MELANOMA RISK FACTORS WITHIN THE PROSTATE, LUNG, COLORECTAL, AND OVARIAN CANCER SCREENING TRIAL

by

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ABSTRACT

Melanoma is among the leading causes of cancer death in younger adults. Established risk factors are mostly nonmodifiable with the exception of exposure to ultraviolet radiation. Because melanomas are not limited to areas of the body that are exposed to ultraviolet radiation and because other risk factors do not account for many cases of melanoma, it is expected that there are yet unidentified risk factors.

Overall, melanoma incidence rates continue to rise despite efforts to educate people about the risk of sun exposure and tanning beds. This increase combined with the aggressive and dangerous nature of melanoma in advanced stages has fueled campaigns for prevention and early diagnosis. When caught early, melanoma treatment is relatively successful when treated with surgery.

The present study evaluates risk factors that have been suggested by previous research done primarily on non-U.S. populations. These include vitamin D levels, body mass index, and height. The databases in some European countries are extensive and have provided a platform to investigate these risk factors. The limitations of this thesis are few but important. Germaine to proving the necessity of this study is the limitation that the cohorts are very geographically narrow.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer cohort provides a large and geographically diverse U.S. population for this study. It enrolled and followed over 150,000 people for 13 years each to evaluate the efficacy of screening for each of

the 4 cancer types. Incidence of all other cancer types were also recorded but not studied as they are not the primary aims of the PLCO.

In this review of the data provided by the PLCO, the following associations or lack thereof were found:

High self-reported vitamin D intake seemed to predict an increased risk of melanoma among men but not women. There was no dose response curve or trend between reported vitamin D intake and melanoma risk. Serum vitamin D levels did not seem to predict disease severity as measured by tumor thickness.

There was an interesting correlation between melanoma risk and body mass index (BMI) calculated from reported height and weight at age 20. In men, being underweight at age 20 seemed to be protective while in women being overweight at age 20 seemed to be protective. BMI did not correlate with disease severity as measured by tumor thickness.

Height seemed to be correlated to melanoma risk. There was significant trend between increasing height and melanoma risk in men and women. Those in the highest quartile of height were at a significantly increased risk compared to those in the lowest quartile.

In summary, this analysis of PLCO data confirms the difficulty of identifying risk factors for melanoma. We corroborated the finding that height is positively correlated with melanoma risk; however, BMI and vitamin D findings were not as clear.

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I commit to continue to use this education and my expanded abilities to better the community and people that surround me.

CHAPTER 1

INTRODUCTION

Melanoma is most commonly a cancer that originates in the skin. In 2016, it is expected that there will be more than 75,000 cases of melanoma and more than 10,000 deaths in the US.[1] The lifetime risk of melanoma continues to rise and may affect as many as 1 in 50 people in the US. It is currently accepted that the primary modifiable risk factor for melanoma is exposure to ultraviolet (UV) light. Knowledge of this risk factor has allowed public awareness campaigns to stem the tide of melanoma rates in Australia.[2-4] While it is hoped that public awareness in the US will have a similar effect, the rates of melanoma continue to increase steadily.[1] Other known risk factors for melanoma are not modifiable. They include lighter skin complexion, higher numbers of or clinically atypical nevi (moles), genetic predisposition, age, and gender. While altitude and latitude play into risk, they do so by modification of UV exposure.

Understanding the risk factors of melanoma has proven beneficial in at least two ways. When possible, primary prevention through reduction of UV exposure has been proven in Australia.[5] Secondary prevention (reduction of disease specific morbidity and mortality) has also been effective as evidenced by the steady mortality rate relative to the steady increase in incidence of melanoma in the US. The National Cancer Institute's "Surveillance, Epidemiology and End Results Program" (SEER) shows that while melanoma rates are increasing in the US, 5-year disease-specific survival has increased

from 81% in 1975 to 93% in 2012.[1] While there have been advances in melanoma therapies that started in 2010, [6] these data do not reflect those advances. It is likely that the improvement in rates is attributable to secondary prevention (ie, earlier diagnosis).

Melanoma is an aggressive cancer due to the melanocyte's embryonic origin in the neural crest. As melanocytes are derived from the neural crest, they have an ability to migrate through the body. The spread of melanoma (metastasis) requires tumor cells to penetrate deep into the dermal anatomy to access the vascular or lymphatic bundles that lie in the dermis. Thus, secondary prevention (ie, early diagnosis and treatment before metastasis occurs) is crucial. This also explains why the most important prognostic factor at diagnosis is the thickness of the tumor (also known as Breslow depth).[7]

In an effort to further understand the risk factors of melanoma and potentially allow more focused efforts in primary and secondary prevention, this dissertation will evaluate low vitamin D levels, increased BMI, and increased height as potential risk factors of both incidence and severity of melanoma. The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial data will be used for secondary data analysis to accomplish these aims.

1.1 Vitamin D and Melanoma

The benefits of adequate vitamin D levels are well known. However, it appears that low vitamin D levels may be relatively common. More than half of some racial minorities have been found to have low serum levels of vitamin D.[8] The obvious consequences of low vitamin D include rickets and bone fragility. Adequate vitamin D levels have been shown to protect against some cancers[9,10] and has been shown to reduce the severity of some chronic illnesses.[11-14]

With increasing evidence of the benefit of adequate levels of vitamin D, more efforts are being made to increase vitamin D levels. These efforts include dietary and behavioral interventions (increasing UV exposure). [15-17] Dietary sources of vitamin D are helpful, but in the absence of adequate dietary intake or supplementation, increased sun or UV exposure is required to increase vitamin D levels. The danger in this is the corresponding increased risk of skin cancer related to UV exposure. Wrapped up in this complex interaction of variables is the question of what influence vitamin D levels have on skin cancer and, in particular, melanoma risk and behavior. In this dissertation, we aim to evaluate the relationship of vitamin D intake and melanoma risk and Breslow thickness within the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer cohort. It is hypothesized that high vitamin D intake and high serum levels are correlated and protective against melanoma. Also, high vitamin D levels are hypothesized to be associated with a shallower Breslow thickness at the time of melanoma diagnosis

1.2 BMI and Melanoma

While there seems to be a reproducible increase in the risk of melanoma among males with high BMI,[18,19] there is yet to be any physiologic explanation for this phenomenon. The largest study conducted in a U.S. population did not show an association between BMI and melanoma risk but only included women.[20] A confirmatory study looking at BMI within a larger U.S. cohort of men and women is, therefore, warranted. Studies done outside the US that included men suggested a higher risk of melanoma among men in the highest groupings of BMI.[19] Sergentanis et al found a similar increased risk among men who were overweight.[18] A corresponding dose response or trend was not seen in these studies raising the question of unidentified effect

modifiers or confounders and raises doubt about the strength of evidence for this proposed association.

1.3 Height and Melanoma

Some studies suggest an unexplained increased risk of melanoma among men in higher categories of BMI. The lack of a physiologic explanation or a predictable linear relationship between BMI and melanoma suggests other factors may be at play. There have been a few studies that suggest height as a potential risk factor independent of weight.[19,21-23] Moreover, there seems to be a linear relationship with increased risk of melanoma and increased height. One study, in particular, associated height with an increased nevus count.[24] Studies of melanoma cell lines in vitro have revealed a high level of growth hormone receptors.[25] Meyle et al found that increased childhood height was correlated with a higher risk of melanoma as an adult.[21] When all of these factors are considered in the context of the evidence that UV exposure during childhood and teenage years is more damaging, one possibility may be that human growth factor influences melanocytes in a way that makes them more susceptible to UV damage.

1.4 The Present Study

The majority of studies evaluating these potential risk factors of melanoma have included large cohorts that are either demographically limited or not based in the US. The PLCO is of particular value given that it represents a larger U.S. cohort that is demographically and geographically diverse.

The methods of the PLCO have been previously published in detail.[26] It is a population-based randomized trial developed to evaluate the effect of screening for prostate, lung, colorectal, and ovarian cancers on cancer-specific mortality. The trial

included 10 screening centers across the US and enrolled 78,216 women and 76,685 men all between the ages of 55 and 74.

Each participant completed a baseline and dietary questionnaire. The dietary questionnaire has been validated in three different studies.[27-29] After meeting enrollment criteria, each participant was randomized into the intervention arm (receiving intervention screening for the targeted cancers) or the control arm (standard of care). Those in the intervention arm received PLCO cancer-specific screening for the first 6 years and were then followed for 7 additional years.

Evaluating these risk factors (vitamin D, BMI, and height) using the data collected by the PLCO may shed new light on the topic and may strengthen or refute associations with melanoma seen in smaller or non-U.S. cohorts.

CHAPTER 2

VITAMIN D INTAKE, TUMOR THICKNESS, AND MELANOMA RISK WITHIN THE PROSTATE, LUNG, COLORECTAL, AND OVARIAN COHORT

2.1 Abstract

2.1.1 Introduction

The incidence rate of melanoma continues to increase despite public awareness campaigns. Other than limiting ultraviolet (UV) light exposure, a few factors are known to prevent or reduce severity of melanoma. Limiting UV exposure may cause vitamin D deficiency, a very prevalent condition with known detrimental health implications. This study aims to evaluate a potential relationship between vitamin D intake and melanoma risk within the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer cohort.

2.1.2 Methods

The PLCO followed more than 150,000 people for 13 years. Each participant's health status was tracked and participants were asked to fill out multiple surveys including a food frequency questionnaire. Oral (both diet and supplemental) vitamin D intake was collected from this questionnaire. Health histories and demographic information were collected from each participant at the time of enrollment. A small subset of participants had serum vitamin D levels available as well. Over 1,300 PLCO

participants developed melanoma during the course of follow up. Both Cox and linear regressions were used to estimate the risk of melanoma and the association with tumor thickness.

2.1.3 Results

While not statistically significant, there was a suggestion of an increased risk of melanoma among men within the highest quartile of vitamin D intake (HR 1.27, 95% CI 0.99, 1.61). Participants in the highest quartile of vitamin D intake who enrolled at low UV index centers may be at higher risk for melanoma than individuals who were in the high vitamin D intake quartile and enrolled at high UV centers (HR 1.24, 95% CI 0.99, 1.56). When including only invasive melanoma, women in the highest quartile of vitamin D intake experience decrease risk (HR 0.63, 95% CI 0.41, 0.96). Tumor thickness was inversely correlated with higher levels of education ($p < .001$) and being White ($p < .001$). Serum vitamin D levels did not seem to predict tumor thickness. The correlation between serum vitamin D levels and reported dietary intake of vitamin D was weak ($r = 0.17$, $p < .001$).

2.1.4 Conclusion

High reported vitamin D intake in this study seemed to predict an increased risk of melanoma among men. When looking at invasive melanoma in women, there was a protective effect of increasing levels of vitamin D intake.

2.2 Introduction

It is estimated that there will be more than 75,000 cases of melanoma and approximately 10,000 melanoma-related deaths in the US in 2016.[1] The lifetime risk of developing melanoma is 1 in 50.[30] Despite the efforts of the medical community,

incidence rates of melanoma are still on the rise.[31] Limiting exposure to ultraviolet radiation, remains the only modifiable risk factor for melanoma. Current preventive strategies focus on avoidance of tanning beds, education about sun safe behaviors, and proper use of sun block or sun screen.[32,33] There is insufficient evidence to concretely support or refute most dietary factors as protective or harmful in regards to melanoma risk. One of the key dietary suspects in this process is vitamin D; a vitamin produced, in part, in the skin using the same radioactive rays that are known to contribute to melanoma risk. Finding a balance between this risk and the known benefits of adequate vitamin D levels has become paramount.

The Institute of Medicine (IOM) released its guidelines for vitamin D in 2011 which immediately attracted criticism as being too conservative (ie, not recommending an adequate daily allowance of vitamin D).[34,35] According to the IOM, the serum vitamin D levels should be above 20ng/ml. A U-shaped distribution was seen when relating vitamin D levels to cardiovascular disease, bone injury due to falls, and pancreatic cancer suggesting that there is a point of maximum benefit in vitamin D levels. This was estimated at approximately 50ng/ml. Using 20ng/ml as a threshold for deficiency, Forrest et al showed that more than 41% of the U.S. population would be considered vitamin D deficient with more than 80% of African-Americans being deficient.[36] It has been suggested that a lower limit for normal be set at 30ng/ml.[37] Using this level as the cutoff might put more than half of the U.S. population in the deficient category.

Two case-control studies evaluated melanoma risk by dietary vitamin D levels assessed by food frequency questionnaires. One of these reported an odds ratio for developing melanoma of 0.61 (95% CI 0.40-0.95) when comparing the highest 20% of vitamin D levels to the lowest 20%.[38] The second study did not detect a difference in risk

of melanoma among those who ingested more vitamin D rich foods.[39] Three case-control studies have evaluated the influence of vitamin D on nonmelanoma skin cancer (NMSC) using food frequency questionnaires. One of these showed no relationship (OR = 0.8, 95% CI 0.58, 1.10), one showed an inverse relationship (OR in highest quartile of vitamin D intake = 0.54, 95% CI 0.31, 0.96), and one showed an inverse relationship when relying on hip fracture as a surrogate of vitamin D level (OR = 0.90, 95% CI 0.85–0.94).[40-42]

Three case-control studies measured serum vitamin D. Among these, one showed no difference in vitamin D levels between melanoma cases and controls,[43] one showed significantly lower levels of vitamin D in patients with stage IV melanoma compared to patients with earlier stage disease,[44] and one showed that weekend sun exposure was correlated with higher serum vitamin D levels and had a protective effect (OR = 0.46, 95% CI 0.30-0.72).[45] The last of these three studies was the largest but did not include serum vitamin D levels on the majority of population based controls, and therefore did not report specific data on vitamin D levels. Additionally, these studies did not adjust for dietary intake of vitamin D or for small sample size. One large prospective cohort study failed to show any relationship between vitamin D and melanoma but was limited by the lack of serum vitamin D levels.[46]

Tumor thickness, measured microscopically to the hundredth of a millimeter, is the most accurate predictor of prognosis in melanoma. The measurement is objective and is defined as the thickness of the tumor starting at the granular layer of the epidermis. One prospective cohort showed that a 20 nmol/L increase in serum vitamin D levels was correlated with a lower tumor thickness at diagnosis (p = .002) and was protective against relapse and death (HR = 0.79, 95% CI 0.64–0.96).[47] This study seems to be the most

persuasive and suggests that higher vitamin D levels may be both protective prior to diagnosis and beneficial after diagnosis. A second, smaller prospective cohort looked at levels of serum vitamin D at the time of diagnosis and found that low levels of vitamin D were associated with thicker melanomas. It did not find that high vitamin D levels were associated with a better prognosis.[48] Additionally, Saiag et al[49] found that fluctuations in serum vitamin D levels after melanoma diagnosis conferred a poorer prognosis.

The effect of vitamin D on melanoma risk has yet to be clearly defined. It is apparent that accurately measuring UV exposure (a significant contributor to vitamin D levels and melanoma risk, as noted above) presents a formidable obstacle. While there is not significant evidence that adequate vitamin D levels are protective against melanoma, there is evidence to suggest adequate levels may be beneficial in patients with late stage disease.[44] This review of the PLCO cohort is the largest U.S. cohort to look at the influence of vitamin D on melanoma risk. It also has a benefit of having serum vitamin D levels on a subset of the cohort. Finally, tumor thickness (the most important prognostic indicator) is available on nearly 500 melanoma cases.

2.3 Methods

2.3.1 PLCO Methods

The PLCO is a population-based randomized trial developed to evaluate the effect of screening for prostate, lung, colorectal, and ovarian cancers on cancer specific mortality.[26,50] The trial included 10 screening centers across the US and enrolled 78,216 women and 76,685 men all between the ages of 55 and 74 at baseline.[26]

At enrollment, PLCO study participants were asked to complete a gender-specific baseline questionnaire. Both questionnaires were 8 pages long; the male version included

49 questions and the female version included 61 questions. Participants also completed an extensive dietary questionnaire that included 156 items over 20 pages. A second dietary questionnaire was implemented later in the study allowing for a second measure on some participants. Dietary questionnaires are available on more than 125,000 study participants. Other data available on these patients include a baseline questionnaire including: family history of cancer, demographic data, alcohol/tobacco use, and metabolic measurements including weight and height, and reproductive factors. Certain oral medication use was collected where relevant. On a limited number of these study participants, serum vitamin D levels have also been measured. The dietary questionnaire has been validated in three different studies.[27-29] Additional details on the methods of this trial were published previously.[26]

We analyzed the data using Stata/IC 14.1.[51] Of the 154,897 PLCO participants, 111,270 were included in this study (see Figure 2.1). The majority of those excluded did not have a self-reported vitamin D intake available (*n* excluded = 31,293). A smaller number did not complete a baseline questionnaire (*n* excluded = 4,896) or had history of cancer prior to the baseline questionnaire (*n* excluded = 6,848). Of the remaining participants, 854 had melanoma.

Descriptive statistics were used to define the variables of interest for this study. Age in years was divided into 4 categories (55–59, 60-64, 65–69, 70 and above). Because there were so few non-White PLCO participants who developed melanoma, race was categorized into White and non-White categories only. Education categories were divided into those who did not finish high school, high school graduates, those who did some college or posthigh school education, and college graduates.

2.3.2 Vitamin D

The amount of vitamin D consumed was calculated from the food frequency questionnaires and included supplement/vitamin use. Nutrient databases were developed for the dietary questionnaire based on the U.S. Department of Agriculture food supply database[52] and the Nutrition Data System for Research at the University of Minnesota.[53] The nutrient values (including vitamin D) were calculated from the database for each subject based on the frequency with which individuals reported they ate/drank each food or beverage and the corresponding portion size. Vitamin D intake was reported in mcg/day separately for food sources and supplements as well as sum total of all vitamin D intake. This variable was divided into quartiles for this study.

Serum vitamin D levels, reported as ng/ml, were available from 5,906 of the PLCO participants. Blood collection was categorized by season of draw to control for seasonal variation of vitamin D as follows: December to February, March to May, June to August, and September to November. Each season's quartiles were then combined back into one variable to take into account the season of blood draw. In other words, season-specific quartiles were created, so that the vitamin D quartiles are not simply a reflection of the season of blood sample collection (see Table 2.1). Correlations between serum and dietary vitamin D levels were calculated using the adjusted quartiles for both.

2.3.3 UV Exposure

UV exposure was based on the average UV measure of the study center where the person was enrolled. The average UV index for the last 4 years for each city was used to generate an average UV index for that city. These numbers were assessed by the Environmental Protection Agency and were reported by www.homefacts.com[54] as annual

averages. For each city, the average of the annual UV index for the years 2011-2015 was calculated. High UV index was defined as 5 or greater and low UV index was less than 5 for the model stratified on UV index.

2.3.4 Tumor Thickness

Tumor thickness is recognized as the most accurate prognostic factor in melanoma but was not reported to the PLCO. In order to evaluate effects on tumor thickness, de-identified pathology reports, if available, were obtained for those participants who developed melanoma. Of the 1,432 cases of melanoma, 520 had available pathology reports. These were individually reviewed to record tumor thickness which was available in 473 cases.

2.3.5 Statistical Analysis

Two sample *t* tests and chi-square analysis were used to evaluate the difference between melanoma cases and noncases among demographic groups. A Cox proportional-hazards model was used to estimate the risk of melanoma based on dietary and serum vitamin D levels. A second analysis focused on the subset of participants with invasive melanoma and estimated risk by dietary vitamin D only. In this model, univariate analysis was used for crude hazard ratios and multivariate analysis included sex, age, average UV at study center, education, and race. Additional similar models were used to stratify on sex and on high versus low UV centers.

2.4 Results

Table 2.2 shows the characteristics of the PLCO cohort participants who developed melanoma compared to the PLCO participants who did not. Participants who developed melanoma were slightly older (mean age at study entry 63 years) compared to

those who did not (mean age at study entry 62.5 years, $p = .033$). Of participants who developed melanoma, more were male than female (62.4% compared to 37.6%, $p < .001$). Melanomas were nearly all seen in White participants ($n = 848$, 99.3%) with only 6 (0.7%) cases developing in participants of other races ($p < .001$). The risk of melanoma increased with education level. Those who did not graduate high school represented 6.5% of the total population but had less than 3% of the melanomas while those with college degrees represented roughly 35% of the population and had 50% of the melanomas (p trend < .001). The majority of participants had a BMI within the normal and overweight range. The distribution of melanoma did not vary significantly differently by BMI.

In univariate analysis, the risk of melanoma in participants who reported ingesting 13.5 mcg/day or more of vitamin D was roughly 1.36 (95% CI 1.12–1.64) times that of those who reported ingesting less than 3.86 mcg/day of vitamin D (Table 2.3). This hazard ratio reduced to 1.17 (95% CI 0.97–1.42) when adjusted for sex, age, average UV at the study center, education, and race. In the univariate analysis, there was a significant trend reflecting an increased risk with increased vitamin D consumption (univariate p for trend =.006). This trend was not seen in multivariate analysis. When stratifying on sex, an increased risk of melanoma was suggested for men with higher vitamin D intake. Among participants from low UV centers who were in the highest quartile of vitamin D intake, the HR of 1.24 was very close to statistically significant (95% CI 0.99, 1.56).

Univariate analysis of the subset that excluded in situ melanomas showed significant results when looking at male participants in the highest quartile of vitamin D intake (Table 2.4). These participants had an increased risk of invasive melanoma (crude HR 1.42, 95% CI 1.05, 1.92) but this did not persist in multivariate analysis. There was a protective effect seen in multivariate analysis among women who were in the highest

quartile of vitamin D intake (HR 0.63, 95% CI 0.41, 0.96). A significant trend was noted with increasing vitamin D intake relating to lower invasive melanoma risk (p trend = .038).

When evaluating the subset of participants for whom serum vitamin D measurements were available, an association with melanoma was not observed (data not shown). In this subset, an intra-participant correlation between the self-reported dietary vitamin D quartiles and objective serum vitamin D quartiles taking into account the season of draw was seen ($r = .17$, $p < .001$).

In multivariate linear regression, vitamin D intake did not seem to influence the tumor thickness in the cases where a path report was accessible (Table 2.5). Factors that did influence tumor thickness included race and education. Tumor thickness increased with higher levels of education (p for trend < .001) and was, on average 2.9 mm greater among those with a race other than White ($p < .001$).

2.5 Discussion

This study suggests that higher intake of vitamin D does not generally protect against melanoma. In fact, males in the highest quartiles of vitamin D intake may have an increased risk of melanoma. The small cohort studied by Wyatt et al[48] seemed to suggest this point as well. Furthermore, the subset excluding in situ melanomas showed an association between low levels of vitamin D (those in the second to lowest quartile) and risk of invasive melanoma in those who were in high UV areas. This pattern, namely lower levels of vitamin D increasing risk and higher levels not being protective has also been described in the literature.[49] This likely reflects a complex biological interaction between melanoma and vitamin D and may also reflect the difficulty to control for UV

exposure adequately.[55,56] It may hint at a paradoxical influence of vitamin D on melanoma disease inception compared to disease progression.

When considering only invasive melanomas among women, however, there seems to be a protective effect. Not only was there a significant protective benefit from vitamin D intake among woman in the highest quartile, but there was also a trend suggesting decreased risk with increasing vitamin D intake. This may highlight a biological difference of melanoma in women compared to men as suggested by Nosrati et al[57]

The fact that risk related to higher vitamin D was higher for those who enrolled at a low UV index center was unexpected. While this would support the argument that vitamin D increases the risk of melanoma independently, it may also be the result of unmeasured confounders. It is possible that those participants with the highest levels of vitamin D intake include those who are aware of vitamin D health benefits. This group is likely to get more UV exposure in an effort to ensure higher levels of vitamin D in combination with adequate or high dietary intake. The use of average UV indices at the study center would not adequately control for the variability within the participants at each study center. Conversely, albeit less likely, it is possible that higher vitamin D intake is somehow independently related to melanoma risk.

While there did not seem to be an association between vitamin D intake and tumor thickness, there was the suggestion of a trend towards deeper tumors in higher quartiles of vitamin D intake. The fact that non-White race and lower education level[58] (as a proxy for socioeconomic status) may be correlated with a deeper tumor has been described in other studies. There is also clear evidence that the rate of low vitamin D is more prominent among non-White races. It is possible that a higher number of invasive melanomas with accurate tumor thicknesss might have pushed these data towards more

significance. In other words, perhaps we did not have adequate statistical power to detect associations with tumor thickness. Because there were few participants with both serum vitamin D and tumor thickness, we were unable to analyze the association between these two factors.

This study is novel in two ways. First, it is among the few that also evaluated serum vitamin D levels prior to the diagnosis of melanoma, and second, we attempted to correlate serum levels and self-reported intake while controlling for season of blood draw. The correlation between these two measures was positive but relatively weak. Dietary vitamin D did not influence tumor thickness and weakly correlated with serum levels. These data suggest that careful monitoring of serum levels, dietary levels, and UV exposure in a prospective fashion may be the best approach to further studying these possible associations.

The size of the study population and the data available over a 13 year period for each participant provides strength to the findings. It is among the first of its size based on a cohort in the US. It included an *a priori* validated food frequency questionnaire as well as detailed questionnaires and data collection about potential covariates/confounders. Due to the methods of collection and the accuracy of the study timeline, there is also less temporal ambiguity between data collection, blood sample vitamin D measures, and incident melanoma.

Oral intake of vitamin D was assessed by a self-reported food frequency questionnaire that may not have been done at the same time as the serum draw. The lack of temporal correspondence in some cases between completing the intake assessment and serum collection may have reduced the amount of correlation between the two measures. However, a study of long term stability of vitamin D levels within the PLCO suggests

relative long term stability despite seasonal variation over 5 years (Spearman correlation coefficient 0.53). [59] Understanding the long term stability makes the effect of temporal variation seem less likely to have significantly impacted the results of this study. Other limitations include the lack of serum vitamin D levels on all participants and the lack of tumor thickness on a portion of the melanoma cases. A better method to control for UV exposure and socioeconomic status might also improve the accuracy of findings. Our study used the UV indices at the study center as a proxy of UV indices at the participant's home. Using each participant's zip code or partial zip code may have allowed more accuracy. In addition, each participant's occupation and hobbies may influence how much UV exposure they get and should be controlled for. On the other hand, it is not likely that occupation and hobbies would influence vitamin D consumption.

2.6 Conclusion

The rates of melanoma in the PLCO trial were consistent with the published rates in the US, suggesting that the PLCO population is a representative sample. Known disparities based on race and economic status are reinforced and must continue to be addressed.

High reported vitamin D intake in this study was associated with an increased risk of melanoma among men. This does not fit with the findings in the rest of the literature[42,46,56] and may call into question the adequacy of self-reported measures to estimate vitamin D. However, our study showed a correlation between the self-reported measures and the serum levels, where available. Further research may elucidate better boundaries of where using these methods is appropriate.

When looking at invasive melanoma in women, there was a protective effect of

increasing levels of vitamin D intake. Because we did not have serum levels available, further studies to evaluate this effect are necessary. Additionally, melanoma biology may be different between men and women particularly when it comes to vitamin D.

When combining the literature and the findings of this study, it seems likely that low levels of vitamin D connote higher risk of melanoma while higher levels do not appear to be protective. As low levels of vitamin D are common and known risk factors for many other diseases,[60-67] it seems reasonable to encourage screening and supplementation. Further investigation before recommending supplementing with vitamin D for groups with higher risk of melanoma seems warranted. Future prospective studies incorporating UV controlled, serum vitamin D sampling are needed.

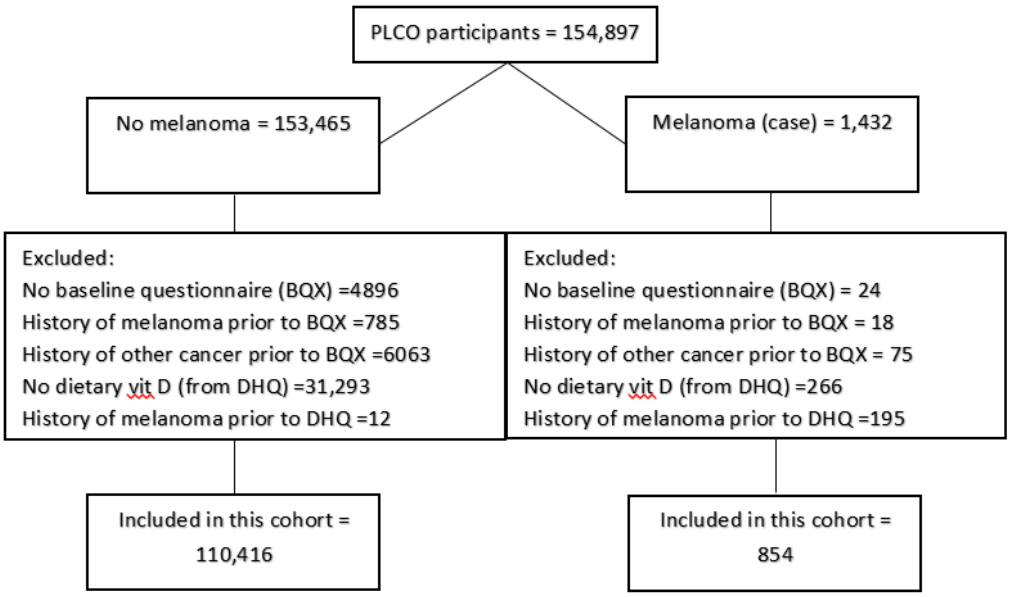

Figure 2.1. CONSORT Diagram for Vitamin D.

Table 2.1. Serum Vitamin D Ranges by Season of Draw and Quartile (ng/ml)

Quartile	Winter	Spring	Summer	Fall
1	3.2–16.3	2.5–16.4	3–21.1	4.1–20.6
2	16.4–21.3	16.5–21.7	21.2–26	20.7–26.1
3	21.4–27.3	21.8–27.5	26.1–32	26.2–31.9
4	27.4–75.5	27.6–70.8	32.1–89.4	32–72.8

Table 2.2. Comparison of Characteristics of Participants Who Developed Melanoma to Those Who Did Not

Characteristic	Melanoma		No melanoma		*p*
Average age (in years)	854	63.0	110,416	62.5	.033
	n	%	*n*	%	
Categories by age (in years)					
<60	252	29.5	37,093	33.6	
60–64	260	30.4	34,311	31.1	
65–69	223	26.1	24,927	22.6	
≥70	118	13.8	14,085	12.8	
Sex					
Male	533	62.4	54,469	49.3	
Female	321	37.6	55,947	50.7	<.001
Race					
White	848	99.3	99,874	90.5	
Other	6	0.7	10,542	9.5	<.001
BMI					
<18.5	8	0.9	711	0.6	
18.5–24.9	269	31.5	35,678	32.3	
25–29.9	391	45.8	46,621	42.2	
≥30	175	20.5	25,913	23.5	
Missing	11	1.3	1,493	1.4	.132
Education					
Did not graduate high school	25	2.9	7,136	6.5	
High school graduate	130	15.2	25,893	23.5	
Some college or posthigh school training	266	31.1	37,889	34.3	
College graduate	430	50.4	39,273	35.6	
Missing	3	0.4	225	0.2	<.001

Note. Chi-square analysis.

Table 2.3. Vitamin D and Risk of Melanoma

Characteristic	Crude hazard ratio (95% *CI*)	*p*	Multivariate hazard ratio (95% *CI*)	*p*
Dietary vitamin D estimate (mcg/day)[a]				
Dietary D q1 (<3.86)	1.00		1.00	
Dietary D q2 (3.86–10.73)	1.19 (0.98, 1.45)	.083	1.06 (0.87, 1.29)	.555
Dietary D q3 (10.74–13.49)	1.09 (0.89, 1.33)	.394	1.05 (0.85, 1.28)	.665
Dietary D q4 (≥13.5)	**1.36 (1.12, 1.64)**	**.002**	1.17 (0.97, 1.42)	.109
p trend		**.006**		.129
Serum vitamin D (n = 6,729)[b]				
Quartile 1	1.00		1.00	
Quartile 2	0.86 (0.38, 1.92)	.711	1.02 (0.47, 2.21)	.961
Quartile 3	1.21 (0.58, 2.52)	.609	0.84 (0.37, 1.92)	.686
Quartile 4	1.35 (0.66, 2.79)	.410	1.59 (0.78, 3.26)	.205
p trend		.214		.236
Risk of melanoma stratified by sex[c]				
Male				
Dietary D q1 (<3.86)	1.00		1.00	
Dietary D q2 (3.86–10.73)	1.17 (0.91, 1.50)	.214	1.09 (0.85, 1.39)	.517
Dietary D q3 (10.74–13.49)	1.18 (0.90, 1.54)	.237	1.07 (0.82, 1.40)	.617
Dietary D q4 (≥13.5)	**1.44 (1.13, 1.83)**	**.003**	1.27 (0.99, 1.61)	.055
p trend		**.003**		.058
Female				
Dietary D q1 (<3.86)	1.00		1.00	
Dietary D q2 (3.86–10.73)	1.12 (0.80, 1.55)	.515	1.03 (0.74, 1.43)	.874
Dietary D q3 (10.74–13.49)	1.10 (0.81, 1.49)	.530	1.00 (0.74, 1.35)	.994
Dietary D q4 (≥13.5)	1.17 (0.85, 1.61)	.326	1.02 (0.74, 1.40)	.912
p trend		.362		.957
Risk of melanoma stratified by UV[d]				
High UV				
Dietary D q1 (<3.86)	1.00		1.00	
Dietary D q2 (3.86–10.73)	1.07 (0.73, 1.56)	.727	0.89 (0.61, 1.31)	.579
Dietary D q3 (10.74–13.49)	0.86 (0.58, 1.26)	.439	0.80 (0.54, 1.18)	.256
Dietary D q4 (≥13.5)	1.23 (0.86, 1.77)	.252	0.98 (0.68, 1.41)	.925
p trend		.445		.850
Low UV				
Dietary D q1 (<3.86)	1.00		1.00	
Dietary D q2 (3.86–10.73)	1.24 (0.99, 1.56)	.067	1.12 (0.89, 1.42)	.321
Dietary D q3 (10.74–13.49)	1.19 (0.94, 1.51)	.144	1.16 (0.91, 1.47)	.223
Dietary D q4 (≥13.5)	**1.41 (1.13, 1.77)**	**.003**	1.24 (0.99, 1.56)	.058
p trend		**.006**		.061

[a] Covariates include gender, age, average UV at study center, education, and race.
[b] Based on season of draw, see Table 2.1 for ranges
[c] Covariates include age, average UV at study center, education, and race
[d] Covariates include gender, age, education, and race

Table 2.4. Vitamin D and Risk of Invasive Melanoma

Characteristic	Crude hazard ratio (95% *CI*)	*p*	Multivariate hazard ratio (95% *CI*)	*p*
	Dietary vitamin D estimate (mcg/day)[a]			
Dietary D q1 (<3.86)	1.00		1.00	
Dietary D q2 (3.86–10.73)	1.05 (0.82, 1.35)	.669	0.93 (0.73, 1.20)	.611
Dietary D q3 (10.74–13.49)	1.00 (0.78, 1.28)	.979	0.97 (0.76, 1.25)	.841
Dietary D q4 (≥13.5)	1.15 (0.91, 1.47)	.247	0.99 (0.78, 1.26)	.785
p trend		.331		.948
	Risk of melanoma stratified by sex[b]			
Male				
Dietary D q1 (<3.86)	1.00		1.00	
Dietary D q2 (3.86–10.73)	1.14 (0.84, 1.56)	.397	1.07 (0.78, 1.46)	.678
Dietary D q3 (10.74–13.49)	1.25 (0.89, 1.74)	.193	1.13 (0.81, 1.58)	.468
Dietary D q4 (≥13.5)	**1.42 (1.05, 1.92)**	**.022**	1.26 (0.93, 1.70)	.139
p trend		**.018**		.117
Female				
Dietary D q1 (<3.86)	1.00		1.00	
Dietary D q2 (3.86–10.73)	0.83 (0.54, 1.26)	.371	0.77 (0.51, 1.17)	.222
Dietary D q3 (10.74–13.49)	0.84 (0.57, 1.22)	.359	0.77 (0.52, 1.12)	.172
Dietary D q4 (≥13.5)	0.72 (0.47, 1.10)	.127	**0.63 (0.41, 0.96)**	**.032**
p trend		.145		**.038**
	Risk of melanoma stratified by UV[c]			
High UV				
Dietary D q1 (<3.86)	1.00		1.00	
Dietary D q2 (3.86–10.73)	1.09 (0.66, 1.78)	.746	0.90 (0.55, 1.48)	.682
Dietary D q3 (10.74–13.49)	0.78 (0.46, 1.30)	.340	0.73 (0.43, 1.22)	.229
Dietary D q4 (≥13.5)	1.28 (0.80, 2.05)	.303	1.01 (0.63, 1.61)	.983
p trend		.532		.894
Low UV				
Dietary D q1 (<3.86)	1.00		1.00	
Dietary D q2 (3.86–10.73)	1.05 (0.79, 1.39)	.757	0.95 (0.71, 1.26)	.716
Dietary D q3 (10.74–13.49)	1.08 (0.81, 1.44)	.592	1.07 (0.80, 1.42)	.654
Dietary D q4 (≥13.5)	1.11 (0.84, 1.47)	.466	0.98 (0.74, 1.30)	.884
p trend		.445		.798

[a] Covariates include gender, age, average UV at study center, education, and race.
[b] Covariates include age, average UV at study center, education, and race
[c] Covariates include gender, age, education, and race

Table 2.5. Tumor Thickness and Dietary Vitamin D

Covariate	Coefficient			
	Univariate (95% CI)	*p*	Multivariate (95% CI)	*p*
Dietary vitamin D estimate (mcg/day)				
Dietary D q1 (<3.86)	—		—	
Dietary D q2 (3.86–10.73)	-0.24 (-0.63, 0.14)	.219	-0.04 (-0.42, 0.33)	.830
Dietary D q3 (10.74–13.49)	0.03 (-0.36, 0.42)	.890	0.27 (-0.11, 0.65)	.166
Dietary D q4 (≥13.5)	0.08 (-0.29, 0.45)	.683	0.23 (-0.13, 0.59)	.205
p trend		.325		.076
Race				
White	—		—	
Non-White	**3.33 (2.14, 4.51)**	**<.001**	**2.90 (1.62, 4.18)**	**<.001**
Sex				
Male	—		—	
Female	-0.09 (-0.33, 0.15)	.441	-0.09 (-0.36, 0.19)	.533
Study center UV	0.02 (-0.04, 0.08)	.538	0.12 (-0.03, 0.26)	.107
Education level				
Did not graduate high school	—		—	
High school graduate	**-1.25 (-1.97, -0.54)**	**.001**	**-0.37 (-1.20, 0.46)**	**.382**
Some college or posthigh school	**-1.67 (-2.36, -0.99)**	**<.001**	**-0.92 (-1.71, -0.14)**	**.021**
College grad	**-1.74 (-2.42, -1.07)**	**<.001**	**-0.99 (-1.76, -0.22)**	**.012**
p trend		**.001**		**.001**

Note. *n* = 473.

CHAPTER 3

BODY MASS INDEX, TUMOR THICKNESS, AND MELANOMA RISK WITHIN THE PROSTATE, LUNG, COLORECTAL, AND OVARIAN COHORT

3.1 Abstract

3.1.1 Introduction

The incidence of melanoma continues to increase despite public awareness campaigns directed at reducing exposure to ultraviolet (UV) light. Other than UV light exposure, there are few modifiable factors that are known to prevent or reduce severity of melanoma. Previous literature has suggested an increased risk of melanoma in people with higher body mass index (BMI).

3.1.2 Methods

The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer cohort followed more than 150,000 people for 13 years. Each participant's health status was tracked and participants were asked to fill out multiple surveys, including a food frequency questionnaire. Health histories and demographic information were collected from each participant at the time of enrollment and are available for study. Over 1300 of these participants developed melanoma. Using these data, the relationship between BMI at age 20 and melanoma was explored. Both univariate and multivariate Cox regressions were

used as well as univariate and multivariate linear regression.

3.1.3 Results

Using the standard categories of BMI, the risk of melanoma in participants with a low BMI (<18.5) at age 20 was decreased when compared to participants who had a normal BMI (normal BMI range 18.5–24; HR = 0.68, 95% CI 0.53, 0.88). When stratified on sex, the reduced risk of melanoma associated with low BMI at age 20 persisted in males (HR = 0.58, 95% CI 0.38, 0.87) while the opposite was seen in females, in whom a reduced risk for melanoma approached significance in those who were considered overweight (BMI 25–29) at age 20 (HR = 0.62, 95% CI 0.38, 1.01). Percent weight gain between age 20 and age 50 may be associated with melanoma risk in multivariate analysis (HR = 0.71, 95% CI 0.49, 1.02). BMI did not have a significant influence on tumor thickness.

3.1.4 Conclusion

The risk of melanoma may be influenced by BMI during young adulthood. This risk differs between men and women. A protective association was observed in men with low BMI at age 20. A similar protective association was observed in women who were overweight at age 20.

3.2 Introduction

It is estimated that there were roughly 75,000 cases of melanoma and nearly 10,000 melanoma-related deaths in the US in 2015.[30] The lifetime risk of developing melanoma is 1 in 50.[30] Despite efforts to educate about and prevent melanoma, incidence rates are still on the rise.[31] Exposure to ultraviolet radiation remains the only modifiable risk factor. Current preventive strategies focus on avoidance of tanning beds, education

on sun safe behaviors, and proper use of sun block or sun screen.[32,33] Because of the increased body surface area, obesity has also been implicated as a risk factor although not proven.

Obesity is at epidemic proportions. More than 35% of men and 40% of women are obese, and the rate is increasing in women.[68,69] Obesity is known to contribute to many health concerns. An association between BMI and melanoma has been inconsistent across studies.

Among the largest studies conducted, Thune et al reviewed a database of over 1.3 million people in Norway.[19] There were more than 4,900 cases of melanoma in this cohort over a 12 year period. This large cohort showed slightly elevated melanoma risk for males in the highest quintile of BMI (RR = 1.26, 95% CI 1.10, 1.45).

Dennis et al reported a significant odds ratios for melanoma among individuals with elevated BMIs in a U.S. cohort.[70] The OR for melanoma among individuals with BMI of 25 or higher was 2.55 (95% CI 1.52, 4.53) and those with the highest BMI had on OR for melanoma of over 2.0.

The Me-Can (Metabolic Syndrome and Cancer Project[71]) study evaluated melanoma risk factors among multiple large European cohorts. Again, an increased BMI was associated with an increased risk of melanoma in quintiles 2-5 when compared to the lowest quintile of BMI. In women, an increased risk of melanoma was seen only in the 2nd to lowest quintile (HR = 1.42, 95% CI 1.09, 1.86). An increased risk of fatal melanoma was also seen in this study for all participants who were in the highest quintile of BMI (HR = 1.61, 95% CI 1.00, 2.61). While mortality data related to melanoma is not available for the PLCO cohort, melanoma tumor thickness remains the most accurate prognosticator. Little is known about the influence of BMI on melanoma tumor thickness.

In a meta-analysis conducted by Sergentanis et al where the pooled effect estimate from 15 studies was found to be 1.31 (95% CI 1.18, 1.45) among overweight and obese men.[18] A large Danish prospective cohort failed to find any relationship between BMI and melanoma.[72]

A separate study of 1171 Australian men and women suggested that height might be associated with melanoma risk in men (RR per 5cm increment = 1.55; 95% CI 0.97–2.47, $p = .067$)[22], an association also seen by Thune et al[19] One attempt to explain the physiologic relationship focuses on larger body surface area. This theory seems to be refuted by the lack of a corresponding dose response between BMI and melanoma risk and a complete lack of this relationship among women.[20]

The aim of our study was to investigate the possible association between BMI at age 20, percent weight change from age 20 to 50, and the risk of melanoma in a cohort study. We also aim to evaluate what influence BMI might have on tumor thickness.

3.3 Methods

3.3.1 PLCO Methods

The PLCO is a randomized trial developed to evaluate the effect of screening for prostate, lung, colorectal, and ovarian cancers on cancer specific mortality. The trial included 10 screening centers across the US and enrolled 78,216 women and 76,685 men between the ages of 55 and 74. Participants were excluded if they were currently undergoing treatment for cancer or had been previously diagnosed with one of the four cancers being studied, had surgical removal of colon, lung, or prostate, were on another cancer screening/prevention trial, or had colonoscopy, sigmoidoscopy, or barium enema in the 3 years prior to enrolling. Men were excluded if they were taking finasteride in the

6 months prior to enrolling or if they had more than one PSA test in the 3 years prior to enrollment. Before October 1996, women with previous surgical removal of both ovaries were excluded. Before April 1, 1999, women were excluded from the trial if they were currently taking or had taken tamoxifen or raloxifene in the 6 months prior to randomization.

Each participant completed a baseline questionnaire and a validated dietary questionnaire.[27-29] After meeting inclusion criteria, each participant was randomized into the intervention arm (receiving intervention screening for the targeted cancers) or the control arm (standard of care). Those in the intervention arm received PLCO cancer specific screening for the first 6 years and were then followed for 7 additional years. The screening exams included a flexible sigmoidoscopy and chest x-ray for all participants; men received digital rectal exam and PSA, while women received transvaginal ultrasound and CA-125. Those in the control arm received standard of care and were followed for 13 years. Enrollment took place at the 10 study centers from 1993 until 2001. Additional details on the methods of this trial were published previously.[26]

We analyzed the data using Stata/IC 14.1.[51] Of the 154,897 PLCO participants, 143,036 were included in this study (see Figure 3.1).

Descriptive statistics were used to define the variables of interest for this study. Age in years was divided into 4 categories (55-59, 60-64, 65-69, 70-78). Because there were so few non-White PLCO participants who developed melanoma, race was categorized into White and non-White categories only. Education categories were divided into those who did not finish high school, high school graduates, those who completed some college or posthigh school education, and college graduates.

3.3.2 UV Exposure

UV exposure was based on the average UV measure of the study center where the person was enrolled. The average UV index for the last 4 years for each city was used to generate an average UV index for that city. These numbers were assessed by the Environmental Protection Agency and were reported by www.homefacts.com[54] as annual averages. For each city, the average of the annual UV index for the years 2011-2015 was calculated. High UV index was defined as 5 or greater and low UV index was less than 5 for the model stratified on UV index.

3.3.3 Tumor Thickness

Tumor thickness is recognized as the most important prognostic factor in melanoma but was not reported to the PLCO. In order to evaluate effects on tumor thickness, de-identified pathology reports were obtained, if available, for those participants who had melanoma. Of the 1,432 cases of melanoma, 520 had available pathology reports. These were individually reviewed to record tumor thickness, which was available in 473 cases.

3.3.4 Body Mass Index

BMI was reported by study participants as they enrolled in the PLCO trial. They were asked to recall their weight and height at age 20 and age 50. Weight and height at study entry was also recorded. BMI was categorized to standard ranges: below 18.5 (underweight), 18.5-24.9 (normal), 25-29.9 (overweight), and 30 and above (obese). Weight change was also calculated as a percentage by dividing the difference between weight at age 20 and weight at age 50 by weight at age 20. This was multiplied by 10 to create a continuous variable in 10% increments.

3.3.5 Statistical Analysis

Two-sample *t* tests (continuous variables) and chi-square tests (categorical variables) were used to evaluate the difference between melanoma cases and the rest of the cohort for demographic factors. A Cox proportional-hazards model was used to estimate the risk of melanoma based on BMI at age 20. In this model, univariate analysis was used for crude HRs and multivariate analysis included sex, age, height, average UV at study center, education, and race. Both univariate and multivariate linear regression were used to evaluate a potential relationship between BMI at age 20 and melanoma tumor thickness. The multivariate model included sex, race, study center UV index (high vs. low), and education level.

3.4 Results

Participants who developed melanoma were slightly older (mean age at study entry 63 years) compared to those who did not (mean age at study entry 62.6 years, $p = 0.016$). Melanomas were nearly all seen in White participants ($n = 1{,}302$; 99.0%) with only 13 (1.0%) cases developing in other races ($p < .001$). The risk of melanoma increased with education level. The majority of participants had a BMI within the normal or overweight ranges. The distribution of melanoma did not vary significantly by BMI (see Table 3.1).

In multivariate analysis (Table 3.2), a significantly reduced risk of melanoma among participants in the lowest BMI category (underweight) was observed (HR = 0.68, 95% CI 0.53, 0.88) as well as in those who were overweight (HR = 0.85, 95% CI 0.72, 0.99). When stratified on sex, the reduced risk of melanoma associated with low BMI at age 20 persisted in males (HR = 0.58, 95% CI 0.38, 0.87) and bordered on significance in

females (HR = 0.75, 95% CI 0.52, 1.02). A more significant shift of the protective effect was seen in overweight females (BMI 25–29 kg/m^2), who had a reduced risk of melanoma (HR = 0.62, 95% CI 0.38, 1.01) compared to normal weight women. A significant benefit was seen in obese females (HR = 0.78, 95% CI 0.32, 1.88).

As weight increased (10% increments) between age 20 and age 50 the decrease in risk bordered on significance (HR = 0.97, 95% CI 0.93, 1.00; $p = .07$).

BMI was not associated with melanoma tumor thickness (see Table 3.3). Race other than White was associated with a deeper tumor thickness (univariate coefficient 3.33, 95% CI 2.14, 4.51; multivariate coefficient 2.93, 95% CI 1.75, 4.12). Less education also correlated with a deeper tumor thickness (see Table 3.3). Compared to those who did not graduate high school, those with a high school degree had a tumor thickness nearly 1mm less (-0.96, 95% CI -1.67, -0.25; $p = .008$) on average. Those with some college or posthigh school education had a tumor thickness nearly 1.5mm less (-1.43, 95% CI -2.10, -0.75; $p < .001$). Those with a college or postgraduate degree had a tumor thickness 1.52 mm less (95% CI -2.18, -0.85; $p < .001$).

3.5 Discussion

Our study found a reduced risk of melanoma among those who were considered underweight at age 20. No increased risk was seen in those who were overweight or obese. Additionally, weight change from age 20 to 30 did not seem to influence risk. BMI did not seem to influence tumor thickness.

This study may represent the largest U.S.-based cohort to examine the relationship between BMI and melanoma. It is novel in that it evaluates the relationship between melanoma and BMI at age 20, as it is thought that a significant proportion of UV skin

damage is accumulated in these younger years. The primary association in the literature seems to be association between BMI and melanoma among men but not women.[71] The direction of the relationship in the literature suggests increased risk with increased BMI but does not seem to represent a dose response curve.

This study suggests that men who are underweight at age 20 had a decreased risk of melanoma in later years. Furthermore, as a person's weight increased, their risk of melanoma probably decreased. While this does not disprove the idea that higher BMI is associated with higher risk of melanoma, it calls this assumption into question as well as the theory that body surface area explains that risk. It seems likely that melanoma risk behaviors at a younger age vary by BMI and influence risk in later years. While the same relationship between BMI and melanoma is not seen in women, the theory that BMI influences melanoma risk behaviors at younger ages may explain the decreased risk in women who are overweight during these socially formative years. Further research is necessary on this point especially in light of the lack of a protective benefit for women who were obese at age 20.

Regardless of the exact causes of the association, this study shows an association between BMI at age 20 and risk of melanoma later in life. It is important to recognize that there are other biologic factors that may modify the effects of BMI and UV exposure and obscure the association when looking at BMI in later adulthood.

This study represents a very large and geographically diverse U.S.-based population. Having BMI at age 20 and confirmed cases of melanoma in such a large cohort is an obvious strength. Data on confounding factors included in the PLCO are also a strength. The largest weakness of this study is the lack of adequate UV exposure data for participants. This limitation is nearly ubiquitous in studies of this type. This

shortcoming includes a lack of occupation and hobbies which inevitably influence UV exposure. Future studies might prospectively collect these specific data points in addition to BMI and evaluate if controlling for these might show a more predictable association with melanoma.

3.6 Conclusion

The rates of melanoma in the PLCO population are similar to those published for the US, suggesting that the PLCO population is a representative sample. Accepting the potential modifying influence of biologic differences between men and women on the confounding influence of UV exposure does not seem to negate an apparent dichotomy in the direction of the association between sexes. It seems likely that BMI mediates the risk of melanoma primarily by influencing social and risk behaviors such as clothing choices combined with outdoor activities. This would be supported by the suggested decreased risk in those who gain weight from age 20 to 50.

Further research is warranted to understand these behaviors in a prospective manner. As the relationship among BMI, UV risk behaviors during young adulthood, and melanoma become clearer, public health interventions may be developed or strengthened.

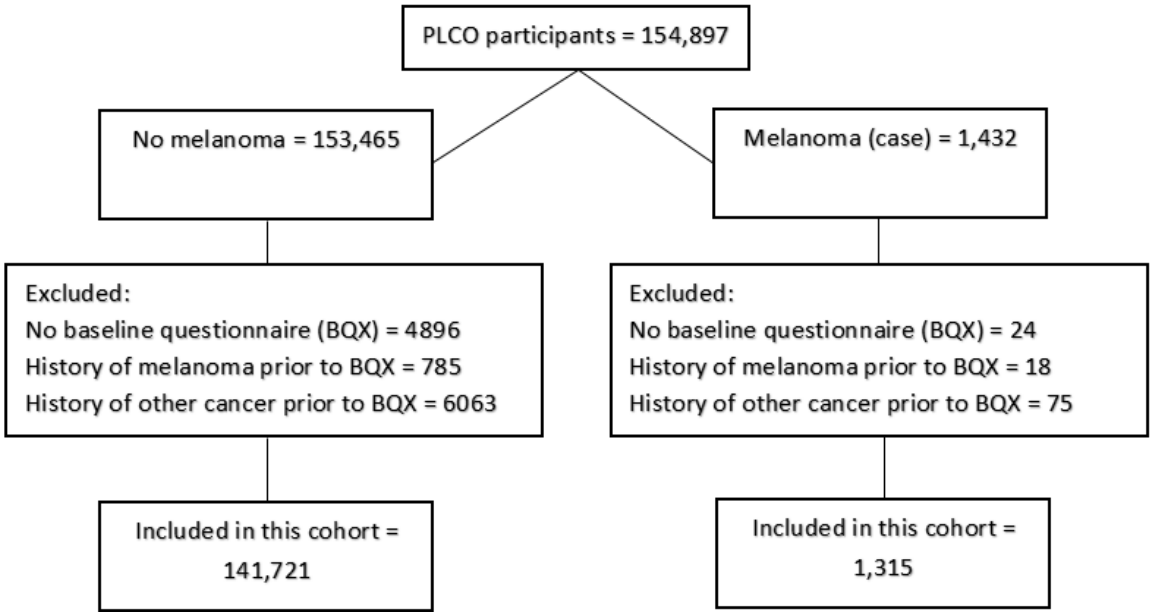

Figure 3.1. CONSORT Diagram for BMI and Melanoma in the PLCO.

Table 3.1. Comparison of Participants Who Developed Melanoma to Those Who Did Not

Characteristic	Melanoma		No melanoma		*p*
Average age (in years)	1,315	63	141,271	62.6	.016[a]
	n	%	*n*	%	
Categories by age (in years)					
<60	390	29.7	47,355	33.4	
60–64	399	30.3	43,754	30.9	
65–69	341	25.9	31,851	22.5	
≥70	185	14.1	18,761	13.2	.004[b]
Sex					
Male	828	63.0	71,287	50.3	
Female	487	37.0	70,434	49.7	<.001[b]
Race					
White	1,302	99.0	124,958	88.2	
Other	13	1.0	16,763	11.8	<.001[b]
BMI					
<18.5	66	5.0	11,153	7.9	
18.5–24.9	1,037	78.9	106,220	75.0	
25–29.9	171	13.0	19,076	13.5	
≥30	23	1.7	2,651	1.9	
Missing	18	1.4	2,621	1.8	.001[b]
Education					
Did not graduate high school	44	3.3	10,530	7.4	
High school graduate	202	15.4	32,587	23.0	
Some college or posthigh school training	405	30.8	48,596	34.3	
College graduate	660	50.2	49,638	35.0	
Missing	4	0.3	370	0.3	<.001[b]

[a] Two-tailed *t* test

[b] Chi-square test

Table 3.2. BMI and Risk of Melanoma

BMI at age 20[a]	Crude hazard ratio (95% *CI*)	*p*	Multivariate hazard ratio (95% *CI*)[a]	*p*
Full sample				
<18.5	**0.62 (0.48, 0.79)**	**<.001**	**0.68 (0.53, 0.88)**	**.003**
18.5–24	1.00		1.00	
25–29	0.95 (0.80, 1.11)	.498	0.85 (0.72, 0.99)	.046
≥30	0.96 (0.64, 1.45)	0.849	1.01 (0.66, 1.54)	0.980
p trend		.071		.0732
Male only[b]				
<18.5	**0.59 (0.39, 0.90)**	**.014**	**0.56 (0.38, 0.87)**	**.010**
18.5–24	1.00		1.00	
25–29	0.87 (0.73, 1.04)	.133	0.89 (0.75, 1.06)	.203
≥30	1.06 (0.66, 1.69)	.725	1.12 (0.69, 1.81)	.657
p trend		.841		.598
Female only[b]				
<18.5	0.74 (0.54, 1.01)	.055	0.75 (0.54, 1.02)	.070
18.5–24	1.00		1.00	
25–29	0.55 (0.34, 0.89)	.015	0.62 (0.38, 1.01)	.053
≥30	0.62 (0.26, 1.51)	.294	0.78 (0.32, 1.88)	.573
p trend		.619		.983
Each 10% weight increase from age 20 to age 50	**0.93 (0.90, 0.96)**	**<.001**	0.97 (0.93, 1.00)	.070

[a] Controlling for age at enrollment, sex, race, study center UV, and education level

[b] Controlling for age at enrollment, race, study center UV, and education level

Table 3.3. Multivariate Linear Regression of Melanoma Tumor Thickness. BMI, Sex, Race, Study Center, and Education Level

	Coefficient			
Covariate	Univariate (95% CI)	*p*	Multivariate (95% CI)[a]	*p*
BMI at age 20				
<18.5	-.040 (-0.96, 0.17)	.168	-0.31 (-0.85, 0.22)	.251
18.5–24	—		—	
25–29	0.05 (-0.26, 0.37)	.743	0.00 (-0.30, 0.31)	.987
≥30	-0.42 (-1.29, 0.45)	.346	-0.45 (-1.28, 0.38)	.289
Sex				
Male	—	—	—	—
Female	-0.09 (-0.33, 0.14)	.441	-0.12 (-0.36, 0.12)	.327
Race				
White	—	—	—	—
Non-White	**3.33 (2.14, 4.51)**	**<.001**	**2.93 (1.75, 4.12)**	**000**
Study center UV				
Low	—	—	—	—
High	0.02 (-0.04, 0.08)	.538	0.16 (-0.08, 0.39)	.595
Education level				
Did not graduate high school	—	—	—	—
High school graduate	**-1.25 (-1.97, -0.55)**	**.001**	**-0.96 (-1.67, -0.25)**	**.008**
Some college or posthigh school	**-1.67 (-2.36, -0.99)**	**.001**	**-1.43 (-2.10, -0.75)**	**.001**
College grad	**-1.74 (-2.42, -1.07)**	**.001**	**-1.52 (-2.18, -0.85)**	**.001**

[a] Multivariate linear regression including all of the variables in this table.

CHAPTER 4

THE INFLUENCE OF HEIGHT ON RISK OF MELANOMA AND TUMOR THICKNESS WITHIN THE PROSTATE, LUNG, COLORECTAL, AND OVARIAN COHORT

4.1 Abstract

4.1.1 Introduction

Melanoma is among the most frequently diagnosed cancers and, in later stages, is aggressive and hard to treat. Other than ultraviolet (UV) light exposure, there are few modifiable factors that are known to prevent or reduce severity of melanoma. Previous literature has suggested an increased risk of melanoma in taller people.

4.1.2 Methods

The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer cohort followed more than 150,000 people for 13 years each. Each participant's health status was tracked and participants were asked to fill out multiple surveys. Health histories and demographic information were collected from each participant at the time of enrollment and are available for study. Over 1300 participants developed melanoma. Using these data, the relationship between height and melanoma was explored. Cox regression was used to model the hazard of melanoma; linear regression was used to model tumor thickness.

4.1.3 Results

In general and when stratified on sex, there was a significant trend for increasing risk of melanoma with increasing height ($p < .001$). These significant trends persisted in multivariate analysis with an overall p for trend under .001, a p for trend in men of .037, and a p for trend in women of .003. The tallest quartile had a significantly increased risk of melanoma compared to the shortest. Height had no effect on melanoma tumor thickness.

4.1.4 Conclusion

A consistent linear relationship is noted between increasing height and risk of melanoma. It is possible that biologic processes that contribute to height may make individuals more susceptible to UV radiation damage.

4.2 Introduction

It is estimated that there were 75,000 cases of melanoma and 10,000 melanoma-related deaths in the US in 2016.[1] The lifetime risk for a person living in the US of developing melanoma is 1 in 50. Despite efforts to educate and prevent, incidence rates of melanoma are still on the rise.[31] Exposure to ultraviolet radiation, whether natural or not, remains the only modifiable risk factor. Current preventive strategies focus on avoidance of tanning beds, education of sun safe behaviors, and proper use of sun block or sun screen.[32,33] Anthropometric (factors that quantify the size and shape of the human body) risk factors have been evaluated in some settings and suggest higher risk of melanoma in some demographics.

Theories that might explain a potential relationship between these factors and melanoma include the thought that increased body surface area and or their influence on

behavior (UV exposing behaviors in particular) portend higher risk of melanoma. Another theory is that the biologic factors leading to larger body size (human growth hormone) might alter the susceptibility of skin to UV driven mutations.

In a previous study, we evaluated a potential association between BMI at age 20 and melanoma risk using the PLCO cohort. While the findings suggested a reduced risk of melanoma in underweight men (HR = 0.68, 95% CI 0.53, 0.88) and in overweight women (HR = 0.62, 95% CI 0.38, 1.01), there were not associated dose response curves to suggest that BMI was the driving factor. Height was therefore evaluated as a potential modifier in this relationship.

A number of ecological studies have evaluated the risk of multiple cancers based on population height. Jiang et al looked at 24 different cancer sites and found that increased average population height was associated with increased cancer risk at most sites, including melanoma. Other studies have also suggested a similar association and include melanoma as one of the cancers evaluated.[73-80] While these findings suggest that factors related to height also are related to cancer risk, none of these studies focused solely on melanoma and therefore, in some cases, lacked adequate control for confounders, primarily UV exposure.

One of the paramount studies looking at height as it pertains to melanoma risk was performed by Thune et al in 1993. This study looked at a cohort of roughly 1.3 million people between the ages of 30 and 84 in Norway and adjusted for age, birth cohort, geographic location, and BMI. In this cohort, there were approximately 5000 incident melanomas. Height was broken into 5 relatively equal categories. They found that risk of melanoma increased significantly as height category increased.[19] A more recent U.S.-based study looking at all keratinocyte cancers and melanoma suggested

similar results but used a very small cohort.[22]

While height is not a modifiable risk factor, it is one of the elements of BMI. The relationship between BMI and melanoma is difficult to explain as it does not follow a predictable pattern. This study aims to evaluate how melanoma risk may be influenced by height independent of BMI in a U.S. cohort with control for UV exposure.

4.3 Methods

4.3.1 PLCO Methods

The PLCO is a randomized trial developed to evaluate the effect of screening for prostate, lung, colorectal, and ovarian cancers on site-specific cancer mortality. The trial included 10 screening centers across the US and enrolled 78,216 women and 76,685 men between the ages of 55 and 74. Participants were excluded if they were currently undergoing treatment for cancer or had been previously diagnosed with one of the four cancers being studied, had surgical removal of colon, lung, or prostate, were on another cancer screening/prevention trial, or had colonoscopy, sigmoidoscopy, or barium enema in the 3 years prior to enrolling. Each participant completed a baseline questionnaire and dietary questionnaire. Those in the control arm received standard of care and were followed for 13 years. Enrollment took place at the 10 study centers from 1993 until 2001. Additional details on the methods of this trial were published previously.[26]

The current study employed a secondary data analysis of the PLCO data. These data were obtained and analyzed using Stata/IC 14.1.[51] Of the 154,897 PLCO participants, 141,866 were included in this study (see Figure 4.1).

Descriptive statistics were used to define the variables of interest for this study. Age in years was divided into 4 categories (55-59, 60-64, 65-69, 70-78). Because there

were so few non-White PLCO participants who developed melanoma, race was categorized into White and non-White categories only. Education categories were divided into those who did not finish high school, high school graduates, those who did some college or posthigh school education, and college graduates.

4.3.2 UV Exposure

UV exposure was based on the average UV measure of the study center where the person was enrolled. The average UV index for the last 4 years for each city was used to generate an average UV index for that city. These numbers were assessed by the Environmental Protection Agency and were reported by www.homefacts.com[54] as annual averages. For each city, the average of the annual UV index for the years 2011-2015 was calculated. High UV index was defined as 5 or greater and low UV index was less than 5 for the model stratified on UV index.

4.3.3 Tumor Thickness

Tumor thickness is recognized as the most accurate prognostic factor in melanoma but was not captured in the PLCO Trial. In order to evaluate effects on tumor thickness, de-identified pathology reports, if available, were obtained for those participants who had melanoma. Of the 1,432 cases of melanoma, 520 had available pathology reports. These were individually reviewed to record tumor thickness, which was available in 473 cases.

4.3.4 Body Mass Index

BMI was reported by study participants as they enrolled in the PLCO trial. They were asked to recall their weight at age 20 and age 50. Weight and height at study entry was also recorded. BMI categories are the standard BMI categories: below 18.5

(underweight), 18.5-24.9 (normal), 25-29.9 (overweight), and above 30 (obese). Weight change was also calculated as a percentage by calculating the difference between weight at age 20 and weight at age 50 and then dividing by weight at age 20.

4.3.5 Height

Height was reported as a continuous variable in inches. The cohort was divided first by sex and then into quartiles by height. Table 4.1 shows a breakdown of the ranges of height by sex and quartile. According to the CDC, the average height of U.S. adult men is 69.3 inches and adult women is 63.8 inches.[81] The PLCO cohort was slightly taller on average (69.9 inches in men and 64.2 inches in women).

4.4 Statistical Analysis

Two-sample *t* tests and chi-square analysis were used to evaluate the difference in melanoma rates between men and women, White and non-White, different age groups, study centers, and categories of height. A Cox proportional-hazards model was used to estimate the risk of melanoma based on height. In this model, univariate analysis was used for crude HRs and multivariate analysis included variables that may influence height and risk of melanoma. These factors are sex, age, average UV at study center, and race. Univariate and multivariate linear regression were used to evaluate the relationship between height and melanoma.

4.5 Results

Table 4.2 shows the characteristics of the PLCO cohort participants who developed melanoma compared to the PLCO participants who did not. Participants who developed melanoma were slightly older (mean age at study entry 63 years) compared to those who did not (mean age at study entry 62.6 years). Of participants who developed

melanoma, more were male than female (62.8% compared to 37.2%, $p < .001$). Melanomas were nearly all seen in white participants (n = 1,295; 99.0%) with only 13 (1.0%) cases developing in other races ($p < .001$). Height in men ranged from 49 to 84 inches and from 48 to 78 inches in women (Table 4.1). When divided into quartiles, proportionately more melanomas were seen in the taller two quartiles (Table 4.2).

In univariate analysis (Table 4.3), all quartiles of height had an increased risk of melanoma when compared to the lowest quartile. When stratified on sex, this held true in all except the second quartile in women. In general and when stratified on sex, there was a significant trend for increasing risk of melanoma with increasing height ($p < .001$). These significant trends persisted in multivariate analysis (p for trend in all < .001, p for trend in men = .037, and p for trend in women = .003). In each case (all, men, and women), the tallest quartile had a significantly increased risk of melanoma compared to the shortest. This was most pronounced in women with the tallest quartile having a HR of 1.46 (95% CI 1.09, 1.96; p = .012) compared to the lowest quartile.

The effect of height on melanoma tumor thickness was evaluated in univariate and multivariate linear regression and not found to be predictive (Table 4.4). With the exception of race, no variable had a significant impact on tumor thickness. Melanomas in non-Whites were more than 3 mm thicker than in Whites (coefficient = 3.28, 95% CI 2.06, 4.50; $p < .001$).

4.6 Discussion

Previous studies suggested a connection between height and risk of multiple cancers. The majority of those did not focus on melanoma and did not control for UV exposure. This study supports the association between height and risk of melanoma and

attempts to control for UV exposure. It further evaluates the difference between sexes when it comes to height and melanoma.

Overall, two things seem apparent from this study. First, there is a trend of an increased risk of melanoma with increasing height. This was seen in the entire cohort and persisted when evaluating men and women separately. Second, there is a significantly increased risk of melanoma in the tallest quadrant of height. While height increases risk of melanoma, it does not seem to influence severity of disease (tumor thickness).

As mentioned, one of the largest studies on this topic showed similar increased risk of melanoma among the highest quintile relative to the lowest in men and women.[19] Similar controls were included for UV exposure based on geographic region. Thune's study was based on a Norwegian population and therefore may have had less geographic diversity. It is also worth noting that there were over a million people in that study and roughly 5000 melanomas. Our study was smaller but had a higher rate of melanoma (3 per 1000 in Norway vs 9 per 1000 in the PLCO). In the Norwegian cohort, a relative risk of 1.60 was seen in the highest quintile of men and 1.59 in the highest quintile of women. A trend of increasing risk with height was also observed. In this study, a HR of 1.31 (95%CI 1.04, 1.65) was seen in men in and 1.46 (95%CI 1.09, 1.96) in women. The Norwegian cohort showed nearly identical increases in risk between men and women while this study showed a possible difference between risk in men and women.

When comparing previously published studies to the findings of this study, it seems clear that there is a relationship between melanoma risk and height. While there are similarities between study findings, the subtle differences may be reflective of differences in population make up and geographic diversity. Furthermore, it is likely that there are different risk factors or modifiers between men and women. These might

include differing behaviors and social norms that might influence UV exposure and biologic differences including hormones among others. The basic biology behind cancer is a study of control over cell division or a lack thereof. Processes that stimulate increased growth must also rely on the pathways that speed up cell division. It seems logical that exposure to carcinogenic entities while an individual is in a phase of increased cell division would result in increased risk of cancer.

Hormones that play a role in height include testosterone, thyroid hormones, and human growth hormones. Testosterone has been long studied for its effect on melanocytes. While it may not increase melanocyte numbers,[82] it may influence the melanocyte function.[83] While thyroid hormone may influence vitamin D synthesis and other skin processes,[84] it does not have a proven direct effect on melanocytes. Growth hormone has shown to have some influence on melanoma cell lines.[25] It has also been suggested that the growth hormone receptors may be important in melanoma pathogenesis.[85] While each of these hormones may play a part in the relationship between melanoma risk and height, growth hormone appears to be the most promising prospect for exploration.

The strengths of this study include the number of participants in the PLCO, their geographic diversity, and duration of time they were followed. In addition, this is among the largest U.S. cohorts to be evaluated for risk of melanoma by height. Weaknesses include the fact that the cohort was not developed with melanoma as an original focus. As such, more detailed pathologic and staging information about those participants who developed melanoma was not available. As noted in most studies of melanoma, the lack of an ideal control for true UV exposure is a constant weakness.

4.7 Conclusions

The relationship between height and all cancer risk has been documented but biologically is not well understood. It is not surprising then that a similar risk between height and melanoma exists. While height may be the underlying risk factor in the relationship between body mass index and melanoma, it also raises questions about the biology that leads to growth and how it might impact the skins susceptibility to UV radiation. Because increasing height correlates with increased melanoma risk and increasing BMI does not, it may be assumed that body surface area is not a contributing risk factor for melanoma. The magnitude of the risk increase associated with height seems to vary by geography and race as would be expected but may be used to look at biologic differences as well where race and geography have innate biological differences. A differing risk based on biologic differences between men and women is something that warrants further inspection.

Finally, while height is not a modifiable risk factor, a further investigation of the biologic reason for this may support behavior modifications to reduce risk. Even without specific proof that the biology behind height is important in carcinogenesis, it seems worthwhile to add this to the cadre of reasons why we should teach appropriate sun behaviors to adolescents/teenagers in particular.

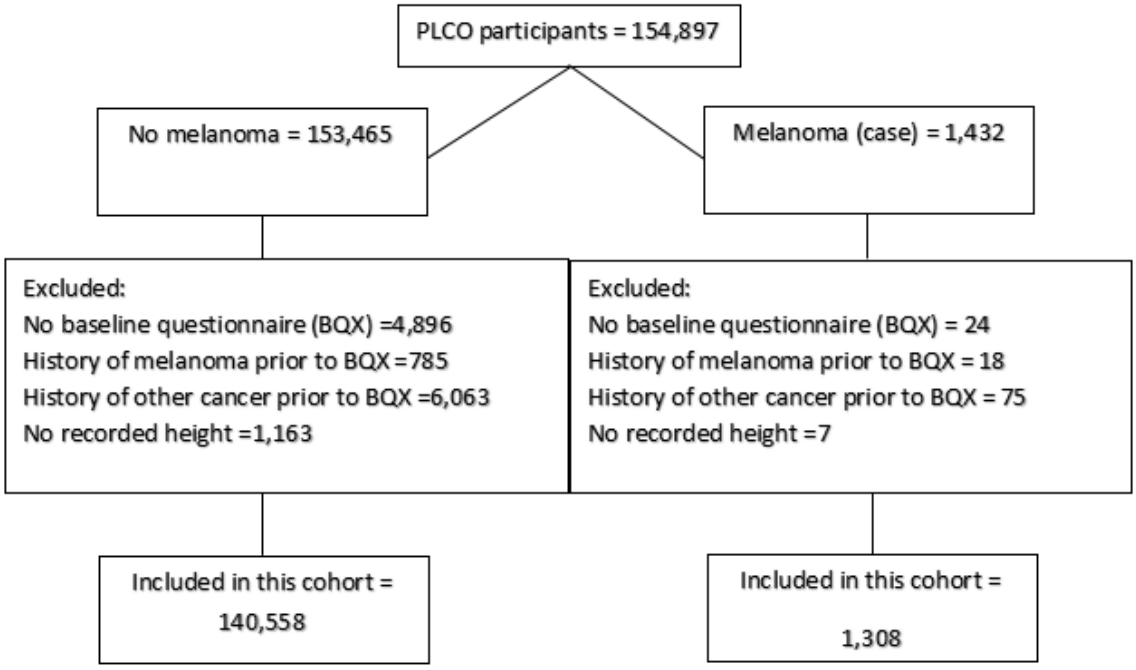

Figure 4.1. CONSORT Diagram for Height and Melanoma.

Table 4.1. Height in Inches by Quartile and Sex

	Male		Female	
Quartile	*n*	Height	*n*	Height
1	20,861	49–68	18,095	48–62
2	20,410	69–70	21,230	63–64
3	18,249	71–72	18,768	65–66
4	11,888	73–84	12,365	67–78

Table 4.2. Comparison of Participants Who Developed Melanoma to Those Who Did Not

Characteristic	Melanoma		No melanoma		*p*
Average age (in years)	1,308	63.0	140,558	62.6	.001
	n	%	*n*	%	
Categories by age (in years)					
<60	385	29.4	47,030	33.5	
60–64	399	30.5	43.397	30.9	
65–69	340	26.0	31,561	22.5	
≥70	184	14.1	18,570	13.2	.004
Sex					
Male	822	62.8	70,586	50.2	
Female	486	37.2	69,972	49.8	<.001
Race					
White	1,295	99.0	124,020	88.2	
Other	13	1.0	16,538	11.8	<.001
Height (quartile)					
1	284	21.7	38,672	27.5	
2	370	28.3	41,270	29.4	
3	367	28.1	36,650	26.1	
4	287	21.9	23,966	17.1	<.001

[a] Two-tailed *t* test

[b] Chi-square test

Table 4.3. Height and Risk of Melanoma

Quartile of height	Crude hazard ratio (95% *CI*)	*p*	Multivariate hazard ratio (95% *CI*)[a]	*p*
All				
1	1.00		1.00	
2	**1.21 (1.04, 1.42)**	**.014**	1.06 (0.91, 1.25)	.439
3	**1.36 (1.17, 1.59)**	**<.001**	1.17 (0.99, 1.37)	.066
4	**1.64 (1.39, 1.93)**	**<.001**	**1.37 (1.14, 1.65)**	**.001**
p trend		**<.001**		**<.001**
Male only[b]				
1	1.00		1.00	
2	**1.29 (1.07, 1.56)**	**.009**	1.08 (0.89, 1.32)	.432
3	**1.34 (1.10, 1.63)**	**.003**	1.09 (0.89, 1.34)	.415
4	**1.66 (1.35, 2.04)**	**<.001**	**1.31 (1.04, 1.65)**	**.023**
p trend		**<.001**		**.037**
Female only[b]				
1	1.00		1.00	
2	1.15 (0.89, 1.50	.292	1.03 (0.79, 1.34)	.839
3	**1.47 (1.14, 1.90)**	**.003**	1.28 (0.98, 1.67)	.068
4	**1.70 (1.29, 2.23)**	**<.001**	**1.46 (1.09, 1.96)**	**.012**
p trend		**<.001**		**.003**

[a] Controlling for age at enrollment, sex, race, weight age 20, and study center UV

[b] Controlling for age at enrollment, race, weight age 20, and study center UV

Table 4.4. Multivariate Linear Regression of Melanoma Tumor Thickness, Height, Age, Sex, Weight at Age 20, and Study Center

	Coefficient			
Breslow depth in mm (n = 468)	Univariate (95% CI)	p	Multivariate (95% CI)[a]	p
Height (quartiles)				
1	ref	—	ref	—
2	0.16 (-0.14, 0.47)	.304	0.16 (-0.15, 0.47)	.319
3	-0.04 (-0.36, 0.28)	.803	-0.01 (-0.33, 0.32)	.951
4	0.15 (-0.18, 0.49)	.366	0.14 (-0.22, 0.50)	.445
Age	0.01 (-0.01, 0.03)	.331	0.00 (-0.02, 0.03)	.658
Sex				
Male	ref	—	ref	—
Female	-0.09 (-0.33, 0.15)	0.462	0.01 (-0.31, 0.33)	0.965
Weight at age 20	0.00 (-0.01, 0.01)	0.215	0.00 (-0.01, 0.01)	.290
Race				
White	ref	—	ref	—
Non-White	**3.32 (2.14, 4.51)**	**<.001**	**3.28 (2.06, 4.50)**	**<.001**
Study center UV				
Low	ref	—	ref	—
High	0.20 (-0.04, 0.44)	.107	0.10 (-0.14, 0.34)	.425

[a] Multivariate linear regression including all variables in this table

CHAPTER 5

CONCLUSIONS

The search for additional risk factors of melanoma is necessary as not all cases are attributable to UV exposure. UV attributable melanoma estimates range from 65% to more than 90%. [86,87] In addition, the rate of disease may be lower in non-White populations[1] but the disease severity in this population appears to be worse.

It is possible that practitioners may not have melanoma high on their clinical radar when evaluating patients with darker skin tones leading to a delay in diagnosis. It is also likely that people with lower innate risk (darker skin) have less concern for skin lesions, again, leading to a delay in diagnosis. Regardless, it is important to understand why melanoma is more severe in non-White races. In all three studies, the only factors that influence tumor thickness were race and education. These data show a clear health disparity.

Other factors are likely at play in addition to delayed diagnosis in this context. Vitamin D levels are low in a large majority of ethnic minorities. This study contributes additional understanding to the vitamin D question. Understanding that women in the highest quartile of vitamin D intake have a lower risk of invasive melanoma could guide education efforts. Additionally, our study is novel in that it shows a weak but statistically significant correlation between self-reported vitamin D intake and actual serum levels of vitamin D.

The potential that BMI at age 20 potentially has an opposite effect on risk in men compared to women (namely a potential protective effect in men who are underweight and women who are overweight) adds a new vein of questioning to the current melanoma literature. Behaviors influenced by BMI as well as sex-specific hormones should be evaluated for potential risk modifiers.

Finally, the striking linear relationship between height and melanoma risk and the presumption that the majority of risk is accumulated in the form of UV at a younger age raises multiple unanswered questions. This may identify that the melanocytes are indeed more susceptible to UV damage during the formative teen and young adult year. Growth hormone and other hormones related to height should be evaluated. One way to evaluate this is in a case-control setting following people who have used growth hormone replacement therapy compared to their peers who were the same height and age when the therapy was started. Regardless of methods, this relationship should be explored further.

This research benefited from a number of strengths. Most importantly, the data supplied by the PLCO represent a longitudinal database that is among the largest for evaluating melanoma risk factors in the US. Prospectively collected information on each participant including extensive food and diet information allowed us to evaluate dietary risk factors with confidence. Likewise, prospectively collected serum provided serum vitamin D levels on a subset of participants and evaluation of the relationship between serum vitamin D levels and estimates of intake based on self-reported surveys. Finally, with 10 different centers of enrollment, an objective proxy measure for UV exposure was available.

The limitations of this research include inconsistent reporting of melanoma characteristics, an issue inherent to the lack of uniform reporting criteria across

pathologists. Ideally, serum vitamin D levels would have been assessed on all individuals to more exactly solidify the relationship between vitamin D levels and melanoma in a larger group and further evaluate the relationship between self-reported measures and actual serum levels. The PLCO incorporated a broad swath of the U.S. population geographically but did not include participants younger than 55. While the majority of melanomas are seen in older individuals, including younger participants might have shown a different relationship stratified on age. Lastly, the inability to adequately control for individual UV exposure remains a limitation.

Any future study needs to consider and, if possible, compensate for the complex nature of the confounding influence of UV exposure. The best method to control for this is to measure UV exposure for each individual over a period of time, however, this is nearly impossible to measure so estimates must be performed. Having participants wear a UV dosimeter that can be worn similar to a wrist watch is ideal but is limited by cost due to the amount of monitoring that would need to be done. The mutations that result in melanoma are usually the result of decades of UV exposure making a time-limited UV measurement less exact. In addition, behaviors (and thus UV exposures) may change over the course of aging. Taking a small measure of UV exposure at one point and extrapolating over time is therefore problematic. In addition, people may not stay in the same area for long periods of time so mobility must be accounted for as latitude and elevation influence UV exposure. Taking into account the need for large population-based studies, this becomes even less attainable. Depending on funding and study aims, the best solution may be to track UV indexes and account for amount of time spent outdoors by each participant.

While the primary aims of this research focused on the incidence of melanoma,

the striking disparity in severity of melanoma between races is important. Future research might focus on those groups with more severe disease at onset. The most obvious approach would be to identify the reasons the increased severity exists (most likely a delay in diagnosis) and do root cause analyses. This can then lead to population-based interventions with health care providers and the higher risk groups.

By looking at both height and BMI, the important aspects of body size and shape become more apparent. The apparent explanation that height is more indicative of melanoma risk does not completely explain why some categories of BMI at age 20 had a protective effect. Body size and shape as it relates to body image has been a hot topic. Body image is self-perceived in the context of our cultural norms and cues. The fact that BMI has some influence on melanoma risk, should cause us to question how body image plays into behaviors or avoidance of behaviors that influence melanoma risk.

APPENDIX

SUPPLEMENTARY TABLES

Table A.1. Mean Serum Vitamin D Levels by Study Center

		Serum D			Average UV index
	n	*M*	Range		
Pacific	149	30.3	9.8	54.3	9.5
Colorado	591	25.2	6.7	70.7	6.1
Utah	698	25.0	5.5	75.5	5.8
Minnesota	1,416	24.7	2.5	89.4	3.9
Marshfield	916	24.5	3.0	61.1	3.9
Georgetown	419	24.2	3.2	62.5	4.8
Alabama	223	24.1	6.7	51.1	6.1
St. Louis	666	24.0	2.5	72.8	4.9
Pittsburgh	861	23.8	3.4	63.5	4.3
Henry Ford	759	22.9	4.1	59.1	4.1

Note. Correlation coefficient between serum D and study center UV = .70. $p < .001$.

Table A.2. Regression of Serum Vitamin D (ng/ml) by Quadrant of Vitamin D Intake

Vitamin D intake	Coefficient (95% CI)	*p*
Low	ref	—
Med	1.61 (0.98, 2.25)	<.001
High	2.93 (2.28, 3.57)	<.001
Very high	3.94 (3.30, 4.58)	<.001

Table A.3. Range of Total Vitamin D Intake by Quartile

Quartile	*n*	*M*	Range	
1	27,712	2.31	0.00	3.86
2	27,624	6.64	3.86	10.73
3	27,684	12.18	10.74	13.50
4	27,656	16.31	13.50	169.83

Note. NIH recommends 15 mcg/day in adults age 51-70 and 20 mcg/day in adults >70.

Table A.4. Demographic Comparison of Participants Who Developed Melanoma With a Pathology Report Available Compared to Those Who Developed Melanoma But Did Not Have Pathology Report Available

	Has path n (%)	No path n (%)	*p*
Sex			
Men	321 (40.4)	474 (59.6)	
Women	166 (31.9)	354 (68.1)	.002 (Chi2)
Average age in years	69.5	70.6	.004
Education			
No high school	13 (2.5)	31 (3.9)	
High school	76 (14.6)	126 (15.9)	
Some college	157 (30.3)	248 (31.3)	
College grad	273 (52.6)	387 (48.9)	.367 (Chi2)
Race			
White	515 (99.0)	787 (99.0)	
Other	5 (1.0)	8 (1.0)	.936 (Chi2)
Dietary D intake avg	9.8	10	.557
Serum D average	25.9	25.9	.987
BMI			
Under	21 (4.1)	45 (5.8)	
Normal	404 (78.5)	633 (81.0)	
Over	81 (15.7)	90 (11.5)	
Obese	9 (1.7)	14 (1.8)	.104 (Chi2)
Height (in inches avg)	68.6	68.2	.0843

Table A.5. Demographic Comparison of PLCO Participants Who Had Serum Vitamin D Levels Available Compared to Those Who Did Not

	Has serum D	No serum D	
Sex			
Men	3,472(4.8%)	68643(95.2%)	
Women	3,264(4.6%)	67657(95.4%)	$p = .058$ (Chi2)
Avg age	75.5	74	$p < .001$
Education			
No high school	494(7.3%)	10080(7.4%)	
High school	1512(22.5%)	31277(23.0%)	
Some college	2274(33.8%)	46727(34.4%)	
College grad	2449(37.0%)	47849(35.2%)	$p = .253$ (Chi2)
Race			
White	6291(93.4%)	119969(88.0%)	
Other	445(6.6%)	16331(12.0%)	$p < .001$ (Chi2)
Dietary D intake avg	9.35	9.36	$p = .939$

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