (0.99-1.14)	0.97 (0.86-1.10)	0.24

Multivariable-adjusted OR2 (95% CI)[2]	1.00	1.06 (0.98-1.15)	1.01 (0.94-1.09)	1.04 (0.95-1.13)	0.94 (0.81-1.09)	0.94

Note: bold font indicates statistical significance

Abbreviation: NMSC, non-melanoma skin cancer; OR, odds ratio; CI, confidence interval

[1]Further adjusted for: sex (male, female), education (categorical – college or university degree; A level/AS level; O level/GCSE, CSE; NVQ, HND, or HNC; other professional degree; none of the preceding), income (categorical – less than £30,999, £31,000 - £51,999, £52,000 and up, missing), physical activity (categorical – low, moderate, high, missing), BMI (continuous), smoking status (categorical – never, previous, current), alcohol intake (categorical – never/special occasions only, < 3 times/week, ≥3 times/week)

[2]Additionally adjusted for: coffee intake (continuous – mean cups/day), ease of tanning (categorical – never tan, mildly/occasionally tan, moderately tan, very tanned), childhood sunburn occasions (continuous), natural hair color (categorical – red/blonde, light brown, dark brown/black, other), skin color (categorical – dark/light olive, fair, very fair), average time spent outdoors in summer (continuous – hours/day), sunlamp/solarium use (continuous – times/year), sun/UV protection use (categorical – always, most of the time, sometimes, never/rarely), and total energy intake (quartiles – KJ).

CHAPTER III: CITRUS-GENE INTERACTION AND MELANOMA RISK

Introduction

Incidence of melanoma, the most deadly form of skin cancer, is increasing faster than any other cancer.[2,5] The rapid observed growth in melanoma incidence is not artifactual,[7] and with rates increasing by over 3% per year in the US,[7] and by 3-7% per year globally,[5] incidence is doubling every 10-20 years.[6] Melanoma is also associated with considerable mortality, as it is expected to projected to claim 6,850 US lives in 2020,[4] and, globally, is the fastest growing cause of cancer death save for non-Hodgkin's lymphoma, lung cancer in women, and testicular cancer.[2]

The etiology of melanoma is multifactorial, involving environmental risk factors, genetic variants, and the interactions between them. High citrus consumption is an environmental factor that has received increased attention in recent years due to citrus products' natural abundance of psoralens, a type of furocoumarin known to be photosensitizing and photocarcinogenic[21] in mice[44,45] and in humans.[46-49] Previous research from the NHS/HPFS,[25] WHI,[27] EPIC,[26] and from the UKBB (presented in chapter I) have suggested a positive association between citrus consumption and melanoma risk; however, none of these studies have investigated the role of possible nutrient-gene interaction. It has also been established that an individual's genotype may influence melanoma risk. Previous candidate gene studies and genome-wide association studies (GWAS) have identified several genes that are associated with melanoma risk,[71-76] but there is currently no evidence as to whether genetic variation modulates the association between melanoma risk and citrus consumption, representing a large gap in our understanding of melanoma.

As it is critical to identify nutrient-gene interactions that may influence the etiology and pathophysiology of melanoma, the purpose of the current study was to address this gap in the melanoma knowledge base by conducting, to our knowledge, the first genome-wide analysis of citrus-gene interactions on risk of melanoma. I believe the results of the current study will increase knowledge of melanoma pathology, identify genetic variants and gene-environment (G-E) interactions underlying photocarcinogenesis in melanoma, and, upon further validation, could serve as an empirical basis for the development of a skin cancer prediction model, eventually leading to improved precision prevention.

Methods

Data Collection, Genotyping, Imputation, and Quality Control

A more detailed description of the UKBB genomic methodology is described elsewhere.[77] The UKBB is a large, prospective cohort with extensive genomic data collected for all approximately 500,000 participants. Participants were all from the UK and were all aged 40-69 years at recruitment from 2006-2010. Each participant was assessed at one of 22 assessment centers throughout the UK and provided blood samples from which DNA was extracted and sent to Affymetrix Research Services Laboratory for genotyping. Upon receipt at Affymetrix, samples were then processed on the GeneTitan Multi-Channel Instrument in 96-well plates containing 94 UKBB samples and two control samples from the 1000 Genomes Project. Genotyping was carried out in 106 batches of approximately 4,700 samples. The first 50,000 participants were genotyped on the UK BiLEVE Axiom Array, and the following 450,000 participants were genotyped using the UK Biobank Axiom Array. Although different arrays were used, they share 95% of the same marker content, and only markers present on both arrays were used. Autosome phasing was performed using SHAPEIT3, with the 1000 Genomes phase 3 dataset as the reference panel. The UKBB was also imputed using merged UK10K and 1000 Genomes phase 3 reference panels, resulting in 93,095,623 autosomal SNPs.

Poor quality markers were identified using statistical tests to check for consistency of genotype calling. These included tests for batch effects, plate effects, departures from Hardy-Weinberg equilibrium, sex effects, array effects, and discordance across control replicates. Markers failing at least one test in a batch had the genotype calls in that batch set as missing, and if a marker was not reliable across all batches, it

was excluded altogether. Markers were also removed if they had at least a 5% overall missing rate or if they had a minor allele frequency <0.0001.

Poor quality samples were identified using missing rate and heterozygosity that were computed using 605,876 high quality autosomal markers typed on both arrays. Samples that were outliers for heterozygosity or missing rate were removed, as were a small number of samples identified as duplicates and approximately 10 samples that were mishandled in the laboratory. Overall, these filters and exclusions resulted in a dataset with 93,095,623 autosomal SNPs, short indels and large structural variants in 487,442 samples.

Citrus Intake, Melanoma Ascertainment, and Measurement of Covariates

As further described in chapter I, citrus consumption in the UKBB were collected via five 'rounds' of 24-hour recall questionnaires and a total of n=210,126 participants completed at least one 24-hour dietary recall to provide complete citrus consumption data. Consumption of orange, grapefruit, satsuma, orange juice, and grapefruit juice were categorized into four intake groups: 0, half, >half-1, and >1 serving. A cumulative average of this citrus consumption over the 5 'rounds' of nutritional data collection was used to assess total citrus consumption. ICD codes (C43.0-9) were used to identify melanoma outcome data. These codes were acquired by linking with national registries that obtain cancer diagnosis data from various sources (such as hospitals, nursing homes, death certificates, general practices, etc.) dating back to the early 1970s. Age of the participants was derived based on date of birth provided at the assessment center. It refers to participants' age when they first visited the center, truncated to whole year. A participant's sex was acquired from the National Health Service at recruitment, and, in

some cases, updated by the participant. Due to its noted strength as a melanoma risk factor,[17,78] tanning ability was also included as a covariate. Tanning ability was measured by asking "What would happen to your skin if it was repeatedly exposed to bright sunlight without any protection?", with the following as our coded responses for this variable: "get very tanned", "get moderately tanned", "get mildly or occasionally tanned", and "never tan, only burn".

Statistical Analysis

Of the n=210,126 with complete citrus data, n=11,162 non-Caucasian participants (5.3%) were excluded as done in previous analyses[25,27] due to low melanoma incidence in ethnic minorities.[33-35] Genetic data for another n=4,105 (2.0%) were also excluded due to quality control procedures, leaving n=194,859 Caucasian UKBB participants available for this analysis. From this sample, I included SNPs with a minor allele frequency >0.01 and an imputation quality score >0.3.

I created a quantile-quantile (QQ) plot and calculated lambda (λ) to assess genomic inflation. Interactions between citrus consumption and genetic variants were evaluated by performing the joint 2-degrees-of-freedom (df) test of genetic main effect and G-E interaction. The 2-df joint test performed a test of SNP marginal effects and their interaction with citrus consumption by conducting likelihood ratio tests between the full linear regression model (containing covariates, SNP, and citrus consumption) and the reduced model (excluding SNP and the interaction term). This approach has been found to be much more powerful than the standard test and better suited for discovering new genetic markers and investigating new potential G-E interactions.[79,80] Of the significant

results ($p<5x10^{-8}$), one index SNP was selected (SNP with the lowest p-value) from among highly correlated variants ($r^2 >0.6$).

Next, to gauge whether the joint 2-df test results were being primarily driven by interaction or genetic main effect, I also performed the standard 1-df logistic regression test by testing the multiplicative interaction terms added to the adjusted linear regression. This test was performed on index SNPs first, and then for the remaining SNPs found significant by the 2-df joint test. I used SAS version 9.4 (SAS Institute, Cary, NC), PLINK version 2.0 (www.cog-genomics.org/plink/2.0/), and R version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria) for the described analyses. All data storage and programming were performed in Karst, a high-performance computing cluster at Indiana University.

Results

Our analyses were conducted on a total of 194,859 Caucasian UKBB participants, including 1,563 cases and 193,296 controls. As illustrated in Figure 1, the genomic variants in our analysis have a fairly normal chi-squared distribution with little evidence of genomic inflation (λ=1.031). After adjusting for age, gender, tanning ability, and the first 15 principal components, the 2-df joint test revealed a total of 380 SNPs that were significant at a p-value <5e-08 (Appendix D), including one on chromosome three, 278 on chromosome nine, and 101 on chromosome 16. Of these, 3 index SNPs were identified: rs183783391 (p=4.25e-08) on chromosome 3 (3p13), rs869329 (p=1.98e-10) on chromosome 9 (9p21.3), and rs11446223 (p=4.93e-13) on chromosome 16 (16q24.3) (Table 3.1). These three SNPs are mapped to *MITF*, *MTAP*, and *DEF8*, respectively. Although p-values for these index SNPs reached statistical significance for the joint test, neither rs183783391 (p=0.73), rs869329 (p=0.24), or rs11446223 (p=0.12) showed evidence of interaction with citrus consumption according to the conventional 1-df test. Evidence of interaction (p<0.05) was observed in 7 of the 380 SNPs found to be significant (p<5e-08) by the 2-df joint test (Table 3.2). These SNPs included rs199600347, rs111822773, rs113178244, rs3803683, rs73283867, rs78800020, and rs73283871, all mapped to *AFG3L1P* on chromosome 16. However, these SNPs are all in close proximity to, and highly correlated with, rs11446223 (linkage disequilibrium $r^2 \geq 0.7155$), but with a less significant p-value for the joint 2-df test.

Discussion

Although noted for challenges and some inconsistent/inconclusive results,[81-83] genome-wide studies to identify G-E interactions influential to common traits and cancer are of critical importance and some have provided evidence of environment-associated genetic effects.[84-87] Although previous epidemiological evidence has suggested that high citrus consumption may increase melanoma risk,[25-27] little is known regarding the genetics of citrus metabolism, and the potential role of genetic variants involved in citrus-associated melanoma risk had been previously unexplored. In the current analysis, I tested the hypothesis that the increased risk of melanoma associated with high citrus consumption is an effect of G-E interaction. I identified three index SNPs that were highly significant for the joint 2-df test: rs138783391 (*MITF*), rs869329 (*MTAP*), and rs11446223 (*DEF8*) – all of which have been previously linked with melanoma carcinogenesis.

Located at 3p13, *MITF* (microphthalmia-associated transcription factor) plays a major role in the development, function, and survival of pigment-producing melanocytes.[88,89] As melanoma tumors are derived from melanocytes, *MITF* has been recognized for its role in driving melanoma progression and has been shown to regulate senescence, differentiation, proliferation, apoptosis, and migration of melanoma cells.[89-92] Additionally, due to its role in the transformation of immortalized melanocytes and its expression in conjunction with $BRAF^{V600E}$, *MITF* demonstrates oncogenic properties.[92,93] Genetic epidemiology studies have also linked *MITF* with melanoma risk. Previous research has elucidated the role of *MITF* in human pigmentation,[94,95] a known melanoma

risk factor.[15] Additional evidence has directly linked *MITF* with human melanoma risk, highlighting its role in familial melanoma.[96,97]

MTAP (methylioadenosin phosphorylase), located at 9p21.3, is critical to polyamine metabolism and the salvage of adenine and methionine. It also acts in catalyzing the phosphorylation of methylthioadenosine, which plays a role in the inhibition of methyltransferases and polyamine aminopropyltransferase.[98] Although typically expressed in cells and tissues, malignant cells tend to have decreased *MTAP* and have been shown to secrete methylthioadenosine rather than metabolize it.[98-100] As *MTAP* is in close physical proximity to *CDKN2A*, a gene linked to an estimated 40% of familial melanoma cases,[101] *MTAP* and *CDK2NA* are frequently co-deleted, causing *MTAP* loss to often be attributed to *CDKN2A*.[102] However, evidence has suggested that *MTAP* may have tumor suppressor function independent of *CDK2NA*.[98,99] Previous genome-wide research has also found melanoma risk to be linked with *MTAP*, whether directly,[103] or through its association with cutaneous nevi,[102,104] another known melanoma risk factor.[105] Additionally, a study by McMeniman et al. specifically found that single primary melanoma patients with melanoma at a site of visible UV-damage were significantly more likely to carry rs869329 relative to controls (OR=1.4 [CI=1.1-1.7]).[106]

Current knowledge is limited regarding the precise role and function of *DEF8* (differentially expressed in FDCP 8 homolog) located at 16q24.3. *DEF8* encodes an activator of intracellular signal transduction,[107] however, as it is located just downstream of *MC1R*, a melanoma-susceptibility gene known to play a role in skin pigmentation and sun sensitivity,[108,109] it is unclear whether this signal is due to *MC1R* proximity or whether *DEF8* has a more prominent independent role.[110] Although unclear, another

recent publication also described a significant association between *DEF8* and melanoma risk,[111] demonstrating the possibility that *DEF8* may have independent melanoma-susceptibility properties.

Although, these genes have been previously found to be associated with melanoma risk, none of the index SNPs identified by the 2-df joint test were significant for the standard 1-df test, indicating that these results are being primarily driven by the genetic main effects rather than citrus consumption or citrus-gene interaction. However, testing the remaining significant 2-df test significant SNPs revealed a possible G-E interaction between citrus consumption and seven SNPs on the pseudogene gene *AFG3L1P* for melanoma risk. A couple of possibilities exist that could explain this evidence of interaction with *AFG3L1P*.

Firstly, although these signals were strong for *AFG3L1P*, it is possible that this gene may not represent the true susceptibility variants, but rather tag *MC1R* within the same locus for which there is a biologically plausible association with melanoma.[112] Furocoumarins have been demonstrated to reach peak concentration in the skin within four hours of oral intake and remain detectable in cutaneous tissue for at least seven hours after intake.[113] These furocoumarins, when exposed to UV radiation, can cause the formation of reactive oxygen species (ROS) and thereby induce photo-oxidative damage by accessing epidermal, dermal, and endothelial cells.[113,114] UV exposure to furocoumarin-sensitized skin can also modify proteins, inactivate enzymes, and produce mutagenic and carcinogenic effects.[115,116] Therefore, it is biologically plausible to observe an interaction between furocoumarins obtained through citrus intake and *MC1R*, which influences pigment metabolism and the ability to protect against UV radiation[117] and also

plays a role in the growth and development of melanoma cells via its influence on keratinocyte and melanocyte proliferation and differentiation.[118-120]

Secondly, it is also possible for *AFG3L1P* to play an independent role in this association. Although pseudogenes are typically superfluous and nonfunctional, evidence suggests that some of these genes are translated, and therefore may play a meaningful, functional role in human biology.[121] Evidence from Bánfai et al. suggests that *AFG3L1P* is one of these rare exceptions, indicating it is transcribed and appears to be translated.[122] Furthermore, Bánfai et al. conclusively mapped a consistently detected peptide to a novel exon downstream of the pseudogene transcriptional unit that is both beyond the parental gene similarity region and absent in the parental gene locus.[122] This research provides meaningful support of *AFG3L1P* having a novel, protein-coding function distinct from the parental gene,[122] and possibly having an independent function in the association between citrus consumption and melanoma risk. Although further validation studies are needed, *AFG3L1P* may possibly play a previously unknown role in citrus metabolism, photocarcinogenesis, or psoralen/furocoumarin absorption.

As with all studies, our study is subject to limitations. Due to differences in allele frequencies and linkage disequilibrium patterns across differing populations, it is possible that our results do not generalize to other populations. Similarly, another limitation of our study is that, as with all environmental variables, possible population-to-population or country-to-country variance in citrus consumption may limit our results to this specific British cohort. Although, since Brits and Americans are reported to consume roughly the same amount of fruit per day,[50-52] it is possible that the citrus consumption variable may not pose a major barrier if comparing British and American populations. Additionally, it

is possible that our sample size (1,563 melanoma cases included in the analysis) may not be large enough to detect modest effects. Lastly, our analyses and estimates are based on common SNPs, and it is therefore plausible that rare variants could have contributed meaningful data to this analysis.

In conclusion, in this genome-wide analysis, I found that rs183783391 (*MITF*), rs869329 (MTAP), and rs11446223 (*DEF8*) are significantly associated with melanoma according to the joint 2-df test; however, 1-df tests found no evidence of citrus-gene interaction, demonstrating that these findings are primarily driven by gene main effects, and not by citrus consumption. Further analyses revealed that 7 SNPs on *AFG3L1P*, which could possibly serve as a tag for *MC1R* or have independent citrus metabolism or psoralen absorption effects, were significant on both the joint and standard tests, giving evidence of possible citrus-gene interaction.

Figure 3.1. QQplot of Joint 2DF Test across 22 Chromosomes

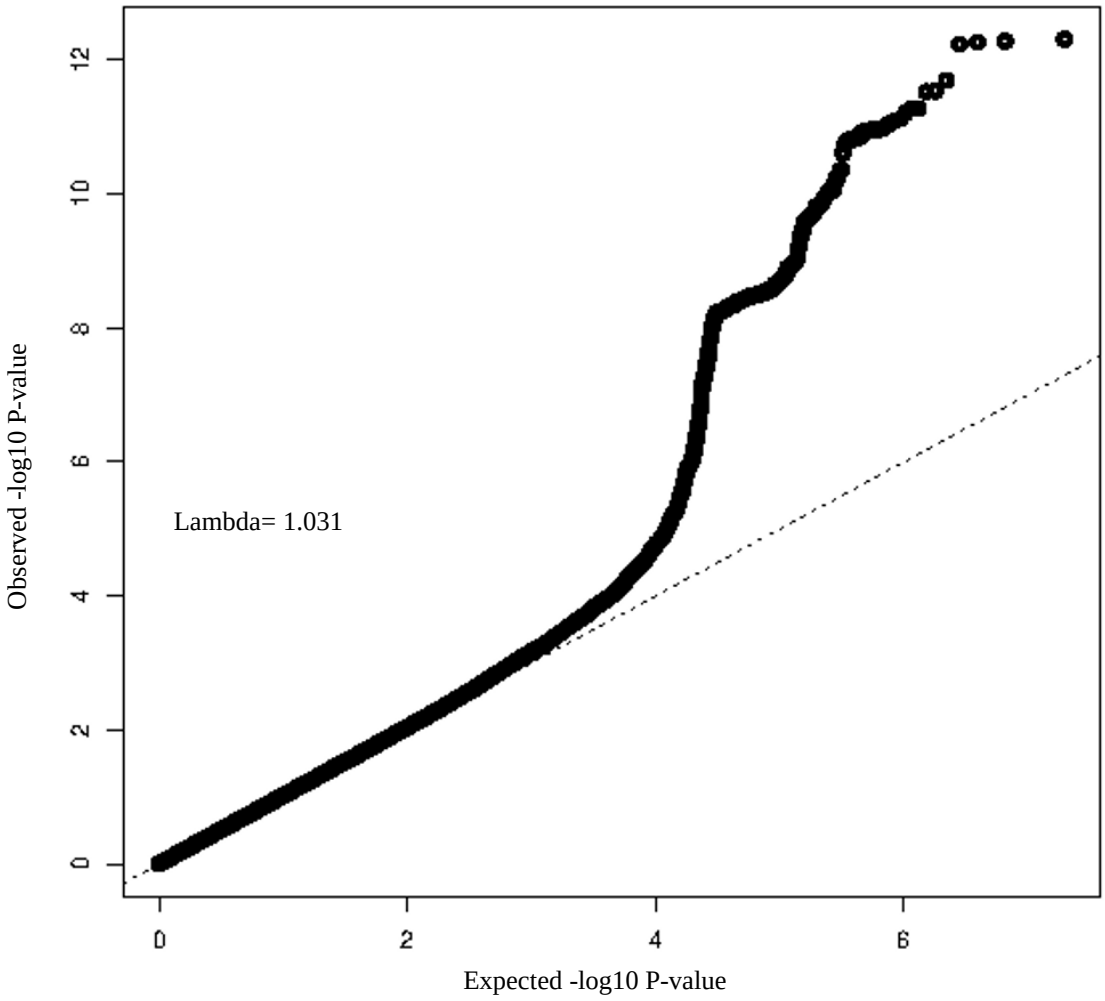

Table 3.1. Index single nucleotide polymorphisms (SNPs) resulting from a genome-wide analysis of citrus consumption and melanoma risk.

SNP ID	Chr	Position	Region	Associated gene	Ref allele	Minor allele	MAF	Info score	p-2DF	p-1DF
rs183783391	3	69950451	3p13	MITF	C	C	0.013	0.95	4.25e-08	0.73
rs869329	9	21804693	9p21.3	MTAP	A	A	0.48	0.99	1.98e-10	0.24
rs11446223	16	90022484	16q24.3	DEF8	G	G	0.17	0.99	4.93e-13	0.12

Abbreviations: Chr, chromosome; Ref allele, reference allele; MAF, minor allele frequency; Info score, imputation quality score; p-1DF, p-value for the conventional 1 degree-of-freedom test; p-2DF, p-value for the 2 degree-of-freedom joint test

Table 3.2. Non-index SNPs significant for the joint 2 degrees-of-freedom test and with evidence of citrus-gene interaction.

SNP ID	Chr	Position	Region	Closest gene	Ref allele	Minor allele	MAF	Info score	p-2DF	p-1DF
rs199600347	16	90052245	16q24.3	AFG3L1P	T	T	0.10	0.91	3.53e-10	0.023
rs111822773	16	90054089	16q24.3	AFG3L1P	A	A	0.11	0.98	3.62e-09	0.043
rs113178244	16	90056195	16q24.3	AFG3L1P	C	C	0.11	0.99	5.00e-09	0.049
rs3803683	16	90060281	16q24.3	AFG3L1P	T	T	0.17	0.99	3.55e-10	0.047
rs73283867	16	90066260	16q24.3	AFG3L1P	T	T	0.096	1.00	9.54e-12	0.050
rs78800020	16	90067136	16q24.3	AFG3L1P	G	G	0.096	1.00	1.12e-11	0.045
rs73283871	16	90067202	16q24.3	AFG3L1P	T	T	0.096	1.00	1.09e-11	0.045

Abbreviations: Chr, chromosome; Ref allele, reference allele; MAF, minor allele frequency; Info score, imputation quality score; p-1DF, p-value for the conventional 1 degree-of-freedom test; p-2DF, p-value for the 2 degree-of-freedom joint test

APPENDICES

Appendix A. Risk of NMSC according to frequency of total citrus consumption in the UK Biobank (includes participants with history of melanoma).

Appendix B. Risk of NMSC according to frequency of total citrus consumption in the UK Biobank (creation and controlling of susceptibility score).

Appendix C. Creation of a susceptibility score to serve as a summary/composite variable of phenotypic susceptibility to non-melanoma skin cancer based on skin color, natural hair color, and tanning ability.

Appendix D. All SNPs found to be significant at 5E-08 according to the joint two-degree-of-freedom test.

Appendix A. Risk of NMSC according to frequency of total citrus consumption in the UK Biobank (includes participants with history of melanoma).

Citrus type	Serving category					
	None	½ serving	>½-1 serving	>1-2 servings	>2 servings	*p*-trend
Total citrus						
N (number of cases)	82,297 (3,790)	36,828 (1,928)	45,829 (2,369)	26,740 (1,427)	7,270 (359)	
Age-adjusted OR (95% CI)	1.00	**1.11 (1.05-1.17)**	**1.07 (1.01-1.13)**	**1.09 (1.03-1.17)**	1.00 (0.90-1.12)	0.018
Multivariable-adjusted OR1 (95% CI)[1]	1.00	**1.08 (1.02-1.14)**	1.03 (0.98-1.09)	1.05 (0.98-1.12)	0.96 (0.86-1.07)	0.45
Multivariable-adjusted OR2 (95% CI)[2]	1.00	**1.08 (1.01-1.16)**	1.00 (0.93-1.06)	1.04 (0.96-1.12)	0.92 (0.80-1.05)	0.83

Note: bold font indicates statistical significance

Abbreviation: OR, odds ratio; CI, confidence interval

[1]Further adjusted for: sex (male, female), education (categorical – college or university degree; A level/AS level; O level/GCSE, CSE; NVQ, HND, or HNC; other professional degree; none of the preceding), income (categorical – less than £30,999, £31,000 - £51,999, £52,000 and up, missing), physical activity (categorical – low, moderate, high, missing), BMI (continuous), smoking status (categorical – never, previous, current), alcohol intake (categorical – never/special occasions only, <3 times/week, ≥3 times/week, daily or almost daily), and total energy intake (quartiles – KJ).

[2]Additionally adjusted for: coffee intake (continuous – mean cups/day), ease of tanning (categorical – never tan, mildly/occasionally tan, moderately tan, very tanned), childhood sunburn occasions (continuous), natural hair color (categorical – red/blonde, light brown, dark brown/black, other), skin color (categorical – dark/light olive, fair, very fair), average time spent outdoors in summer (continuous – hours/day), sunlamp/solarium use (continuous – times/year), and sun/UV protection use (categorical – always, most of the time, sometimes, never/rarely)

Appendix B. Risk of NMSC According to Frequency of Total Citrus Consumption in the UK Biobank (creation and controlling of susceptibility score).

Citrus type	Serving category					
	None	½ serving	>½-1 serving	>1-2 servings	>2 servings	*p*-trend
Total citrus						
N (number of cases)	81,691 (3,699)	36,551 (1,884)	45,431 (2,305)	26,511 (1,381)	7,188 (344)	
Age-adjusted OR (95% CI)	1.00	**1.11 (1.05-1.18)**	**1.07 (1.01-1.13)**	**1.09 (1.02-1.16)**	0.99 (0.88-1.11)	0.040
Multivariable-adjusted OR1 (95% CI)[1]	1.00	**1.08 (1.02-1.14)**	1.04 (0.98-1.09)	1.05 (0.98-1.12)	0.95 (0.84-1.06)	0.55
Multivariable-adjusted OR2 (95% CI)[2]	1.00	**1.08 (1.01-1.16)**	1.00 (0.93-1.06)	1.03 (0.95-1.11)	0.91 (0.79-1.05)	0.65

Note: bold font indicates statistical significance

Abbreviation: OR, odds ratio; CI, confidence interval

[1]Further adjusted for: sex (male, female), education (categorical – college or university degree; A level/AS level; O level/GCSE, CSE; NVQ, HND, or HNC; other professional degree; none of the preceding), income (categorical – less than £30,999; £31,000 - £51,999; £52,000 and up; missing), physical activity (categorical – low, moderate, high, missing), BMI (continuous), smoking status (categorical – never, previous, current), alcohol intake (categorical – never/special occasions only, <3 times per week, ≥3 times/week), and total energy intake (quartiles – KJ).

[2]Additionally adjusted for: coffee intake (continuous – mean cups/day), susceptibility Score (high/low), childhood sunburn occasions (continuous), average time spent outdoors in summer (continuous – hours/day), sunlamp/solarium use (continuous – times/year), and sun/UV protection use (categorical – always, most of the time, sometimes, never/rarely).

Appendix C. Creation of a susceptibility score to serve as a summary/composite variable of phenotypic susceptibility to non-melanoma skin cancer based on skin color, natural hair color, and tanning ability.

Variable	**Susceptibility score**
Skin color	
Light/dark olive	1
Fair	2
Very fair	3
Natural hair color	
Dark brown/black	1
Light brown	2
Red/blonde	3
Tanning ability	
Very/moderately tanned	1
Mildly/occasionally tanned	2
Never tan, only burn	3
Score range	3-9
Susceptibility score details	
Median score among controls	5
Creation of binary susceptibility score variable	≤5 = low susceptibility, >5 = high susceptibility
Percent low (high) susceptibility	65.9% (34.1%)
P for citrus intake*susceptibility score interaction for NMSC risk	0.1116

Appendix D. All SNPs found to be significant at 5E-08 according to the joint two-degree-of-freedom test.								
SNP ID	Chr	Position	Ref allele	Minor allele	MAF	Info score	p-2DF	p-1DF
rs183783391	3	69950451	C	C	0.013	0.95	4.25E-08	0.73
rs10114692	9	21725261	C	C	0.474	1.00	3.65E-09	0.44
rs10116090	9	21723055	T	T	0.475	1.00	2.20E-09	0.40
rs10116451	9	21727352	G	G	0.474	1.00	3.99E-09	0.42
rs10116546	9	21727693	G	G	0.475	1.00	3.33E-09	0.45
rs10116567	9	21727702	G	G	0.473	1.00	4.28E-09	0.48
rs10118262	9	21759891	C	C	0.474	1.00	4.36E-09	0.44
rs10119658	9	21757590	T	T	0.475	1.00	4.68E-09	0.47
rs10283756	9	21731529	A	A	0.474	1.00	4.63E-09	0.49
rs10637623	9	21722394	G	G	0.474	0.99	6.37E-09	0.48
rs10738595	9	21745004	T	T	0.475	1.00	5.61E-09	0.48
rs10738597	9	21746396	T	T	0.474	1.00	5.59E-09	0.48
rs10738599	9	21774467	T	T	0.475	1.00	2.28E-09	0.38
rs10757236	9	21715890	G	C	0.486	0.99	2.30E-09	0.19
rs10757237	9	21727369	G	G	0.474	1.00	3.67E-09	0.44
rs10757238	9	21732466	C	C	0.474	1.00	3.85E-09	0.46
rs10757239	9	21733113	G	G	0.476	0.99	4.45E-09	0.48
rs10757240	9	21734449	G	G	0.474	1.00	4.02E-09	0.46
rs10757241	9	21734480	G	G	0.474	1.00	4.06E-09	0.46
rs10757242	9	21739592	G	G	0.475	1.00	5.94E-09	0.52
rs10757243	9	21744802	C	C	0.475	1.00	5.51E-09	0.48
rs10757245	9	21746496	C	C	0.474	1.00	5.59E-09	0.48
rs10757246	9	21746587	A	A	0.475	1.00	5.70E-09	0.48
rs10757247	9	21747859	C	C	0.474	1.00	5.60E-09	0.48
rs10757250	9	21754226	C	C	0.475	1.00	4.66E-09	0.47
rs10757251	9	21754372	T	T	0.474	1.00	4.60E-09	0.47
rs10757252	9	21754588	C	C	0.475	1.00	4.65E-09	0.47
rs10757253	9	21772267	T	T	0.475	1.00	2.68E-09	0.38
rs10757254	9	21775061	A	A	0.474	1.00	2.17E-09	0.38
rs10757255	9	21776631	G	G	0.475	0.99	1.98E-09	0.37
rs10811583	9	21698355	G	G	0.488	0.94	1.42E-08	0.95
rs10811584	9	21701005	T	T	0.461	0.99	4.23E-09	0.65
rs10811592	9	21715201	A	G	0.488	0.99	1.51E-08	0.18
rs10811595	9	21715801	T	G	0.486	0.99	2.32E-09	0.18
rs10811596	9	21720826	T	T	0.477	0.99	3.50E-09	0.61
rs10811600	9	21734802	A	A	0.474	1.00	4.08E-09	0.46

rs10811601	9	21734833	G	G	0.474	1.00	4.08E-09	0.46
rs10811602	9	21734836	C	C	0.474	1.00	4.08E-09	0.46
rs10811604	9	21738437	C	C	0.474	1.00	5.73E-09	0.49
rs10811605	9	21738444	T	T	0.474	1.00	5.95E-09	0.49
rs10811613	9	21775342	C	C	0.474	1.00	2.76E-09	0.37
rs10811617	9	21790067	A	A	0.469	0.99	1.23E-09	0.23
rs10811618	9	21790142	G	G	0.469	0.99	1.22E-09	0.23
rs10965122	9	21775508	A	A	0.474	1.00	2.03E-09	0.38
rs10965127	9	21778976	A	A	0.474	1.00	1.24E-09	0.37
rs113126107	9	21803729	T	T	0.477	0.99	3.38E-10	0.21
rs113276233	9	21723265	T	T	0.473	0.99	5.05E-09	0.47
rs11384803	9	21760452	T	T	0.476	0.99	3.83E-09	0.49
rs11394388	9	21710108	T	T	0.453	1.00	2.30E-08	0.54
rs12344842	9	21793177	T	T	0.470	0.99	1.40E-09	0.18
rs12380505	9	21695893	A	A	0.463	0.98	5.01E-09	0.81
rs1335498	9	21711637	A	A	0.452	0.99	3.28E-08	0.53
rs1335499	9	21711647	C	C	0.454	1.00	3.03E-08	0.57
rs1335500	9	21711675	G	G	0.454	1.00	2.90E-08	0.56
rs1335501	9	21711815	C	C	0.459	0.98	2.09E-08	0.63
rs1335502	9	21736274	A	A	0.474	1.00	4.05E-09	0.46
rs1335504	9	21743393	C	C	0.474	1.00	5.35E-09	0.48
rs1335505	9	21748484	C	C	0.475	1.00	5.56E-09	0.49
rs1335506	9	21750267	G	G	0.475	1.00	5.32E-09	0.48
rs1335507	9	21750445	C	C	0.474	1.00	5.42E-09	0.48
rs1335508	9	21750587	T	T	0.475	1.00	5.47E-09	0.48
rs1335512	9	21761440	C	C	0.475	1.00	3.98E-09	0.44
rs1345022	9	21785304	C	C	0.469	1.00	1.27E-09	0.27
rs1345025	9	21745412	G	G	0.475	1.00	5.64E-09	0.48
rs1345027	9	21751962	A	A	0.474	1.00	6.49E-09	0.45
rs1345028	9	21752068	G	G	0.475	1.00	4.63E-09	0.47
rs1372057	9	21747110	T	T	0.474	1.00	5.58E-09	0.48
rs1372058	9	21747311	G	G	0.474	1.00	5.53E-09	0.48
rs1372059	9	21747420	C	C	0.474	1.00	5.53E-09	0.48
rs1414228	9	21773541	A	A	0.474	1.00	1.76E-09	0.39
rs1414232	9	21711062	G	G	0.453	1.00	4.46E-08	0.60
rs1414233	9	21711125	C	C	0.453	1.00	4.65E-08	0.60
rs141423324	9	78911401	G	A	0.057	0.97	0.772806	0.73
rs1414234	9	21712193	C	C	0.453	0.99	2.82E-08	0.55
rs1414235	9	21726306	G	G	0.474	1.00	3.36E-09	0.44

rs1414236	9	21732544	C	C	0.474	1.00	4.10E-09	0.46
rs1414237	9	21732912	G	G	0.474	1.00	3.99E-09	0.46
rs141423762	9	39147330	A	T	0.186	0.89	0.522055	0.39
rs1414238	9	21737149	C	C	0.474	1.00	4.64E-09	0.48
rs1414240	9	21743650	G	G	0.475	1.00	5.69E-09	0.48
rs1414241	9	21744392	G	G	0.475	1.00	5.67E-09	0.48
rs1414242	9	21748239	T	T	0.478	1.00	4.65E-09	0.69
rs1414244	9	21748532	A	A	0.475	1.00	5.81E-09	0.48
rs141424432	9	14514321	T	T	0.303	0.99	0.272974	0.53
rs1414245	9	21750069	A	A	0.475	1.00	5.50E-09	0.48
rs1414246	9	21750075	A	A	0.475	1.00	5.48E-09	0.48
rs1414247	9	21750170	T	T	0.475	1.00	5.26E-09	0.47
rs1414248	9	21750884	C	C	0.475	1.00	5.47E-09	0.48
rs1414249	9	21750980	T	T	0.475	1.00	7.36E-09	0.47
rs1414250	9	21754947	T	T	0.475	1.00	4.83E-09	0.47
rs1414251	9	21755030	A	A	0.475	1.00	4.80E-09	0.47
rs1414252	9	21755140	C	C	0.475	1.00	4.69E-09	0.47
rs1414255	9	21755894	A	A	0.476	1.00	4.77E-09	0.48
rs1414256	9	21755896	G	G	0.479	0.98	4.81E-09	0.43
rs1414257	9	21757767	T	T	0.474	1.00	4.55E-09	0.47
rs141425775	9	106371170	A	G	0.137	0.98	0.991558	1.00
rs143899253	9	21698799	C	C	0.481	0.94	1.05E-08	0.90
rs1452658	9	21700795	G	G	0.461	0.99	3.84E-09	0.64
rs145511817	9	21702286	A	A	0.462	0.99	5.78E-09	0.68
rs1542074	9	21786304	C	C	0.469	1.00	1.25E-09	0.26
rs1542075	9	21790669	C	C	0.469	0.99	9.92E-10	0.20
rs1542076	9	21790755	A	A	0.480	0.99	5.03E-10	0.24
rs1556696	9	21741985	C	C	0.475	1.00	5.69E-09	0.48
rs1556697	9	21741993	A	A	0.475	1.00	8.38E-09	0.47
rs1561651	9	21742746	T	T	0.475	1.00	5.63E-09	0.48
rs1561652	9	21742816	T	T	0.475	1.00	5.62E-09	0.48
rs1832075	9	21726490	A	A	0.474	1.00	3.35E-09	0.44
rs1832076	9	21726664	A	A	0.474	1.00	3.34E-09	0.44
rs1840050	9	21700530	C	C	0.462	0.99	4.59E-09	0.67
rs1889680	9	21695460	T	T	0.461	0.98	1.10E-09	0.76
rs1932236	9	21725149	G	G	0.474	1.00	3.53E-09	0.44
rs1932237	9	21758768	G	G	0.474	1.00	4.29E-09	0.44
rs1965153	9	21752105	T	T	0.475	1.00	4.74E-09	0.47
rs2004627	9	21707492	C	C	0.455	1.00	2.33E-08	0.49

rs2027162	9	21737916	A	A	0.474	1.00	5.91E-09	0.49
rs2027163	9	21738133	T	T	0.474	1.00	5.17E-09	0.47
rs2043991	9	21731081	A	A	0.474	1.00	3.78E-09	0.46
rs2119465	9	21723709	T	T	0.475	1.00	2.46E-09	0.39
rs2119466	9	21745990	T	T	0.475	1.00	5.68E-09	0.48
rs2119467	9	21746107	C	C	0.474	1.00	5.60E-09	0.48
rs2152272	9	21773416	A	A	0.474	1.00	1.75E-09	0.39
rs2152273	9	21773347	C	C	0.475	0.99	2.95E-09	0.38
rs2165408	9	21802469	A	G	0.457	0.93	1.63E-08	0.51
rs2165411	9	21730818	T	T	0.474	1.00	3.75E-09	0.46
rs2184551	9	21773222	A	A	0.475	0.99	2.55E-09	0.38
rs2210777	9	21721455	A	A	0.475	1.00	2.67E-09	0.39
rs2210778	9	21721585	C	C	0.475	1.00	2.85E-09	0.39
rs2210780	9	21721714	G	G	0.475	1.00	2.67E-09	0.39
rs2218220	9	21756089	C	C	0.475	1.00	4.81E-09	0.47
rs2383186	9	21728051	T	T	0.474	1.00	5.76E-09	0.48
rs2383202	9	21710215	C	C	0.453	1.00	4.58E-08	0.60
rs2891159	9	21747672	G	G	0.474	1.00	5.60E-09	0.48
rs2891160	9	21732999	C	C	0.474	1.00	4.79E-09	0.46
rs2891161	9	21728291	C	C	0.474	1.00	3.19E-09	0.44
rs2891164	9	21711735	C	C	0.453	1.00	2.24E-08	0.55
rs2891165	9	21711801	G	G	0.460	0.98	1.11E-08	0.62
rs2891166	9	21726819	C	C	0.474	1.00	3.34E-09	0.44
rs34435506	9	21743330	C	C	0.475	1.00	5.59E-09	0.48
rs35974503	9	21741129	A	A	0.478	0.99	6.06E-09	0.55
rs3849929	9	21769412	G	G	0.474	1.00	1.92E-09	0.39
rs3927737	9	21827992	G	G	0.470	0.99	6.14E-09	0.38
rs4275294	9	21727225	A	A	0.474	1.00	3.33E-09	0.44
rs4300088	9	21755266	C	C	0.475	1.00	4.82E-09	0.47
rs4341236	9	21727208	A	A	0.474	1.00	3.33E-09	0.44
rs4350062	9	21733008	T	T	0.474	1.00	4.80E-09	0.46
rs4352937	9	21747749	C	C	0.474	1.00	5.60E-09	0.48
rs4364717	9	21801530	A	G	0.456	0.99	4.83E-08	0.25
rs4384075	9	21736034	G	G	0.475	1.00	3.93E-09	0.42
rs4431674	9	21822483	G	G	0.470	0.99	2.30E-09	0.30
rs4560881	9	21700409	A	A	0.461	0.99	3.28E-09	0.69
rs4595216	9	21719872	G	G	0.475	1.00	3.27E-09	0.39
rs4620362	9	21711788	A	A	0.461	0.98	1.73E-08	0.65
rs4620363	9	21711789	A	A	0.457	0.99	7.56E-09	0.52

rs4636294	9	21747803	A	A	0.474	1.00	5.63E-09	0.47
rs4637939	9	21727963	T	T	0.474	1.00	3.17E-09	0.44
rs5009176	9	21726573	T	T	0.474	1.00	1.01E-08	0.50
rs5009177	9	21726572	A	A	0.474	1.00	1.01E-08	0.50
rs5009178	9	21726571	C	C	0.474	1.00	1.01E-08	0.50
rs55948515	9	21696979	C	C	0.463	0.97	4.61E-09	0.67
rs568707466	9	21698955	C	C	0.477	0.96	5.10E-09	0.69
rs5896948	9	21726628	T	T	0.474	1.00	5.45E-09	0.50
rs6475549	9	21700927	A	A	0.462	0.99	3.35E-09	0.67
rs6475550	9	21701451	A	A	0.462	0.99	3.26E-09	0.68
rs6475551	9	21701639	A	A	0.462	0.99	3.19E-09	0.68
rs6475552	9	21701674	G	G	0.462	0.99	3.50E-09	0.68
rs6475554	9	21716887	T	A	0.486	0.99	3.09E-09	0.19
rs6475555	9	21716997	A	G	0.486	0.99	3.01E-09	0.20
rs6475556	9	21718297	T	T	0.475	1.00	2.85E-09	0.40
rs6475557	9	21718479	A	A	0.475	1.00	3.17E-09	0.39
rs6475558	9	21718639	A	A	0.475	1.00	3.21E-09	0.39
rs6475559	9	21718655	T	T	0.475	1.00	3.21E-09	0.39
rs6475561	9	21725649	A	A	0.474	1.00	3.25E-09	0.44
rs6475562	9	21725765	C	C	0.474	1.00	3.84E-09	0.44
rs6475563	9	21726778	G	G	0.474	1.00	3.34E-09	0.44
rs6475564	9	21728683	T	T	0.474	1.00	3.37E-09	0.44
rs6475565	9	21731867	G	G	0.474	1.00	4.56E-09	0.49
rs6475566	9	21733500	G	G	0.474	1.00	4.06E-09	0.46
rs6475568	9	21733706	G	G	0.474	1.00	4.10E-09	0.46
rs6475569	9	21733889	A	A	0.474	1.00	4.08E-09	0.46
rs6475571	9	21736017	C	C	0.474	1.00	4.94E-09	0.48
rs6475572	9	21736020	T	T	0.474	1.00	4.96E-09	0.48
rs6475574	9	21736052	C	C	0.475	1.00	3.73E-09	0.42
rs6475576	9	21765601	C	C	0.475	1.00	3.72E-09	0.39
rs6475577	9	21769869	T	T	0.474	0.99	2.22E-09	0.39
rs6475578	9	21769897	G	G	0.474	1.00	1.70E-09	0.40
rs6475579	9	21771756	A	A	0.475	1.00	2.67E-09	0.38
rs6475585	9	21826538	G	G	0.471	0.99	5.79E-09	0.37
rs66922395	9	21702293	G	G	0.460	0.99	6.31E-09	0.66
rs7018772	9	21787402	G	G	0.469	1.00	1.15E-09	0.26
rs7019601	9	21741797	T	T	0.475	1.00	5.65E-09	0.48
rs7021012	9	21775957	G	G	0.474	1.00	1.97E-09	0.38
rs7021538	9	21733204	C	C	0.474	1.00	4.72E-09	0.46

rs7022856	9	21788523	A	A	0.469	1.00	1.07E-09	0.25
rs7023299	9	21728406	G	G	0.474	1.00	3.28E-09	0.43
rs7024027	9	21772930	T	T	0.475	0.99	2.66E-09	0.38
rs7027989	9	21817754	A	A	0.469	1.00	3.19E-09	0.34
rs7028913	9	21717395	A	A	0.475	1.00	3.12E-09	0.40
rs7029040	9	21717441	A	A	0.475	1.00	3.15E-09	0.40
rs7029166	9	21717509	A	A	0.475	0.99	2.90E-09	0.40
rs7029274	9	21717599	A	A	0.475	1.00	3.03E-09	0.40
rs7033503	9	21799598	T	T	0.466	0.99	2.52E-10	0.19
rs7036249	9	21745114	T	T	0.475	1.00	5.66E-09	0.48
rs7036257	9	21745120	T	T	0.475	1.00	5.64E-09	0.48
rs7037577	9	21772037	G	G	0.474	1.00	1.91E-09	0.39
rs7038708	9	21788081	T	T	0.468	1.00	1.23E-09	0.25
rs7039487	9	21709997	C	C	0.453	1.00	4.56E-08	0.60
rs7040998	9	21725512	C	C	0.474	1.00	3.51E-09	0.44
rs7041104	9	21725430	G	G	0.475	1.00	2.48E-09	0.39
rs7043827	9	21731447	A	A	0.474	1.00	3.93E-09	0.46
rs7044070	9	21731586	C	C	0.474	1.00	4.65E-09	0.49
rs7044199	9	21731694	C	C	0.474	1.00	4.56E-09	0.49
rs7045768	9	21770709	T	T	0.474	1.00	1.80E-09	0.39
rs7047136	9	21704021	A	A	0.454	0.99	1.30E-08	0.43
rs71334592	9	21699618	T	T	0.469	0.96	3.24E-09	0.56
rs71334597	9	21741166	A	A	0.491	0.97	1.63E-08	0.42
rs72691561	9	21813241	T	C	0.446	0.99	3.06E-08	0.63
rs72691562	9	21813303	A	C	0.446	0.99	3.07E-08	0.63
rs72691563	9	21813495	C	T	0.444	0.99	1.41E-08	0.58
rs72691564	9	21813518	C	T	0.446	0.99	2.92E-08	0.63
rs751173	9	21707372	C	C	0.455	1.00	4.06E-08	0.45
rs75117363	9	37547528	A	C	0.035	0.99	0.21014	0.12
rs7846749	9	21780251	A	A	0.469	1.00	1.79E-09	0.29
rs7846852	9	21718193	T	T	0.475	1.00	2.85E-09	0.40
rs7846943	9	21720108	C	C	0.475	1.00	3.51E-09	0.39
rs7847070	9	21720225	C	C	0.475	1.00	2.69E-09	0.42
rs7847574	9	21720481	G	G	0.475	1.00	2.95E-09	0.42
rs7848230	9	21720921	G	G	0.475	1.00	2.68E-09	0.39
rs7848524	9	21701432	T	G	0.462	0.99	0.0868157	0.42
rs7848524	9	21701432	T	T	0.462	0.99	0.0868157	0.42
rs7848524	9	21701432	T	G	0.462	0.99	4.24E-09	0.42

rs7848524	9	21701432	T	T	0.462	0.99	4.24E-09	0.42
rs7848524	9	21701432	T	G	0.462	0.99	0.0868157	0.68
rs7848524	9	21701432	T	T	0.462	0.99	0.0868157	0.68
rs7848524	9	21701432	T	G	0.462	0.99	4.24E-09	0.68
rs7848524	9	21701432	T	T	0.462	0.99	4.24E-09	0.68
rs7850446	9	21763742	G	G	0.474	1.00	3.71E-09	0.44
rs7851439	9	21721248	G	G	0.475	1.00	3.24E-09	0.39
rs7851460	9	21719507	T	T	0.475	1.00	3.21E-09	0.39
rs7852450	9	21825075	T	T	0.465	0.99	9.22E-09	0.31
rs7852710	9	21760254	T	T	0.474	1.00	4.21E-09	0.44
rs7852900	9	21746796	A	A	0.474	1.00	5.58E-09	0.48
rs7853131	9	21746976	A	A	0.474	1.00	5.52E-09	0.48
rs7854018	9	21734366	C	C	0.474	1.00	4.02E-09	0.46
rs7854222	9	21734348	G	G	0.474	1.00	3.69E-09	0.46
rs7854990	9	21725962	T	T	0.474	1.00	4.00E-09	0.45
rs7855242	9	21729327	C	C	0.474	1.00	6.31E-09	0.47
rs7855253	9	21729366	C	C	0.474	1.00	4.35E-09	0.46
rs7855464	9	21729383	G	G	0.474	1.00	4.46E-09	0.46
rs7856941	9	21761322	T	T	0.475	1.00	3.90E-09	0.44
rs7857279	9	21717884	A	A	0.475	1.00	2.85E-09	0.40
rs7857636	9	21700172	A	A	0.462	0.99	3.39E-09	0.68
rs7858959	9	21700932	G	G	0.462	0.99	3.18E-09	0.68
rs7858991	9	21735856	G	G	0.474	1.00	3.45E-09	0.45
rs7860576	9	21714920	T	C	0.493	0.99	3.12E-09	0.16
rs7865156	9	21719375	G	G	0.475	1.00	3.25E-09	0.39
rs7865620	9	21719996	A	A	0.475	1.00	3.40E-09	0.39
rs7866540	9	21760396	C	C	0.476	1.00	4.44E-09	0.44
rs7866787	9	21760639	A	A	0.476	1.00	4.92E-09	0.44
rs7866885	9	21760621	C	C	0.475	1.00	4.79E-09	0.44
rs7867994	9	21697689	G	G	0.461	0.98	8.97E-09	0.71
rs7868008	9	21697805	C	C	0.463	0.98	7.74E-09	0.65
rs7868091	9	21697699	G	G	0.461	0.98	7.11E-09	0.69
rs7871138	9	21722453	T	T	0.475	1.00	2.66E-09	0.39
rs78711383	9	109337323	A	C	0.028	0.99	0.18287	0.18
rs7871242	9	21722521	T	T	0.470	0.99	1.07E-08	0.60
rs7871256	9	21722562	T	T	0.475	0.99	2.67E-09	0.40
rs7871345	9	21729895	T	T	0.474	1.00	3.58E-09	0.45
rs7874319	9	21735881	T	T	0.474	1.00	3.45E-09	0.45

rs796910922	9	21720827	G	G	0.476	0.99	4.75E-09	0.65
rs80138396	9	21805208	C	C	0.476	0.99	2.63E-10	0.23
rs869329	9	21804693	A	A	0.476	1.00	1.98E-10	0.24
rs869330	9	21804617	A	A	0.476	1.00	2.37E-10	0.24
rs871024	9	21803880	C	C	0.476	1.00	2.07E-10	0.23
rs9298821	9	21699406	G	G	0.461	0.99	4.64E-09	0.68
rs9298822	9	21699444	C	C	0.461	0.99	4.57E-09	0.67
rs9298823	9	21749607	T	T	0.475	1.00	5.99E-09	0.48
rs9298824	9	21749663	T	T	0.474	1.00	5.73E-09	0.46
rs9298825	9	21749670	T	T	0.475	1.00	8.57E-09	0.47
rs935053	9	21783922	G	G	0.469	1.00	1.27E-09	0.26
rs935055	9	21803183	G	G	0.476	1.00	2.22E-10	0.22
rs950770	9	21741662	C	C	0.474	1.00	5.61E-09	0.48
rs9644821	9	21741197	C	C	0.477	1.00	1.25E-08	0.49
rs9644858	9	21741050	C	C	0.475	1.00	5.75E-09	0.48
rs9695494	9	21727799	C	C	0.474	1.00	3.43E-09	0.44
rs9886831	9	21773167	C	C	0.475	0.99	2.69E-09	0.39
rs11076649	16	90059336	C	G	0.170	0.99	6.47E-10	0.05
rs111460975	16	89434541	A	G	0.142	1.00	4.24E-08	0.65
rs111822773	16	90054089	A	C	0.109	0.98	3.62E-09	0.04
rs112001009	16	90047605	A	G	0.106	1.00	3.06E-09	0.05
rs112119225	16	90063461	T	G	0.096	1.00	1.67E-11	0.06
rs112153252	16	90059712	A	G	0.107	0.99	6.22E-09	0.05
rs112233725	16	89693191	T	C	0.088	0.95	1.96E-08	0.26
rs112460025	16	90051337	T	G	0.095	1.00	8.68E-12	0.06
rs112556696	16	90054018	A	G	0.110	0.96	5.52E-09	0.09
rs113178244	16	90056195	C	G	0.107	0.99	5.00E-09	0.05
rs113753049	16	90052934	A	C	0.321	0.96	8.55E-09	0.43
rs113891247	16	90047757	T	A	0.091	1.00	1.43E-11	0.07
rs113923060	16	90054015	G	A	0.096	0.99	1.11E-11	0.05
rs113955373	16	90043036	C	A	0.089	0.98	1.13E-10	0.11
rs113955902	16	89395438	G	A	0.077	0.97	1.10E-09	0.22
rs11648898	16	90045986	A	G	0.170	1.00	5.87E-13	0.18
rs11866420	16	90054704	C	C	0.422	0.99	6.14E-12	0.08
rs12921383	16	89859753	T	C	0.111	0.99	7.39E-09	0.15
rs12924124	16	89791126	C	T	0.095	1.00	1.83E-10	0.22
rs12925026	16	89792856	C	T	0.095	1.00	1.47E-10	0.21
rs12931267	16	89818732	C	G	0.097	1.00	5.79E-11	0.24
rs146972365	16	90022693	T	C	0.091	0.99	5.27E-12	0.06

rs164741	16	89692298	A	A	0.336	0.98	7.83E-09	0.53
rs164752	16	89722390	G	G	0.118	0.99	2.16E-08	0.40
rs1805007	16	89986117	C	T	0.098	1.00	5.31E-13	0.30
rs1991508	16	89672155	C	T	0.091	0.99	3.08E-09	0.33
rs2280374	16	89687407	C	T	0.099	1.00	1.43E-10	0.17
rs258322	16	89755903	A	A	0.121	1.00	3.95E-08	0.27
rs34265416	16	89769725	C	A	0.114	0.99	3.89E-08	0.24
rs34323930	16	89691045	C	T	0.098	0.99	1.27E-10	0.16
rs34395984	16	89659511	C	T	0.086	0.99	9.24E-11	0.28
rs34659644	16	89796017	G	A	0.095	0.99	2.46E-10	0.22
rs34714188	16	89781756	T	A	0.096	0.99	3.94E-10	0.24
rs34934239	16	89675579	G	A	0.098	0.99	1.04E-11	0.22
rs35026726	16	89791279	C	T	0.095	1.00	1.38E-10	0.21
rs35063026	16	89736157	C	T	0.095	0.99	3.19E-09	0.26
rs35414122	16	89742979	A	G	0.114	0.99	2.87E-08	0.28
rs35749174	16	89716493	G	A	0.096	0.99	1.97E-09	0.28
rs35850949	16	89720724	C	A	0.096	0.99	3.04E-09	0.28
rs369230	16	89645437	G	G	0.310	0.98	1.03E-09	0.64
rs375738481	16	89744876	CT	C	0.158	0.91	9.37E-10	0.21
rs3764253	16	89686693	G	T	0.099	1.00	1.51E-10	0.81
rs3764253	16	89686693	G	A	0.099	1.00	1.51E-10	0.81
rs3764253	16	89686693	G	T	0.099	1.00	0.864071	0.81
rs3764253	16	89686693	G	A	0.099	1.00	0.864071	0.81
rs3764253	16	89686693	G	T	0.099	1.00	1.51E-10	0.17
rs3764253	16	89686693	G	A	0.099	1.00	1.51E-10	0.17
rs3764253	16	89686693	G	T	0.099	1.00	0.864071	0.17
rs3764253	16	89686693	G	A	0.099	1.00	0.864071	0.17
rs3803683	16	90060281	T	C	0.175	0.99	3.55E-10	0.05
rs4248913	16	89693099	C	A	0.100	0.93	1.61E-08	0.34
rs4268748	16	90026512	T	C	0.309	0.99	3.03E-12	0.27
rs452176	16	89653032	G	G	0.459	0.96	3.90E-08	0.83
rs45610233	16	90048395	C	T	0.087	1.00	4.55E-11	0.12
rs4968051	16	89714981	T	C	0.108	0.99	3.56E-08	0.22
rs4968054	16	89690079	C	T	0.099	1.00	1.25E-10	0.16
rs533139343	16	90286407	C	T	0.071	0.63	6.52E-09	0.53
rs56850194	16	90043531	C	A	0.090	1.00	5.92E-11	0.09
rs57856222	16	89682190	C	T	0.100	1.00	2.36E-10	0.15
rs58656226	16	89745091	T	G	0.108	0.99	2.94E-08	0.17
rs58827852	16	90058754	G	A	0.110	0.99	5.71E-09	0.07

rs59038611	16	90065956	G	C	0.095	1.00	1.16E-11	0.05
rs59574756	16	90067513	A	G	0.095	1.00	1.85E-11	0.05
rs61408277	16	89685234	G	T	0.099	1.00	1.55E-10	0.17
rs62052243	16	90026152	A	G	0.349	0.99	9.42E-09	0.28
rs62054570	16	90063890	T	G	0.160	0.99	2.03E-12	0.05
rs71396949	16	89714844	G	A	0.095	0.98	3.50E-09	0.19
rs71396950	16	89726550	G	A	0.096	0.99	3.09E-09	0.28
rs71396951	16	89726593	G	C	0.096	0.99	3.08E-09	0.28
rs7191690	16	64592941	G	C	0.272	1.00	0.895079	0.88
rs7191694	16	84013136	C	G	0.120	1.00	0.209542	0.51
rs7191695	16	1909971	T	C	0.135	1.00	0.020815 1	0.01
rs7191697	16	89678165	G	A	0.100	0.99	1.09E-11	0.19
rs7191698	16	10214604	A	A	0.103	1.00	0.893322	0.69
rs73283845	16	90055664	C	T	0.106	0.99	5.01E-09	0.05
rs73283859	16	90062520	G	C	0.092	1.00	1.45E-11	0.06
rs73283867	16	90066260	T	G	0.096	1.00	9.54E-12	0.05
rs73283869	16	90067184	G	A	0.092	1.00	1.21E-11	0.05
rs73283871	16	90067202	T	C	0.096	1.00	1.09E-11	0.05
rs74336735	16	90065033	T	A	0.096	1.00	1.49E-11	0.06
rs74583214	16	90110798	C	T	0.098	0.96	5.57E-09	0.04
rs74800773	16	90024970	C	G	0.105	1.00	7.99E-12	0.22
rs74836424	16	89507330	C	T	0.079	1.00	7.69E-10	0.18
rs75319471	16	90064454	A	G	0.095	1.00	1.47E-11	0.06
rs75570604	16	89846677	G	C	0.096	1.00	1.01E-10	0.23
rs75923656	16	89690990	T	C	0.096	0.97	9.10E-11	0.17
rs76265950	16	90085139	A	C	0.100	0.99	3.19E-09	0.06
rs76581091	16	90065100	T	C	0.096	1.00	1.58E-11	0.06
rs77110324	16	89683288	G	A	0.089	1.00	4.58E-10	0.19
rs77270200	16	90093075	G	A	0.099	1.00	2.07E-09	0.05
rs77381714	16	90078022	T	C	0.091	0.99	4.39E-11	0.05
rs77603042	16	90083239	A	G	0.100	0.99	3.45E-09	0.06
rs77606435	16	90053691	C	G	0.094	1.00	1.59E-11	0.06
rs77733403	16	90080723	T	C	0.179	0.98	2.48E-08	0.32
rs77770855	16	90043010	G	A	0.088	0.98	1.05E-10	0.11
rs78536691	16	90100471	T	C	0.097	0.98	1.92E-09	0.07
rs78800020	16	90067136	G	C	0.096	1.00	1.12E-11	0.05
rs79138604	16	89690991	G	A	0.096	0.97	9.11E-11	0.17
rs79139787	16	89795360	C	T	0.086	0.92	8.87E-11	0.15

rs79172130	16	89687812	G	A	0.099	1.00	1.53E-10	0.17
rs79418450	16	90100505	G	C	0.097	0.98	1.73E-09	0.06
rs8049897	16	90024202	G	A	0.170	1.00	5.48E-13	0.15
rs8051733	16	90024206	A	G	0.343	0.99	2.12E-09	0.27
rs8063160	16	90054709	T	C	0.106	0.99	3.17E-09	0.04
rs9926296	16	89818089	A	A	0.488	1.00	3.54E-08	0.69

Abbreviations: Chr, chromosome; Ref allele, reference allele; MAF, minor allele frequency; Info score, imputation quality score; p-1DF, p-value for the conventional 1 degree-of-freedom test; p-2DF, p-value for the 2 degree-of-freedom joint test

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CURRICULUM VITAE

Andrew Raymond Marley

EDUCATION:

2016-2020	Ph.D. Epidemiology. Minor – behavioral oncology Richard M. Fairbanks School of Public Health, Indiana University Dissertation: The Association between Citrus Consumption and Skin Cancer: An Analysis of Risk and Nutrient-Gene Interaction
2014-2016	MPH – epidemiology. Richard M. Fairbanks School of Public Health, Indiana University
2008-2012	BS – psychology. Concentration – biopsych University of Maryland, Baltimore County

ACADEMIC APPOINTMENTS:

Fall 2018-present	Adjunct Professor Indiana University Fairbanks School of Public Health
Fall 2019-Summer 2020	Teaching Assistant Indiana University Fairbanks School of Public Health
Fall 2016-Spring 2018	Teaching Assistant Indiana University Fairbanks School of Public Health

PROFESSIONAL ORGANIZATION MEMBERSHIPS:

2019-present	American Association for Cancer Research
2016-present	American Association for the Advancement of Science
2016-present	Golden Key International Honour Society

PROFESSIONAL HONORS AND AWARDS:

<u>AWARDS</u>

2019-2020	Outrun the Sun Scholarship
09/2019-06/2020	Graduate Assistantship Indiana University Fairbanks School of Public Health
09/2016-08/2019	Pre-doctoral fellow T32 Interdisciplinary Behavioral Oncology Training Grant

Indiana University School of Nursing

HONORS

05/2018	Certificate of Achievement for Excellence in Cancer Res. 1st place – behavioral and population science/epidemiology
05/2017	Certificate of Achievement for Excellence in Cancer Res. 2nd place – behavioral and population science/epidemiology

CLINICAL ACTIVITY:

June/July 2018	Observing at IU Simon Cancer Center Hematology/oncology
August-December 2019	Observing at IU Simon Cancer Center Dermatology

TEACHING:

ADJUNCT PROFESSOR

Fall 2020	PBHL-E 404 / Cancer Epidemiology / Undergraduate
Spring 2020	PBHL-E404 / Building Cancer Epidemiology course
Fall 2019	PBHL-P 109 / Intro to Public Health / Undergraduate
Spring 2019	PBHL-P / Intro to Public Health / Undergraduate
Fall 2018	PBHL-E / Intro to Public Health / Undergraduate

TEACHING ASSISTANT

Summer 2020	PBHL-E 670 / Overview of Precision Health / Graduate
Spring 2020	PBHL-E 670 / Overview of Precision Health / Graduate
Fall 2019	PBHL-E 670 / Molec Epidemiology of Cancer / Graduate
Spring 2018	PBHL-E 109 / Intro to Public Health / Undergraduate
Fall 2017	PBHL-E 210 / Zombie Apocalypse / Undergraduate
Spring 2017	PBHL-E 210 / Zombie Apocalypse / Undergraduate
Fall 2016	PBHL-E 210 / Zombie Apocalypse / Undergraduate

RESEARCH/CREATIVE ACTIVITY

PRESENTATIONS

LOCAL

Marley, A. R., Carter-Harris, L., Gathirua-Mwangi, W. (2019, May). Smoking and Mammography Screening: The Roles of Knowledge and Health Beliefs. Abstract for poster presentation at the Indiana University Simon Cancer Center Cancer Research Day – Indianapolis, IN

Marley, A. R., Gathirua-Mwangi, W., Champion, V. L. (2018, May). The Relationship Between Mammography Adherence and a Multi-Factor Lifestyle Index. Abstract for poster presentation at the Indiana University Simon Cancer Center Cancer Research Day – Indianapolis, IN.

Marley, A. **R.**, Anderson, K., Zhang, J. (2017, May). Analysis of One-Carbon Nutrients and the Development of Pancreatic Cancer. Abstract for poster presentation at the Indiana University Simon Cancer Center Cancer Research Day – Indianapolis, IN.

NATIONAL

Marley, A. R., Carter-Harris, L., Gathirua-Mwangi, W. (2019, April). Smoking and Mammography Screening: The Roles of Knowledge and Health Beliefs. Abstract for poster presentation at the American Association for Cancer Research – Atlanta, GA

Fan, H., **Marley, A.**, Hoyt, M., Nan, H., Anderson, K., & Zhang, J. (2018, April). Associations between intake of calcium, magnesium, and phosphorus and risk of pancreatic cancer in a population-based case-control study in Minnesota. Abstract for poster presentation at the American Association for Cancer Research – Chicago, IL

Gathirua-Mwangi, W. G., Li, J., Champion, V. L., **Marley, A. R**., Song, Y. (2018, April). Prevalence and Trends of Metabolic Syndrome and Obesity among Cancer Survivors Compared to Adults with no Cancer, NHANES 1999-2014. Abstract for poster presentation at the American Association for Cancer Research – Chicago, IL

Marley, A., Anderson, K., Zhang, J. (2018, April). Analysis of One-Carbon Nutrients and the Development of Pancreatic Cancer. In *Annals of Behavioral Medicine* (Vol. 52, pp. S235-S235). Journals Dept, 2001 Evans Rd, Cary, NC 27513 USA: Oxford Univ Press Inc. Abstract for poster presentation at the Society of Behavioral Medicine – New Orleans, LA.

Biederman, E., **Marley, A. R.,** Champion, V. L. (2017, March). Predictors of Fecal Occult Blood Test (FOBT) Uptake Among Women. Abstract for poster presentation at the American Society for Preventive Oncology – Seattle, WA.

PUBLICATIONS:

<u>ORIGINAL</u>

Marley, A.R., Gathirua-Mwangi, W., Forman, M., Stump, T. E., Monahan, P., Champion, V. L. (2019). The Relationship between Mammography and a Multi-factor Behavioral Index. *Health Behavior and Policy Review*, *6*(6), 582-596.

Hoyt, M., Reger, M., **Marley, A**., Fan, H., Liu, Z., & Zhang, J. (2019). Vitamin K intake and prostate cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial. *The American Journal of Clinical Nutrition*, *109*(2), 392-401.

Champion, V. L., Christy, S. M., Rakowski, W., Gathirua-Mwangi, W. G., Tarver, W. L., Carter-Harris, L., Cohee, A. A., **Marley, A. R**.... & Rawl, S. M. (2018). A Randomized Trial to Compare a Tailored Web-Based Intervention and Tailored Phone Counseling to Usual Care for Increasing Colorectal Cancer Screening. *Cancer Epidemiology and Prevention Biomarkers*, *27*(12), 1433-1441.

Gathirua-Mwangi, W., Cohee, A., Tarver, W. L., **Marley, A**., Biederman, E., Stump, T., ... & Champion, V. L. (2018). Factors Associated with Adherence to Mammography Screening Among Insured Women Differ by Income Levels. *Women's Health Issues*, *28*(5), 462-469.

Marley, A. R., Fan, H., Hoyt, M. L., Anderson, K. E., & Zhang, J. (2018). Intake of methyl-related nutrients and risk of pancreatic cancer in a population-based case-control study in Minnesota. *European journal of clinical nutrition*, *72*(8), 1128

Yang, K., **Marley, A.,** Tang, H., Song, Y., Tang, J. Y., & Han, J. (2017). Statin use and non-melanoma skin cancer risk: a meta-analysis of randomized controlled trials and observational studies. *Oncotarget*, *8*(43), 75411-75417.

<u>REVIEW</u>

Marley, A. R., & Nan, H. (2016). Epidemiology of colorectal cancer. *International journal of molecular epidemiology and genetics*, *7*(3), 105.

GRANTS IN RESEARCH:

<u>SUBMITTED BUT NOT FUNDED</u>

The Association between Citrus Consumption and Skin Cancer: An Analysis of Risk and Nutrient-gene Interaction. / NCI/NIH / PI / Submitted August 2019

SERVICE:

<u>AD HOC REVIEWER</u>

2019	*Cancer Medicine*
2020	*International Journal of Cancer*