Vitamin D Supplementation in Fitzpatrick Skin Types IV-VI as Malignant Melanoma Adjuvant Treatment

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VITAMIN D SUPPLEMENTATION IN FITZPATRICK SKIN TYPES IV-VI AS MALIGNANT MELANOMA ADJUVANT TREATMENT

A Thesis Presented to
The Faculty of the School of Medicine
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Master of Medical Science

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Abstract:

Melanoma is the most lethal form of skin cancer and accounts for the majority of skin cancer deaths. Melanoma is prone to recurrence, and even with early surgical intervention relapse occurs in approximately one-third of patients. The current standard of care following excision is inconsistent and patients would benefit from adjuvant treatment to reduce recurrence rates. This randomized controlled study will investigate whether supplementation with vitamin D reduces risk of melanoma recurrence in adults with Fitzpatrick skin types IV-VI who have been diagnosed and treated for cutaneous melanoma. Outcomes will be measured by relapse-free survival rates over an 18-month period. We hypothesize that the treatment group receiving vitamin D will have a lower rate of relapse of melanoma compared to those not receiving vitamin D supplementation. The results of this study will help inform melanoma management with the goals of decreasing relapse rates in a higher risk patient population.
Chapter I: Introduction

1.1 Background

1.1.1 Malignant Melanoma

Melanoma is a malignant tumor that arises from the proliferation of the pigment-producing cells in the skin called melanocytes. Malignant melanoma is the most lethal form of skin cancer and makes up the majority of skin cancer deaths.\(^1\) Cutaneous melanoma is currently the 6th most common cancer in the United States with an incidence of 21.3 per 100,000 per year. Although melanoma constitutes only 2.3% of all skin cancer diagnoses it is responsible for 75% of all skin cancer deaths.\(^2\) Melanoma is one of the fastest growing cancers and its incidence has continued to rise over the last 50 years.\(^1\) From 1973 to 2002 the incidence of melanoma rose by 270% in the United States, with the largest increases seen in white, elderly and female populations.\(^3\) Although melanoma is more common in whites, people with skin of color have demonstrated more advanced stages, thicker lesions, increased rates of metastasis, earlier age of diagnosis and poorer outcomes.\(^4\) Due to its high mortality rates, melanoma requires aggressive treatment including early surgical excision.

1.1.2 Melanoma Standard of Care and Recurrence

Surgical excision is the current standard of care for the treatment of melanoma, although the precise treatment approach depends on numerous prognostic factors including the stage at diagnosis. Melanoma is excised with wide margins of 0.5-2 cm depending on lesion characteristics. In addition, the current standard of care recommends a sentinel lymph node biopsy to detect micrometastatic melanoma for patients with stages
There are also a number of immunotherapies being used as adjuvant treatments in unresectable or metastatic melanoma with some success. However, even when patients undergo a complete excision of their primary melanoma, they are still at risk for having a recurrence of the primary melanoma or developing a new melanoma. Recurrence rates in stage II-III melanoma have been found to be between 8 and 46% depending on stage, and nearly one-third of all melanoma patients will experience some form of disease recurrence. Approximately half of all recurrences are detected clinically within the first two years, but the median time at which melanoma recurrence is detected varies based on stage. This high rate of recurrence has led the medical community to seek novel approaches to address the issue.

There are a number of adjuvant treatments being tested for malignant melanoma. A 2019 review of adjuvant therapy in melanoma discussed the use of radiotherapy, immune therapy (such as interferon), immune checkpoint inhibitors, molecular-targeted therapy and neoadjuvant therapies as adjuvant treatments in malignant melanoma. Some success has been seen with these various treatments. However, none have become part of the standard of care since the treatments have only been successful in specific situations based on the characteristics of the melanoma and patient population. Many of the beneficial medications for melanoma have been associated with toxic side effects, further limiting their use. Ipilimumab was an early adjuvant treatment found to increase relapse-free survival in malignant melanoma and accordingly was approved for adjuvant use. It was later found to be associated with high toxicity, making its use controversial. There are several new promising options being explored including PD-1 (programmed cell death protein 1) inhibitors and molecular targeted therapies that still require further
There is also some evidence that nivolumab may be a safer substitute for ipilimumab as an adjuvant treatment. Despite these recent advances and interest in adjuvant treatments for malignant melanoma there is still a need to explore novel options with lower toxicity and more general applicability to help improve patient outcomes and to help establish more specific guidelines for standard of care after surgical resection.

1.1.3 Vitamin D Properties and Absorption

Vitamin D is a steroid that can be obtained either through supplements, dietary intake or ultraviolet radiation exposure and has minimal to no harm on the human body at normal consumption levels. Vitamin D₃ is transported to the liver through the bloodstream. The circulating form of vitamin D, 25(OH)D₃ is synthesized in the liver through the hydroxylation of CYP2R1. It then travels to the kidney where it is converted into the active form of vitamin D 1,25(OH)₂D₃ which is known as calcitriol. The active calcitriol can then exert its various effects on the body. Sun exposure is important in the synthesis of vitamin D (cholecalciferol) in the skin as it contributes to over 90% of circulating serum Calcidiol (25(OH)D). Current cultural norms contribute to severely low serum vitamin D levels in some groups. These norms are problematic since there is emerging data suggesting that mild exposure to UV radiation (UVR) or dietary supplementation with oral vitamin D can reduce cancer mortality. Deficiency in 25(OH)D₃ is common in the US population but has been found to occur at a higher rate in African American and Native American populations. 72.8% of healthy African Americans and 19.6% of Native Americans are deficient in vitamin D, which is
significantly higher than the 11.3% of European Americans who are vitamin D deficient. These differences are related to the fact that white skin has been shown to produce vitamin D more efficiently as it is able to synthesize vitamin D with lower levels of sunlight and on cloudy days. Melanin acts as a UVR filter and accordingly, the amount of melanin in the skin is inversely related to vitamin D production in the skin. People with dark skin require at least 10 times more sun exposure than light-skinned individuals to produce equal amounts of vitamin D in their skin. This evidence demonstrates that vitamin D deficiency is far more common in those with darker skin, and accordingly supplemental vitamin D may be beneficial for these populations.

1.1.4 Vitamin D and its Potential Role in Treatment

Previous biological and epidemiological data suggests that a patient’s vitamin D status may affect their risk of cancer and play a role in cancer prevention through antiproliferative effects. More research is required to confirm whether vitamin D has a positive influence on the patient outcome. The active form of vitamin D has been shown to have anticarcinogenic and antimelanoma effects in experimental models through interaction with the vitamin D receptor (VDR). Additionally, in vitro studies have shown that vitamin D has multiple anti-cancer effects including promotion of cell differentiation, apoptosis, inhibition of cell proliferation and tumor angiogenesis. Vitamin D may also have more pronounced local effects in the skin because of the keratinocyte’s ability to synthesize calcitriol, the active form of vitamin D. Research shows that calcitriol may also have anti-inflammatory effects which may contribute to its anti-cancer properties.
Serum 25(OH)D is considered the best indicator of vitamin D status. It is the main circulating form of vitamin D and is both relatively stable and has a long half-life of over 15 days. The optimal level of vitamin D in an individual is a minimum of 30 ng/ml. Less than 10 ng/ml is considered deficient, less than 20 ng/ml is considered vitamin D insufficient and vitamin D becomes toxic at levels of 100-150 ng/ml. Vitamin D3 supplements are used to raise 25(OH)D concentrations. A 2010 study by Norman and Bouillon showed that there is a good safety profile for the current recommended additional vitamin D intake of 1,000 International Units (IU)/day. However, serum concentrations of 25(OH)D reach a plateau after three months when given monthly supplementation doses of 1,000 IU/d of vitamin D3. Supplementation with vitamin D3 can raise concentrations and still be safe when giving an oral loading dose of 500,000 IU followed by an oral 50,000 monthly dose for 2 years. Vitamin D toxicity can occur at very high doses, and the primary cause of the associated symptoms is hypercalcemia. Calcitriol, the active form of vitamin D binds with high affinity to VDRs, which in turn increases intestinal absorption of both calcium and phosphorus. According to a study conducted by Vieth et al., vitamin D toxicity would require a minimum of 10,000 IU/day and most likely would not occur at less than 40,000 IU/day.

The effect of vitamin D on malignant melanoma is still not fully understood but may be due to its non-calcemic systemic effects. Decreased levels of biologically active forms of vitamin D3 can affect disease progression in melanoma and therefore it may be beneficial to include vitamin D3 into melanoma management. Low levels of 25(OH)D are associated with thicker tumors and reduced survival in melanoma patients. In 2015, an Australian study found a significant association between vitamin D levels and
Breslow thickness, ulceration and mitotic rates. The average serum vitamin D levels were higher in the tumors with better prognostic factors which included the tumors without ulceration and with lower mitotic rates. Despite these findings, it is still unclear how vitamin D supplementation influences melanoma incidence and outcomes. Regardless of the mechanism, decreased levels of biologically active forms of vitamin D\textsubscript{3} can affect disease progression in melanoma. Accordingly, it may be beneficial to include vitamin D\textsubscript{3} in melanoma management. 5,29 Adjuvant treatment with vitamin D in melanoma is expected to reduce tumor invasiveness and local metastasis which would both improve the patient’s prognosis and reduce their risk of relapse. 30

Previous studies have found that vitamin D has the potential to be a valid coadjuvant in the treatment of cancers such as melanoma but there is not currently research confirming this hypothesis. 31 It would be advantageous to conduct a randomized controlled trial (RCT) investigating whether increasing vitamin D levels will help improve melanoma outcomes. This would improve our understanding of the potential role of vitamin D in melanoma treatment. Current studies are investigating the relationship between vitamin D supplementation and cutaneous melanoma outcomes, but their research has yet to be published. 2,25 To further the research regarding the possible protective effects of vitamin D supplementation on cutaneous malignant melanoma following surgical resection of the primary melanoma, we will use a multicenter randomized placebo-controlled trial with a follow-up period of 18 months. In addition to investigating relapse-free survival, potential participants will be categorized by Fitzpatrick skin types and would only be included if they are classified as having a Fitzpatrick skin type IV, V or VI. This would allow us to determine whether vitamin D
supplementation would be an effective adjuvant treatment for patients with darker baseline skin tones. These categories of skin color were chosen based on prior studies showing that individuals with darker skin have lower serum vitamin D levels due to decreased synthesis in the skin.

1.2 Statement of the Problem

Melanoma rates continue to rise, and it continues to be the deadliest form of skin cancer. Relapse after surgical excision is not uncommon and occurs in approximately one-third of melanoma patients. The current standard of care following excision is inconsistent and has prompted an interest in finding adjuvant treatments that could reduce relapse rates. The active form of vitamin D₃ has been shown to have anticarcinogenic, anti-inflammatory and antimelanoma effects. Adjuvant treatment with vitamin D in melanoma is expected to reduce tumor invasiveness and local metastasis, which would both improve the patient’s prognosis and reduce their risk of relapse.³⁰

1.3 Goals and Objectives

The primary goal of this study is to determine whether supplementation with vitamin D₃ increases relapse free survival and reduces risk of melanoma recurrence in patients with darker skin tones. The proposed study will use a randomized controlled trial design to establish a potential new adjuvant treatment post-surgical excision that could decrease recurrence rates in patients with Fitzpatrick skin types IV, V, and VI. Additionally, this study aims to determine whether the effectiveness of this treatment varies by Fitzpatrick skin types.
1.4 Hypothesis

There will be a statistically significant difference in relapse-free survival in patients with Fitzpatrick skin types IV, V, VI provided with supplemental vitamin D$_3$ after surgical excision compared to those without vitamin D$_3$ supplementation.
References:
Chapter II: Review of the Literature

2.1 Introduction

An extensive literature search conducted between July 2019 and May 2020 aimed to review studies that used vitamin D as an adjuvant treatment in melanoma treatment. Databases including PubMed, Ovid MEDLINE, and Cochrane were searched using the following keywords: melanoma, malignant melanoma, skin cancer, cancer, skin neoplasms, vitamin D, and calcitriol. The search was limited to studies published since 2009 in order to focus on recent findings. All relevant articles written in English were reviewed for significance to the current study.

2.2 Review of Relevant Studies

This section summarizes the existing evidence pertaining to the use of vitamin D in cancer treatment and more specifically in melanoma treatment. There has been interest in vitamin D as a preventative measure in cancer for a number of years due to its anticarcinogenic properties but its use as an adjuvant treatment in melanoma is relatively new and accordingly the data is limited. Therefore, the focus is on previous literature that has investigated the relationship between vitamin D and tumor progression or formation.

2.2.1 Studies Analyzing the Relationship Between Vitamin D and Cancer

Many studies have investigated the efficacy of vitamin D supplementation in the prevention of various cancers. A 2017 randomized controlled trial conducted across the state of Nebraska by Lappe et al. assessed whether vitamin D3 and calcium supplementation reduces the risk of cancer among postmenopausal women. They found no statistically significant difference in incidence of any type of cancer after four years. A
post-hoc analysis excluding cancers diagnosed in the first year of the study, found a 35\% (Confidence interval (CI) 95\%, p = 0.047) lower incidence of cancer in the active intervention group. Some limitations of the study include that it was not sufficiently powered to detect differences in cancer types between study groups and that its population consisted of predominantly Caucasian women, limiting generalizability. Another limitation was that the baseline average serum 25(OH)D level of the participants was 32.8 ng/mL which is higher than the vast majority of the US population. This may have affected the results as it would be expected that those with lower baseline serum levels of vitamin D$_3$ would benefit more from supplementation.$^1$

The 2018 Vitamin D Assessment Study recruited adult participants in New Zealand to assess whether high-dose vitamin D given monthly was associated with a reduction in cancer incidence and mortality. The 5,108 participants were randomized to receive either an initial 200,000 IU Vitamin D bolus followed by monthly doses of 100,000 IU or a placebo. The participants were followed for an average of 3.3 years. The results of this study suggested that high dose vitamin D supplementation is not associated with reductions in cancer incidence (95\% CI, p=0.95) or mortality in the studied population. Some limitations of this study included monthly dosing versus either weekly or daily dosing. Using either daily or weekly dosing would increase the amount of time vitamin D would be present in blood circulation. Additionally, the majority of the studied population was Caucasian with European ancestry, and there was a low number of participants that began the study with vitamin D deficiency.$^2$

Another RCT was conducted by Manson et al. in 2019 to test whether vitamin D and omega-3 fatty acid supplementation helped prevent cancer and cardiovascular disease.
This randomized controlled trial used high dose daily vitamin D intervention and included a large and ethnically diverse sample size of 25,871 participants. They did not find a significantly lower incidence of invasive cancers (Hazard ratio (HR): 0.96, 95% CI, 0.88 to 1.06) or cardiovascular events (HR: 0.97, 95% CI, 0.85 to 1.12, p = 0.69) in the treatment versus placebo group but did note that the test for proportionality over time excluding early follow-up data did show a significantly lower death rate from cancer in the treatment versus placebo group (HR: 0.75, 95% CI, 0.43 to 0.92). These findings may indicate that vitamin D and omega-3 fatty acid supplementation is useful in cancer prevention in tumors that have yet to begin formation or that are very early in growth. Additionally, there were some non-significant but clinically meaningful differences seen in the group receiving vitamin D including slightly fewer advanced cancers or cancers that had metastasized. One limitation of this study was it was not powered to be able to assess site specific cancers.  

Weinstein et al. performed a prospective study looking at 4,616 cancer cases from a previous controlled primary prevention trial conducted from 1985-1988 in Finnish male smokers. They examined the overall cancer mortality as well as site-specific mortality. The researchers found that having a higher circulating 25(OH)D level years before their cancer diagnosis was associated with lower overall cancer mortality (HR: 0.76, 95% CI, 0.67 to 0.85, p-trend < 0.0001). They also found that having higher vitamin D levels significantly improved survival in malignant melanoma (HR: 0.39, 95% CI, 0.20 to 0.78, p-trend = 0.01), prostate cancer (HR: 0.74, 95% CI, 0.55-1.01, p-trend = 0.005), and kidney cancer (HR: 0.59, 95% CI, 0.35 to 0.98, p-trend = 0.28). There were non-significant improved survivals in other types of cancer as well. Their study did find an
inverse relationship with high vitamin D levels and lung cancer survival. This study only used vitamin D levels taken from a single point of time which may have limited the accuracy of some of the measured associations. Additionally, all the participants were male smokers which may have reduced the generalizability of the results.\textsuperscript{4}

In 2019, Keum et al. performed a meta-analysis of RCTs investigating the effect of vitamin D supplementation on total cancer incidence and mortality. They included 10 RCTs in their analysis of cancer incidence and 5 RCTs in their analysis of cancer mortality. Overall, their meta-analysis revealed that vitamin D supplementation significantly reduced cancer mortality by 13\% (RR: 0.87, 95\% CI, 0.78 to 0.96, p = 0.007) but did not reduce cancer incidence. It was also important to note that the reduction in cancer mortality was seen more in trials using daily dosing versus infrequent bolus dosing. The effects were seen in participants who had a circulating 25(OH)D level of less than 100 nmol/l. The significant reduction in mortality but not in incidence was thought to be in part due to vitamin D working at different stages of carcinogenesis including decreasing the invasiveness and likelihood to metastasize. A strength of this meta-analysis was that it was successful at analyzing the current trends being seen in the associations between vitamin D supplementation and cancer incidence and mortality, but it had some limitations. First, they only used 10 studies and there was no analysis of cancer type-specific trends, meaning there may have been a greater effect for certain types of cancer than others. Second, most of the study populations were predominantly white and the results may not be very generalizable.\textsuperscript{5} This meta-analysis showed evidence for vitamin D supplementation decreasing cancer mortality however there is
still a lack of evidence on its effects in diverse populations and people with low baseline levels of vitamin D.

2.2.2 Vitamin D Effects on Skin Cancer

Due to the trends seen in previous research in regard to vitamin D levels and cancer, some studies examined the relationship between vitamin D supplementation and skin cancer. Tang et al. performed a post-hoc analysis of the Women’s Health Initiative Randomized Control Trial to examine whether supplementation with 400 IU of vitamin D and 1,000 mg of calcium daily would change the incidence of skin cancer. They examined 36,282 post-menopausal participants over a 7 year follow up. They found no difference in non-melanoma or melanoma skin cancer incidences between groups, but notably, they did find a 57% lower risk of melanoma in the treatment group compared to controls among women who had a reported history of non-melanoma skin cancer (HR: 0.43, 95% CI, 0.21 to 0.90). It is important to note that they excluded women who had a melanoma fewer than 10 years prior to the beginning of the study when examining these results, as this potentially excluded melanoma recurrences. A limitation of this study is that participants were allowed to take off-protocol calcium and vitamin D supplementation making it possible that some women in the placebo group could have been taking more vitamin D than in the intervention group due to the low dose of vitamin D provided in the study.6

Caini et al. performed a meta-analysis assessing the effect of vitamin D on melanoma and non-melanoma skin cancer risk and prognostic factors in 2014. They included 20 studies with an overall number of 1,420 cutaneous melanoma cases and
2,317 non-melanoma skin cancer (NMSC.) Their results were suggestive of an inverse relationship between serum vitamin D levels and thickness of melanoma tumor at diagnosis but they found no association with incidence and serum levels.\(^7\) Both this meta-analysis and the Tang et al. study provide important evidence suggesting the role of vitamin D in improving melanoma prognostic factors and risk.

2.2.3 Relationship Between Vitamin D and Melanoma

The potential relationship between vitamin D and melanoma was tested further in a number of studies. A 2016 study conducted by Fang et al., assessed the association between vitamin D levels and outcomes in patients with melanoma after adjustment for c-reactive protein (CRP). They took plasma samples from their 1,042 melanoma patients who were then prospectively observed for a median follow-up of 7.1 years. They found that lower vitamin D levels in patients with melanoma were associated with increased tumor thickness \((p < 0.001)\), ulcerated tumors \((p = 0.0105)\), increased CRP \((p < 0.001)\), later stage of melanoma \((p = 0.0024)\) and poorer overall melanoma-specific survival \((p = 0.0025)\) as well as disease free survival \((p = 0.0466)\). One limitation of this study is that the population was drawn from one large cancer facility and it may not be representative of the overall population. There was also no measure of vitamin D supplementation or intake of the participants, which may have played a role on the serum vitamin D levels observed.\(^8\)

Vinceti et al. examined the relationship between dietary vitamin D intake and melanoma risk in a northern region of Italy known to have a lower vitamin D intake than many western societies. They used a population-based case-control study to examine
their 380 cases and 719 controls. Using an in-depth food frequency questionnaire this study found an inverse relationship between dietary vitamin D intake and melanoma risk. They found this effect to be especially strong in men with phototype IV skin. Some limitations of this study are that they did not include amounts of sun exposure or any information about supplements that may have included vitamin D in their study. They also noted low control group participation which may have skewed the results making the relationship appear stronger than it was. Lastly, the location of the study has a homogenous population which may not apply to a broader population.9

Nurnberg et al. compared serum 25-hydroxyvitamin D levels in melanoma patients at different stages and control patients without melanoma in Germany. They found a significantly reduced serum vitamin D level in patients with stage IV melanoma versus those with stage Ia/Ib melanoma (p = 0.006). Their results also showed trends of greater tumor thickness (p = 0.078) and earlier distant metastasis (p = 0.641) in patients with low serum vitamin D levels (less than 10 ng/ml.) Limitations of this study include a smaller sample size of 205 patients with malignant melanoma and no use of any demographic information to show if the patients were ethnically diverse or representative of the general population.10

In line with these findings, a UK based 2009 case control comparison and meta-analysis of VDR data found that vitamin D3 level at recruitment was inversely proportional to Breslow thickness (p = 0.03).11 Another study with similar findings was a pilot study conducted by Lim et al. in Australia. They retrospectively looked at 109 primary melanoma cases between 2001 and 2013 and their corresponding vitamin D levels within 6 months of diagnosis. They looked at a number of variables of the
melanoma cases and found that high serum vitamin D levels were associated with low Breslow thickness (p = 0.026). They also found that higher levels of vitamin D were significantly associated with two other positive melanoma prognostic factors including non-ulcerated tumors (p = 0.0006) and tumors with lower mitotic rates of 1/mm$^2$ (p = 0.036). It is important to note that a single point vitamin D$_3$ value was used for this study which could lead to a number of confounding effects on the results. A limitation of this study is they did not factor in data such as sun exposure history, use of supplements, or skin phototype. $^{12}$ All of these studies found consistent results showing that higher vitamin D levels are likely associated with better melanoma prognostic factors.

To explain some of the findings from different trials in regard to the mechanism of vitamin D’s effect on melanoma, Spath et al. investigated the biological effects of 1 alpha hydroxycholecalciferol on experimental melanoma models derived from human melanoma cell lines and in-vivo xenografts. They hoped to establish an explanation of the biology behind how vitamin D effects melanoma cells. They found that treating these cells with the 1alpha hydroxycholecalciferol had antiproliferative effects on the melanoma cells both in-vitro and in-vivo (p < 0.001). Additionally, they saw that the cell cycle arrested in the treated cells. After providing daily 1alpha hydroxycholecalciferol for 42 days the biological effects of treatment became statistically significant. In addition to examining cell lines they also tested the serum 25-hydroxycholecalciferol levels in 105 melanoma patients and found that 94% had insufficient vitamin D levels and the 6% of the melanoma patients with normal levels all had either in-situ or microinvasive cases of melanoma. Patients were considered vitamin D deficient if they had a serum level of less than 10 ng/mL. A limitation of this study was the small sample size of patients tested for
vitamin D levels. This study may help explain the biology behind why vitamin D supplementation may be beneficial as an adjuvant treatment for melanoma.\textsuperscript{13}

Cattaruzza et al. conducted a case-control study in Italy with findings congruent with the high frequency of vitamin D insufficiency in melanoma patients seen in Spath et al. This study compared the serum vitamin D levels in 137 melanoma patients to 99 healthy controls. They found a statistically significant difference between the serum vitamin D levels of those with melanoma compared to those without it. 66.2\% of their participants with melanoma were vitamin D deficient (serum vitamin D of $\leq$ 20 ng/ml) compared to only 15.2\% of healthy controls ($p < 0.001$). After controlling for a number of confounders, their results still showed a significant inverse association between melanoma and vitamin D sufficiency versus insufficiency with a $p$-value of $< 0.001$. A limitation of this study was that they did not correct for sun exposure when adjusting for confounders. These results suggest that having sufficient levels of vitamin D may be protective in terms of melanoma risk, although causation cannot be concluded from these results due to the design of the study.\textsuperscript{14}

Saw et al. is conducting a placebo controlled randomized phase II trial assessing adjuvant therapy with high dose vitamin D following primary treatment of melanoma in Australia and New Zealand. They randomized 75 patients with surgically resected stage IIb, IIc, IIIa and IIIb melanoma. Their primary goal is to assess the safety and feasibility of using a vitamin D 500,000 IU loading dose followed by an oral dose of 50,000 IU monthly for two years compared to placebo following excision of melanoma in adult patients. Results of this study are still pending.\textsuperscript{15} This study will help further our current
understanding of what a safe high dose of vitamin D could be in clinical practice moving forward. Most other studies use a significantly lower dose than this dosing.

In an ongoing randomized double-blind controlled phase III trial conducted by De Smedt et al., the group is investigating the protective effect of vitamin D throughout and after participants’ melanoma diagnoses. In this study 500 adult candidates who met the criteria would be given either a monthly dose of 100,000 IU cholecalciferol or placebo with the primary end point being relapse free survival. The subjects would be followed every 3 months for a maximum of 3.5 years. Results have yet to be published for this study but will be stratified based on the amount of time since diagnosis. One limitation of this study is that it does not include any information on participants’ skin phototypes which may play an important factor in vitamin D production and levels at diagnosis. Additionally, the study is being conducted at a total of four hospitals in Europe which may not be representative of a diverse patient population.16

A systematic review published in 2020 examined the association between serum vitamin D levels and risk and/or prognosis of melanoma. They included 25 studies with a total of 11,166 melanoma cases in their analysis. Using nine studies with very heterogenous results they found no significant difference in serum vitamin D levels between the cases and controls. Despite these results, using results from five studies they did find that there was a significantly higher prevalence of vitamin D deficiency in the melanoma patients than in the controls. Additionally, using data from 8 studies they found that serum vitamin D levels were significantly higher in patients with low Breslow thickness (less than 1 mm) with a p-value of 0.09. Using five studies they also found that low serum vitamin D levels were associated with significantly higher mortality with a p-
value of < 0.001. As previously mentioned, one of the major limitations of this meta-analysis is the limited number of studies and very heterogenous results of the studies used to investigate the association between serum vitamin D status and risk of developing melanoma. Furthermore, all of the findings in this study were only associations and show no causality making it important to interpret the results with some caution.17

2.3 Review of Studies Analyzing Possible Confounders

When using vitamin D as an intervention there are many factors including timing of the blood draw, sun exposure level, use of sunscreen, gender, age, ethnicity, diet, treatment and comorbid conditions such as cancer and autoimmune diseases that can play a role in the serum levels obtained.17 Sun exposure has a clear and known effect on vitamin D levels and in previous studies can have confounding effects on results if participants are not matched based on sun behavior. Some trials implement self-report questionnaires about sun exposure to help control for it in their analysis, but these reports may not reflect the participants sun exposure accurately.6,10,18 BMI could also play a small role in results due to the volumetric dilution which could affect the amount of vitamin D necessary to achieve the same serum levels and has been found to be associated with melanoma in the past.3,12,14 Time of blood draw based on season can also cause variation and it has been found previously that vitamin D levels are higher in blood draws conducted in the spring or summer compared to those from the fall or winter.8 Another factor which could play a role in vitamin D serum levels is the amount of vitamin D binding protein participants have circulating in their blood.19
2.4 Review of Relevant Methodology

2.4.1 Study Design

This study will be a multi-center, randomized controlled trial which is a study design that has been used by several previous trials looking at vitamin D levels in regard to melanoma and other cancers. With the use of placebo medication both patients and researchers will be blinded in the study.\textsuperscript{2,3,15,16} Block randomization will be used to help eliminate differences between the groups due the use of multiple sites in this study and to allow for rolling enrollment.\textsuperscript{1} All patients will be consented in accordance with the institutional ethics guidelines and all patient information will be maintained strictly in accordance with Health Insurance Portability and Accountability Act (HIPAA).

2.4.2 Study Population and Selection Criteria

Inclusion criteria requires all participants to be adult individuals with surgically treated malignant melanoma between stages IB-III. Participants will be eligible for inclusion if they are less than one year from diagnosis and can only be included post-surgical excision.\textsuperscript{15,16} Patients must be willing and able to attend all follow-up visits for the duration of the study and provide informed consent.\textsuperscript{15} Unlike previous studies, this study will only include patients with Fitzpatrick skin types IV, V, or VI which are often underrepresented groups in previous studies. Patients who are pregnant, have abnormal serum phosphate or calcium, impaired renal function, known vitamin D sensitivity or malabsorption will not be included in the study for safety reasons.\textsuperscript{16} Patients who exhibit regular sun exposure behavior or use indoor tanning will also be excluded due to their high levels of endogenous vitamin D.
2.4.3 Intervention and Method of Administration

The safety of oral vitamin D has been studied and it appears that vitamin D toxicity would require a minimum of 10,000 IU/day and most likely would not occur at less than 40,000 IU/day, making the dose used in this study safe to use over an extended period of time.\textsuperscript{20} De Smedt et al. used a monthly oral syringe dose of 100,000 IU, had patients take all doses after the initial dose at home, and self-record taking their medication adherence in a diary.\textsuperscript{16} Scragg et al. used a similar intervention but used monthly 100,000 IU oral capsules that were mailed to the participants’ homes and similarly had them self-record their adherence.\textsuperscript{2} Saw et al. used a slightly different method of beginning with a 500,000 IU oral loading dose followed by self-administered and recorded 50,000 IU monthly doses for 23 months.\textsuperscript{15} Unlike the previous trials Manson et al. used daily vitamin D dosing of 2,000 IU.\textsuperscript{3} Similar to that trial, Lappe et al. used daily 2,000 IU vitamin D but with the addition of 1,500 mg/d of calcium as their intervention over a four year trial.\textsuperscript{1} In hopes to improve adherence by making medication once weekly and increase frequency of dosing we propose using a once weekly oral vitamin D dose of 25,000 IU which would be the equivalent monthly dose of 100,000 IU used by previous studies.\textsuperscript{2,5,16}

2.4.4 Outcome Measures

The primary outcome measure of this study will be relapse free survival over the duration of the trial. Other variables will include stage, location of melanoma, and result based on Fitzpatrick skin type. To most effectively analyze the results we will be using a Kaplan-Meier survival curve.\textsuperscript{15} Data will be collected at every three month follow-up
visit with the patient’s primary dermatologist including a full-body skin check assessing for melanoma recurrence or relapse. Participants will continue their supplementation and be followed for 18 months after enrollment into the study.

2.4.5 Safety Concerns

Baseline laboratory tests will be taken at the beginning of the study and subsequent lab tests for safety and monitoring will be taken at every three month follow up visit. Other studies have similarly checked different patient health information such as serum corrected calcium, phosphate, eGFR, liver function tests, calcium/creatinine ratios, tumor status and adherence to dosing regimens during follow-up visits to assess for safety concerns. For safety reasons participants will cease treatment if any of these previous lab findings are > 20% above normal range, if the participant becomes pregnant, has disease progression or develops a renal calculus.15

2.4.6 Sample Size Calculation

The proposed study will examine the efficacy of vitamin D₃ as an adjuvant treatment for surgically resected malignant melanoma in stages IB through III. There are no prior completed clinical trials, and accordingly this sample size calculation was performed using data from previous research. A 2019 retrospective cohort study examining 1931 cases of invasive melanoma found a recurrence rate of 8.8% in stages I-III.21 This expected percent recurrence was used for the sample size calculation as it covers stages I-III and is on the low side of reported relapse rates in the studies analyzed which makes it more realistic in the proposed timeframe of this study. A hazard ratio of 0.40 was used for the treatment group and is consistent with the intermediate effect size
of vitamin D supplementation seen in the Newton-Bishop et al. study.\textsuperscript{16,22} Drop-out and non-adherence will also be accounted for at a higher rate than most similar studies as our study design limits the amount of UV exposure participants can get and requires follow-up every three months for 18 months. Accordingly, the sample size of this proposed study will account for a 25\% drop out rate.

2.5 Conclusion

In conclusion, there are a number of studies whose results demonstrate an inverse relationship between serum vitamin D levels and poor melanoma prognostic factors including increased Breslow thickness, ulceration, and later stage of melanoma.\textsuperscript{7,8,10,12,17} Studies have also shown a decline in some cancers and more specifically melanoma mortality with higher vitamin D levels.\textsuperscript{4,5,17} These effects are likely due to the antiproliferative effects of vitamin D that have been seen both in-vitro and in-vivo.\textsuperscript{13} There is also evidence of an inverse relationship between dietary vitamin D and melanoma risk which was found to be most significant in participants with skin phototype IV.\textsuperscript{9} Some studies have also shown there to be a significantly higher prevalence of vitamin D insufficiency/deficiency in melanoma patients compared to the general population.\textsuperscript{13,14,17} These findings combined would suggest that supplementing vitamin D in populations where levels are known to be low could provide the patients with better chances of survival and may decrease rates of relapse.

This study will be the first study to assess whether supplementation with high dose vitamin D in melanoma patients with Fitzpatrick skin types IV, V, VI would be a beneficial adjuvant treatment to decrease relapse. By conducting this study, we will gain insight on whether vitamin D supplementation may be beneficial in populations that are
known to have lower vitamin D levels at baseline and could provide a relatively safe adjuvant option in these populations.
References


Chapter III: Methods

3.1 Study Design

This study is a multi-centered, double-blind, randomized controlled trial to evaluate the efficacy of supplemental vitamin D₃ for the reduction of recurrent melanoma after wide local surgical excision in Fitzpatrick skin type IV, V and VI melanoma patients.

3.2 Study Population and Sampling

The study population will be patients from nine cancer centers across the USA who meet the inclusion and exclusion criteria. Blocked randomization stratified by site will be used to form the study populations.

3.2.1 Inclusion Criteria

Adults between the age of 18-80 diagnosed and surgically treated for cutaneous malignant melanoma will be enrolled. The participants must have histologically proven malignant melanoma with a high risk of recurrence (stages IB-III.) Patients with a diagnosis within the past year are eligible for enrollment and will only be included after a complete surgical resection of the melanoma has been performed. Additionally, participants will be required to have Fitzpatrick skin types IV, V or VI. Participants must be willing and able to come into the clinic for follow-up every three months for the duration of the study.
3.2.2 Exclusion Criteria

Pregnant patients and those who have abnormal entry serum phosphate or calcium, impaired renal function, known hyperparathyroidism, known vitamin D sensitivity, history of malabsorption, or chronic alcohol use will be excluded from the study. Patients participating in any other trials or taking any drugs known to interact with vitamin D will also be excluded. Patients exhibiting regular sun exposure behavior or indoor tanning behavior will be excluded.

3.3 Recruitment

Recruitment will take place at numerous centers across the United States including: Yale New Haven Smilow Cancer Center (New Haven, CT), UCSF Health (San Francisco, CA), Sloan Kettering Cancer Center (New York, NY), Dana Farber Cancer Center (Boston, MA), MD Anderson Center (Houston, TX), Mayo Clinic (Jacksonville, FL), Mayo Clinic (Scottsdale, AZ), USC/Norris Comprehensive Cancer Center (Los Angeles, CA) and the Harold C. Simmons Comprehensive Cancer Center (Dallas, TX). Due to the use of multiple sites, block randomization will be performed at each individual site. The dermatology clinics in these sites will be asked to participate in this study and for help recruiting eligible patients. Patients who meet the inclusion criteria who express interest in participating will be enrolled in the study if they have undergone surgical excision for stage IB-III melanoma. They will then sign informed consent forms (Appendix A) and be assessed against the exclusion criteria prior to randomization.
3.4 Subject Protection and Confidentiality

We will obtain approval by Yale’s oncology-focused Institutional Review Board (IRB) and Human Investigation Committee (HIC).

Submitting an application to the HIC IRB committee involves a four-step process:

1. All personnel interacting with patients or data must undergo Human Subjects Protection Training.
2. All personnel interacting with patients or data must complete HIPAA training.
3. The principal investigator and co-investigators must file a financial disclosure form with the Yale Conflict of Interest office.
4. Once all the prior steps have been met, the investigators may submit an application to the HIC IRB committee through the IRES IRB system. The application will be submitted to: https://your.yale.edu/research-support/human-research/yale-irbs-yale-university-institutional-review-boards/ires-irb

Throughout the study, confidentiality of participants will be strictly maintained in accordance with HIPAA. To ensure confidentiality, each participant will be assigned a randomly generated identification number which will be used throughout the duration of the study. All electronic records will be kept in encrypted databases on password protected computers, and access to the patient records will only be available to the dermatology teams performing direct patient care. Other study personnel such as research assistants will only have access to de-identified data.
3.5 Study Variables and Measures

Participants who have met the inclusion criteria will be randomized to two groups: either the control group, which will receive the standard of care and placebo, or the intervention group, which will receive the oral vitamin D₃ supplement. At enrollment of each subject, a baseline serum 25(OH)D level and a complete metabolic panel (CMP) of all participants will be obtained and patient information will be reviewed to ensure that they meet the inclusion/exclusion criteria. These same tests will be obtained at every three month follow-up visit to monitor patient adherence and possible side effects.

The intervention group will receive oral vitamin D₃ (cholecalciferol) 25,000 IU once weekly for the duration of the study. The control group will receive a capsule identical in appearance to the intervention group. Both groups will be instructed to take the capsule with the same frequency and return for the same regularity of monitoring including blood tests and total body skin checks to evaluate for melanoma recurrence.

All subjects will use a wireless, battery-free miniature ultraviolet light dosimeter to monitor their ultraviolet light exposure. Since sun exposure of the skin is the most efficient method to obtain vitamin D, it will be important to monitor endogenous production to control for these effects.¹

The primary outcome of the study will be the efficacy of the treatment measured by the difference in relapse-free survival in the intervention vs. placebo group. Other variables will include stage, location of melanoma, and Fitzpatrick skin type.
3.6 Assignment of Intervention and Blinding

At each of the study locations rolling recruitment and block randomization will be used. Participants will be allocated to the control vs. intervention group in a 1 to 1 fashion with a block size of two. Recruitment will end once a sample of 70 total participants is met. After randomization, the participants will be assigned their randomly generated unique identification number to de-identify their personal information. Patients and study personnel will all be blinded to the patient’s study treatment allocation and vitamin D levels by use of the unique identification numbers.

3.7 Data Collection

Clinicians at each site will identify eligible patients, and those who show interest will sign informed consent forms. Patients will undergo a full body skin examination and will have a complete metabolic panel and serum 23 hydroxyvitamin D (23 OHD) level checked for baseline levels on the day of enrollment. Participants that meet the inclusion and exclusion criteria will be randomized and assigned to a treatment group. They will then be asked to return within the next week to meet with a research assistant, obtain their first three-month supply of either the placebo or vitamin D₃ and to complete a demographic survey. Patients will receive explicit instructions on dosage, frequency, and adherence to the medication required to remain in the study. At every three month follow up, data will then be collected by the patient’s dermatologist via full body skin check and CMP, and the patients will receive a new three-month supply of the medication. Side effects and Vitamin D₃ concentrations will be monitored throughout the duration of the study.
3.8 Adherence

Adherence will be monitored through weekly patient logs. They will be offered either paper or electronic log options. The patient will be given a sheet of paper with their pill bottle that has all the weeks listed and a space for a check mark if they have taken their dose for the week. The patient will be asked to bring these logs to each visit. Electronic logs can be completed via phone applications (such as Medisafe, Carezone, Pill Logger, Medica etc.) and can be shared with their providers. To improve adherence, we will also ask all the patients to set a weekly recurring reminder for the day of the week they choose to take their medication.

3.9 Monitoring of adverse events and safety

At the beginning of the study baseline laboratory tests will be checked. Subsequent lab tests for safety and monitoring will be checked at every three month follow up visit. Different patient health information measures such as serum corrected calcium, phosphate, eGFR, liver function tests, calcium/creatinine ratios, and tumor status during follow-up visits to assess for safety concerns will be checked. For safety reasons, participants will cease treatment if any of these previous lab findings are > 20% above normal range, or if the participant becomes pregnant.

3.10 Sample Size Calculation

Using the Power and Precision 4 software, a sample size of 56 participants using a two-tailed test and alpha of 0.05 was determined. This sample size will allow 80% power to detect whether vitamin D supplementation increased relapse free survival with an accrual
period of 6 months. The sample size calculation was based on two previous studies discussed in Chapter II. Adjusting for a 25% dropout/non-adherence rate, the recruitment goal will be 70 participants to be randomized and enrolled into the study. The participants will be randomized in a 1:1 fashion, with a total of 35 participants in each group. The sample size calculation is included in Appendix B.

3.11 Analysis

The primary analysis will be an intent-to-treat analysis of all randomized patients. Analysis will evaluate relapse free survival with a Kaplan Meier time-to event survival curve. Results will be considered to be statistically significant if they have a p-value of less than 0.05. A per protocol analysis will be performed in anticipation of a high non-compliance/dropout rate and an intention-to-treat analysis will likely skew the results towards the null. Demographic data including age, sex, ethnicity, race, stage of melanoma and location will be collected for all patients to compare the treatment and control groups. The categorical variables such as sex, stage of melanoma, and race will be compared using a chi-square test. Age will be compared using an independent sample t-test.

3.12 Timeline and Resources

The total duration of this study including recruitment, randomization and data collection will be two years. Rolling recruitment and enrollment will begin January 2021 and will continue for six months to allow for follow-up and data collection. All of the sites chosen for this study are high volume cancer and melanoma facilities, and accordingly, there
should not be any difficulty obtaining the 70 participants needed for this study. All study subjects will have to meet with a research assistant in the first week of enrollment to receive their medication and trial instructions. Follow up visits will be conducted by their clinical dermatologist every three months for routine melanoma follow-up and data collection. Data collection will end at the beginning of January 2023.

The study will be headquartered in New Haven, CT. Dr. Suguru Imaeda and Shikha Goyal PA-SII will be the primary investigators for this project. Each site will have its own research assistant who will be responsible for identifying and confirming participants who meet the inclusion and exclusion criteria, obtaining informed written consent, and discussing data collection with the dermatologist treating the enrolled patients. They will also be responsible for meeting with the participants following enrollment into the study to provide them with instructions on adherence and follow-up. The patient’s dermatologist will be provided with the patient’s medication including either the three-month supply of weekly 25,000 IU vitamin D₃ pills or the matching placebo to be given at each follow-up appointment.
References:


Chapter IV: Conclusion

4.1 Advantages and Disadvantages

There are a number of strengths to this proposed study. It will be the first clinical trial investigating the use of high dose vitamin D therapy as an adjuvant treatment in patients with Fitzpatrick skin types IV-VI. There are currently a couple of ongoing studies looking at vitamin D use in other populations. However, none of these studies incorporate the differences in Fitzpatrick skin type and the according difference in vitamin D endogenous synthesis.\textsuperscript{1,2} Although sun exposure is a known confounder of vitamin D levels, previous studies in this field rarely accounted for sun exposure in a systematic manner. Most previous studies have not been randomized controlled trials and accordingly have only been able to establish association and not causation.\textsuperscript{3-6}

The use of this study design and double blinding will also decrease selection bias that could influence the results. Block randomization and stratification by site should ensure that the populations are similar, reduce selection bias, and minimize the effects of other confounders. The sufficient sample size of this trial ensures that the study is powered to show causation and also allows the study to withstand participant dropout that would occur in a study of this length. The use of multiple sites will allow us to meet our target study population size within the recruitment period and will also ensure that the results are generalizable to the larger community of individuals with Fitzpatrick skin types IV-VI. Melanoma patients often follow up with their dermatologist every three months. Using these visits with the participant’s primary dermatologist for data collection increases the feasibility, decreases the cost, and should promote adherence.
Despite the many advantages of this design, there are some disadvantages. A limitation of this study is the shorter duration of follow-up compared to similar studies. However, since over half of relapses occur within two years of excision of the primary melanoma this study will add important information on whether vitamin D₃ is an effective adjuvant treatment in this population. A longer duration would allow for more data collection and a more complete ability to assess differences between relapse in the treatment and placebo groups. Another disadvantage of the study is that the use of many clinical sites could lead to some differences in how the study is conducted between sites. These differences will be minimized by providing standard instructions to all sites, providers, and research assistants. There is also not an established ideal dose for high-dose adjuvant vitamin D therapy. Accordingly, this study is using overall dosing in line with other previous studies, but breaking up the dosing to weekly due to evidence that higher frequency of dosing may be more beneficial.²,⁷,⁸ By limiting the study to those with Fitzpatrick skin types IV-VI it is also important to note that these results would not be generalizable to those with fairer complexions.

4.2 Clinical and/or Public Health Significance

Melanoma continues to be the deadliest form of skin cancer, and even after surgical removal it is known to have high rates of relapse and recurrence.¹ Despite this, there is still a lack of safe and effective adjuvant options for melanoma patients.⁹ Vitamin D is known to have anticarcinogenic and antimelanoma effects which have been seen in-vivo and in-vitro.¹⁰-¹² People of color with Fitzpatrick skin types IV-VI have often been underrepresented in study populations examining skin cancer where differences in
pigmentation may play an important role. Due to differences in synthesis, it is more difficult for those with more epidermal melanin to produce endogenous vitamin D from sunlight, leading to the higher rates of vitamin D deficiency seen in darker skinned individuals.\textsuperscript{13-15} These differences may make the role of vitamin D supplementation especially useful in populations with Fitzpatrick skin types IV-VI. It has also been found that, despite lower incidence of melanoma in non-white populations, when melanoma is found in this population, it is often detected at more advanced stages, with thicker lesions, increased rate of metastasis and poorer outcomes.\textsuperscript{16}

This study will provide some of the strongest evidence to date to guide whether vitamin D supplementation could act as a useful adjuvant treatment in patients with Fitzpatrick skin types IV, V and VI. If successful it could provide a new clinically supported, low toxicity, adjuvant treatment option. This study has the unique advantage of accurately measuring and accounting for UV sun exposure, a known confounder of vitamin D levels that has rarely been controlled for in previous related studies. This study will additionally help establish if this dosing of vitamin D is clinically useful and safe. The results of the proposed study would be a logical addition to the existing body of literature, clarifying vitamin D’s utility as an adjuvant treatment in surgically resected melanoma cases in a population with an increased risk of vitamin D deficiency.
References:


CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE

Study Title: Vitamin D Supplementation In Fitzpatrick Skin Types IV-VI As An Adjuvant Treatment For Malignant Melanoma

Principal Investigator: Suguru Imaeda, MD

Funding Source:

Invitation to Participate and Description of Project

We are inviting you to participate in a research study designed to look at whether supplementation with vitamin D reduces risk of melanoma recurrence in adults with Fitzpatrick skin types IV-VI who have been diagnosed and treated for cutaneous melanoma. You have been asked to participate because you are an adult between the age of 18-80 that has had a surgically treated malignant melanoma between stages IB-III, are less than one year from diagnosis and have had the tumor surgically excised. Approximately 70 persons will participate in the study.

In order to decide whether you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you agree to participating in this study, you will be randomly assigned to (a) the control group, which will receive the standard of care and placebo OR (b) the intervention group, which will receive the oral vitamin D₃ supplement. The study has a total duration of 18 months.

If you are pregnant or may become pregnant, if you have abnormal entry serum phosphate or calcium, impaired renal function, known hyperparathyroidism, known vitamin D sensitivity, history of malabsorption, or chronic alcohol use, you cannot participate in this study. If you are participating in any other trials or taking any drugs known to interact with vitamin D you will also be excluded. If you have regular sun
If you agree to be enrolled in this study, a baseline serum 25(OH)D level and a complete metabolic panel (CMP) will be taken and your information reviewed to ensure that you meet the inclusion/exclusion criteria. These same tests will be performed at every three-month follow-up visit to monitor your adherence and possible side effects.

The intervention group will receive an oral vitamin D3 25,000 IU once weekly for the duration of the study. The control group will receive a capsule identical in appearance to the intervention group. Both groups will be instructed to take the capsule with the same frequency and return for the same regularity of monitoring including blood tests and total body skin checks to evaluate for melanoma recurrence.

You will also be given a wireless, battery-free miniature ultraviolet light dosimeter to monitor your ultraviolet light exposure.

A description of this study is available on [http://www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), as required by U.S. Law. This website will not include information that can identify you. The purpose of this database is to allow everyone to see information on what studies are being done, and what studies have been done. At most, the Web site will include a summary of the results. You can search this website at any time.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate. Research results will not be returned to your doctor. If research results are published, your name and other personal information will not be given.

**Risks and Inconveniences**

Vitamin D Supplementation has been studied in several clinical trials for many conditions. The safety of oral vitamin D has been studied and it appears that vitamin D toxicity would require a minimum of 10,000 IU/day and most likely would not occur at less than 40,000 IU/day, making the dose used in this study safe to use over an extended period of time.

If you are pregnant or may become pregnant, if you have abnormal entry serum phosphate or calcium, impaired renal function, known hyperparathyroidism, known vitamin D sensitivity, history of malabsorption, or chronic alcohol use, you cannot participate in this study. If you are participating in any other trials or taking any drugs known to interact with vitamin D you will also be excluded. If you have regular sun exposure behavior or indoor tan you will be excluded.

Other risks from participating in the study include the breach of confidentiality about your health status and participation in the study. This is very unlikely to occur, as all study investigators are trained and certified in research privacy and this is a double
blinded study.

We will also ask you to have your baseline serum 25(OH)D level and a complete metabolic panel (CMP) done at every three-month follow-up visit to monitor your adherence and possible side effects. The risks involved in drawing blood from a vein may include, but are not limited to, momentary discomfort at the site of the blood draw, possible bruising, redness, and swelling around the site bleeding at the site, feeling of lightheadedness when the blood is drawn, and rarely, an infection at the site of the blood draw. There are no major risks associated with these procedures.
Benefits

There are potential benefits resulting from the study including a lower rate of relapse of melanoma compared to those not receiving vitamin D supplementation, and that this research may lead to new treatments in the future.

Economic Considerations

The vitamin D or placebo will be provided free of charge. There are no other costs associated with your participation in the study. Parking will be provided free of charge.

Treatment Alternatives/Alternatives

If you choose not to participate in this study, there are no alternative treatments available, except those that are already being administered by your physician including pharmacotherapy (medications/drugs), surgery, and lifestyle changes. You may choose not to participate.

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Information will be kept confidential by using only identification numbers on study forms, storing signed forms in locked cabinets, and password protecting data stored on a computer. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific permission for this activity is obtained.

We understand that information about your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies your personal health information. This may include information that might directly identify you, such as his or her name and address, telephone number, and email address, or mobile phone number. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you and your coded information, and this link will be kept secure and available only to the principal investigator or selected members of the research team. Any information that can identify you will remain confidential. Information will be kept confidential by using only identification numbers on study forms, storing signed forms in locked cabinets, and password
protecting data stored on a computer. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for 5 years, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

The information about your health that will be collected in this study includes:
- Research study records
- Records about phone calls made as part of this research
- Records about your study visits

Information about your health which might identify your child may be used by or given to:
- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator (Dr. Suguru Imaeda)
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine are required to comply with HIPAA and to ensure the confidentiality of your information.

If you choose to participate in this study, the research assistants will check your electronic medical record at Yale (EPIC) to make sure you qualify. Any access to your electronic medical record will be done consistent with HIPAA regulations.

Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.
You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. This authorization to use and disclose your health information collected during your participation in this study will never expire.

**Voluntary Participation and Withdrawal**

You are free to choose not to participate in this study. Your health care outside the study, the payment for your health care, and your health care benefits will not be affected if you do not agree to participate. However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study. You do not give up any of your legal rights by signing this form.

**Withdrawing From the Study**

If you do not become a subject, you are free to stop and withdraw from this study at any time during its course.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments.

The researchers may withdraw you from participating in the research if necessary. This will only occur if you do not attend the assigned weekly sessions.

If you choose not to participate or if you withdraw it will not harm your relationship with your own doctors or with the Yale School of Medicine and Yale New-Haven Hospital.

**Withdrawing Your Authorization to Use and Disclose Your Health Information**

You may withdraw or take away permission to use and disclose your health information at any time. You do this by calling or sending written notice to the Principal Investigator, Dr. Suguru Imaeda Department of Dermatology, Yale School of Medicine.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.

**You do not give up any of your legal rights by signing this form.**
Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the permission form carefully – as long as you feel is necessary – before you make a decision.

Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject: ______________________________________

Signature: ____________________________________________

Relationship: _________________________________________

Date: ________________________________________________

_________________________________________  ______________________________
Signature of Principal Investigator                      Date

or

_________________________________________  ______________________________
Signature of Person Obtaining Consent                  Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, Dr. Suguru Imaeda at 203-415-9221.

If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.
Appendix B: Sample Size Calculation

Alpha (level of significance): 0.05
Power: 80%
2-tailed hypothesis
N = 28 per group
Factoring in an expected 25% dropout rate the sample size is n=35 per group
Calculated using: Power and Precision 4.
Bibliography


