VITAMIN D ULTRAVIOLET RADIATION AND DISPARITIES: SURVIVAL AND MULTIPLE PRIMARY CANCERS IN COLORECTAL AND PROSTATE PATIENTS

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ABSTRACT OF THE DISSERTATION

VITAMIN D ULTRAVIOLET RADIATION AND DISPARITIES: SURVIVAL AND MULTIPLE PRIMARY CANCERS IN COLORECTAL AND PROSTATE PATIENTS

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Vitamin D, a steroid hormone with documented anti-cancer properties, is largely obtained through environmental exposure. It has been suggested that vitamin D deficiency, which is higher among U.S. Blacks than Whites, may contribute to survival differences from prostate and colorectal cancers. In addition, Blacks may be at higher risk for Multiple Primary Cancers (MPCs) involving these tumor pairings. It is currently unknown what factors other than prior radiotherapy may contribute to MPC development.

The aims of this thesis were to: (1) conduct a systematic review of vitamin D radiation (VDR) and its relationship to prostate and colorectal cancers, including the role of the environment, sun-reactive Skin Types and their correlation with race/ethnicity; (2) examine whether Black/White differences in survival are related to VDR, and if higher levels of VDR are associated with increased survival from prostate and colorectal cancers; and (3) examine if Black/White disparities exit in MPC development for these cancers and if lower levels of VDR are associated with these disparities.

Using a retrospective, population-based cohort design, male patients aged 50 years and older who were diagnosed from 1978 to 2003 with a non-metastatic first primary prostate, colon or rectal cancer were followed for 10 year survival and MPC

development. VDR levels were estimated based on the patient's county of residency at diagnosis. In addition to tumor factors, socio-demographic covariates such as county-level socio-economic deprivation and a proxy for smoking were included. The analysis utilized a multivariate Cox Proportional Hazards model, adjusted for various factors, and an evaluation of competing risks.

The results indicate that VDR may contribute to Black-White differences in survival from prostate and colon cancer, which is strongly modified by urbanicity. While a moderate protective association was observed with increasing VDR among patients residing in all-urban areas, a modest increase in risk was observed among patients in least-urban areas. To a lesser extent, VDR may also contribute to an increased risk of some MPCs. More generally, Blacks are at higher risk for MPCs and several factors including prior radiotherapy, smoking and socio-economic deprivation may increase the risk of their development.

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INTRODUCTION

Among U.S. males, the incidence from colorectal and prostate cancers continues to be higher for non-Hispanic Blacks (Blacks) than non-Hispanic Whites (Whites).[37,38] Advances in the early detection and treatment of these cancers have helped to reduce their mortality over the past 20 years, but disparities in survival between these groups remain.[7,30,43,49] While socio-economic factors are known to contribute,[7-9] it is probable that biologic and/or genetic differences play an important role in the faster disease progression observed among Blacks.[7,42,43,50] In addition to disparities in survival, Blacks also appear to be at higher risk for Multiple Primary Cancers (MPCs) for colorectal-prostate* or prostate-colorectal* tumors,[2] which is of particular note given their generally lower rate of survival from their first primary cancer. It is currently thought that a relatively small portion of these MPCs are attributable to the radiotherapy treatment received for the first cancer,[3,28,41] and that most are due to common risk factors or shared bio-mechanisms between cancers which have yet to be identified.[39,40] Identifying the relative contributions of environmental exposures and patient demographics to the increased risk of MPCs is of high priority, particularly those factors that may be valuable for chemoprevention, screening, and patient follow-up.[39,40]

Several recent papers have suggested that vitamin D deficiency, which is typically 2.5 to 3 times higher among non-Hispanic Blacks compared with non-Hispanic Whites, may contribute to cancer disparities.[11,13,22,23] It is increasingly well documented that vitamin D plays an active role in regulating aspects of cell growth and the cell cycle that are central to the prevention of cancer, and that it may also mediate the pathogenesis and progression of disease.[26,29,34] Solar exposure to the vitamin D action spectrum contained

in ultraviolet-B radiation ("environmental D") is the primary source of vitamin D in adults, which is absorbed through the skin and subsequently synthesized through a complex multi-organ pathway into its bioactive form.[26,27,33] Bioactive D, also called calcitriol, works by binding with vitamin D receptors found in many cells and it is through these receptors that calcitriol exhibits its antiproliferation, pro-differentation and apoptotic effects.[4,26,27,29]

For more than 20 years vitamin D has been studied as a protective factor separately for both colorectal and prostate cancers,[i.e.,17,45] though this hypothesis has yet to be extended to MPC development. To date numerous studies have found that higher levels of vitamin D, measured either as circulating concentrations in the serum or area UV-B levels indicative of environmental D, are generally protective for colorectal cancer incidence and mortality.[i.e.,16,20,21,35] In general the results are less consistent and generally weaker for prostate cancer,[16,19,24] but a moderate protective association on mortality has been observed among individuals with long-term environmental exposure.[15,18] Although the possible effect on disease progression and survival for these cancers are just beginning to be evaluated and many questions remain, vitamin D deficiency appears to substantially increase the risk of death for patients with colorectal cancer and may also increase the risk of progression to fatal disease among prostate cancer patients.[20,21,32,47]

Most studies have not yet examined the relationship between race, vitamin D and associated risks for these cancer; the few ecologic studies that included Black populations have reported inconsistent results, generally concluding that Blacks do not have the same relationship to environmental D as Whites.[13,22,23] While various factors such as diet and the amount of time spent outdoors contribute to observed racial/ethnic differences in

circulating concentrations of vitamin D, the most striking difference between White and Blacks are the relative differences in exposure time needed within the same geographic environment to UV-B light in order to achieve an equivalent dose of vitamin D via cutaneous synthesis.[6,11,25] Dermatological studies have typically classified individuals by Fitzpatrick[14] sun-reactive Skin Types, which range in values from the most sun-reactive (Type I) to least sun-reactive (Type VI) with Type II commonly used as the referent. Studies have found that Type VI individuals need at least 4 times more exposure than Type II individuals in the same environment.[12,48] The correlation between Fitzpatrick sun-reactive Skin Types and self-described race-ethnicity has been explored in two recent U.S. studies,[5,31] where 90-93% of non-Hispanic Whites fall into the Skin Types I-III, while 90-100% of non-Hispanic Blacks fall into Skin Types IV-VI. Hispanics Americans, who may be of any race but largely identify as White, are far more heterogeneous in sun-reactive Skin Type with a tendency to center around Types III or Type IV.[5,31,44]

This dissertation is an analysis on the effect of environmental D in conjunction with race/ethnicity on the survival from prostate and colorectal cancers as well as on the development of MPCs. The first manuscript is an extensive review of vitamin D as a common risk factor for prostate and colorectal cancers, with special attention given to the role of environment and its differential effects by sun-reactive Skin Type and its correlation with race/ethnicity in U.S. populations. Some of this information has been briefly presented in this introduction. This manuscript also includes a consideration of various factors to consider when designing an observational study that explores the relationship between environmental D exposure and cancer in the absence of serum measures. The other manuscripts report the findings from a two-part retrospective,

population-based cohort that attempts to address some of the issues raised in the review paper. In part one, White and Black males, aged 50 years and older, who were diagnosed from 1978 to 2003 with a histologically confirmed, non-metastatic first primary prostate or first primary colorectal tumor were examined to see patients residing in areas with higher county-level environmental D had increased survival from their first primary cancer. In part two, these same patients were examined to see how well their county level environmental D exposure predicted the development of multiple primary cancers, adjusted for other factors.

The patient data used in these analyses was drawn from the *Surveillance, Epidemiology and End Results* (SEER) database of the National Cancer Institute, which is an ideal source for analyzing both survival as well as the MPC development. The general design of this study was inspired by several, SEER-based population-based cohort studies that examined melanoma and estimated environmental exposure levels based on UV levels in the state or county of residence at diagnosis.[i.e.,10,46] The exposure data in this dissertation was from Environment Canada's recently released *Vitamin D action spectrum-weighted UV climatology for North America*, which offers monthly estimates of vitamin D effect radiation as well as the relative difference in minimum minutes of exposure by sun-reactive Skin Type.[12] The general design of MPC analysis is comparable to previous SEER-based studies looking at the effect of prior radiotherapy,[i.e.,1,3,28] with the additional of several county level exposures including environmental D, a proxy for smoking and a socio-economic deprivation index. Both the survival and the MPC analysis utilized a multivariate Cox proportional Hazard model to estimate the risk associated with exposure, adjusted for various tumor and socio-

demographic factors. In both of these analyses, competing risks were also evaluated. As such, the general design of this study has higher internal validity than a purely ecologic study. Manuscript #2 presents the findings from our survival analysis, while Manuscript #3 presents the portion dealing with MPC development.

*This phrase is meant to indicate primary prostate cancer followed by primary colorectal cancer as well as primary colorectal cancer followed by primary prostate cancer, and includes both synchronic (concurrent) as well as metachronic (subsequent) primary tumors.

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VITAMIN D AS A COMMON FACTOR FOR COLORECTAL AND PROSTATE CANCERS

By AMY E. ABRUZZI

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ABSTRACT OF MANUSCRIPT 1 OF 3

VITAMIN D AS A COMMON FACTOR FOR COLORECTAL AND PROSTATE CANCERS

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ABSTRACT

This is a review of vitamin D as a common risk factor for prostate and colorectal cancers, with special attention given to the role of environment, its differential effects by sun-reactive Skin Type, their correlation with race/ethnicity in U.S. and associated vitamin D deficiency levels. It is increasingly well documented that vitamin D plays an active role in regulating aspects of cell growth and the cell cycle that are central to the prevention of cancer, and that it may also mediate the pathogenesis and progression of disease. Solar exposure to the vitamin D action spectrum contained in ultraviolet-B radiation ("environmental D") is the primary source of vitamin D in adults, which is absorbed through the skin and subsequently synthesized through a complex multi-organ pathway into its bioactive form.

To date numerous studies have found that higher levels of vitamin D, measured either as circulating concentrations in the serum or area UV-B levels indicative of environmental D, are generally protective for colorectal cancer incidence and mortality. In general the results are less consistent and generally weaker for prostate cancer, but a moderate protective association on mortality has been observed among individuals with long-term environmental exposure. Current research suggests that vitamin D deficiency

appears to substantially increase the risk of death for patients with colorectal cancer and may also increase the risk of progression to fatal disease among prostate cancer patients. While various factors such as diet and the amount of time spent outdoors contribute to observed racial/ethnic differences in circulating concentrations of vitamin D, it is most striking that Blacks may need at least four times the exposure of Whites to UV-B in order to achieve the same standard dose of vitamin D via cutaneous synthesis in the same environment. Few studies have adequately examined the relationship between race, vitamin D and associated risks for prostate and colorectal cancers.

Ideally, the design of on observational study examining these relationships in the absence of serum measures should have as much individual level data on patients as possible, particularly age and race/ethnicity which are likely to play important roles with respect to exposure needs. Environmental D may be reasonably estimated using county but not state level residence, provided this data accounts for cloud coverage, pollution, and a host of other geo-physical factors. Finally, such a study should also include some way to evaluate or limit the study population to those with long-term or early life exposure, as this is likely to play a key role particularly for prostate cancer.

ABBREVIATIONS USED

adj – adjusted

CI – Confidence Interval

HR – Hazard Ratio

I.U. – International Units

J/m^2 – Joules per square meter

MED – minimal erythemal dose

NCI – National Cancer Institute

ng/mL- nanograms per milliliter

NHANES - National Health and Nutrition Examination Survey

nmol/L - nanomoles per liter

OR – Odds Ratio

RR – Relative risk

SDD – standard dermal dose

SEER – Surveillance, Epidemiology, and End Results

UV – ultraviolet radiation

UV-B – ultraviolet-B radiation

VDR – Vitamin D Receptor

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A. Introduction

The purpose of this review is to provide background information on vitamin D as a common factor in the development of and survival from colorectal and prostate cancers. Several recent reviews have weighed the evidence for the anti-cancer benefits of high circulating concentrations of vitamin D based on clinical trial data for these cancers. [i.e.,51,105] Other reviews have weighed the findings from observational studies which have been largely ecologic in nature and used solar radiation as the exposure characterization.[i.e.,63,66] Researchers have commonly remarked that it is difficult to understand why the findings are in agreement on some aspects of these cancers but not on others, and have particularly bemoaned the lack of higher quality observational studies which could be used to address current research questions. [i.e., 56,58,62] Our review tries to provide an overview of the key issues on these exposure characterizations that have bearing on the design of epidemiologic studies and the comparison of their results. We give special attention to the role that the solar radiation may play in the racial/ethnic disparities observed for these cancers, as well as how to best utilize this data in an observational study with greater internal validity than a purely ecologic design using cancer registry data. Some of the topics included in this paper are the effects of seasonal change on vitamin D status and the importance of sun-reactive Skin Types and their probable relationship to the observed deficiencies in U.S. race/ethnic groups. Both Medline (1950 - March 2013) and Web of Science (1984 – March 2013) were searched using a variety of key terms including: Prostate Cancer (MeSH: Prostatic Neoplasms), Colorectal Cancer (MeSH: Colorectal Neoplasms), Vitamin D, Vitamin D Spectrum, Solar Ultraviolet Radiation. Relevant citations were also checked that appeared in key

papers identified in our database search, which were also updated as using a cited author search in Web of Science. This method was particularly useful for the less widely discussed aspects of these topics.

B. Vitamin D Biology

1. The vitamin D hypothesis

There is considerable evidence that 1,25$(OH)_2$D or calcitriol, the bioactive from of vitamin D, plays a critical role in cellular processes that are central to the prevention and development of cancer.[40,79,83,104] Solar exposure to vitamin D-effective ultraviolet radiation is the primary source of human vitamin D, which is synthesized through the skin then metabolized in a complex pathway that transforms it into its bioactive form.[40,79,83,104] More accurately described as a steroid hormone, calcitriol operates by binding with Vitamin D Receptors (VDRs) found in wide range of cells. [3,40,83,94,104,107,166] Calcitriol's anti-cancer properties are generally attributed to its role in regulating cell growth and the cell cycle, specifically its anti-proliferation, pro-differentiation, and pro-apoptosis effects.[3,40,83,94,104,107] Additional roles in cell-signaling pathways, DNA repair including interactions with BRCA 1 and 2 tumor suppressor genes, and immune modulation are also being investigated.[14,25,40,83] Current research focuses on clarifying calcitriol's role in the molecular etiology of cancer, which is thought to depend in part on the site and stage of cancer. [25,40,100,104]

2. The sources and synthesis of vitamin D

Approximately 90% of an individual's vitamin D is acquired via cutaneous synthesis due to casual exposure to ultraviolet (UV) light, making it the prime determinant of an individual's vitamin D status.[2,76,79,83,99,104] The remaining portion is

obtained via intake, either by consuming naturally rich or fortified foods such as fish oil or milk, or through dietary supplements.[2,76,79,83,99,104] Table 1, adapted in part from Holick 2007, Holick 2011 and other sources, illustrates comparative sources of vitamin D in the U.S. population including that obtained from solar exposure. In general, the body is able to synthesize a far greater amount of vitamin D through cutaneous exposure than can reasonably be consumed in common foods and poses no risk of vitamin D intoxication.[79] Toxicity is a concern when consuming D_3 or D_2 from intake sources, however, and the upper safety limits for dietary supplements are still being determined.[80,84]

The cutaneous production of Vitamin D begins when the skin is irradiated with the portion of UV light containing the vitamin D action spectrum, thus initiating the photochemical conversion of 7-dehydrocholesterol to the vitamin D_3, also known as cholecalciferol.[25,79,83] The D_3 obtained from cutaneous synthesis then enters the bloodstream along with the D_2 or D_3 (hereafter referred to as vitamin D) obtained from intake sources, although the portion acquired via intake may only last half as long as the portion synthesized through the skin.[76,77,79] Vitamin D_3 is then metabolized into its bioactive form through a multistep process that first involves the liver, which produces 25(OH)D, and then the kidneys where it is converted to calcitriol.[25,79,83] Current research suggests that the synthesis of 25(OH)D to calcitriol also occurs in a number of extra-renal organs, which most likely play a critical role in its anti-cancer actions. [3,40,76,79,104]

3. Circulating 25(OH)D concentrations as a bio-indicator of exposure

Of the two serum measures, 25(OH)D is considered best for estimating vitamin D status as it is highly sensitive to changes in exposure and has a half-life of 2 to 3 weeks. [40,76,77,81] Circulating concentrations of calcitriol, on the other hand, are maintained in

homeostasis by the kidneys and may be within normal range even if an individual is vitamin D deficient.[56,76] Unfortunately, while 25(OH)D may be a reasonable marker of exposure, this concentration does not indicate how much calcitriol is stored in or used by body tissues.[56,77,26,127] For cancer research in particular, the optimal bio-indicator of vitamin D status is hypothesized to be the level of calcitriol produced and utilized by non-renal organs, which has yet to be measured. [40,51,56,64,77]

In addition, there are both analytic and methodological concerns with the estimation of circulating 25(OH)D concentrations that have serious implications for epidemiologic studies. Scientists are now aware that there has been considerable variability in the assay methods used to determine 25(OH)D levels, both between and within labs, that have resulted in falsely high or falsely low values. [5,15,16,81,169] In 2009, the National Institute of Standards and Technology made *Standard Reference Material 972 for vitamin D metabolites in human serum* available to labs in response to calls for the standardization of vitamin D measurement.[5,79,80,128,129,169] While this has increased the accuracy and comparability of subjects' 25(OH)D concentrations for current studies, scientists are still advised to be cautious when interpreting and comparing earlier data.[5,128,169] The cut-points defining gradations in vitamin D status have also varied and continue to be a matter of scientific debate.[i.e.,80,84,127] Typically, measured circulating concentrations of 25(OH)D are expressed in nanograms per milliliter (ng/mL) or nanomoles per liter (nmol/L), where 1 ng/mL = 2.496 nmol/L. In most of the studies relevant to this topic, vitamin D deficiency is defined by circulating concentrations of 25(OH)D that are ≤ 20 ng/mL (≤ 50 nmol/L) with insufficiency ranging from >20 - < 30

ng/mL (50 - < 75 nmol/L); preferred levels are estimated to be between 30-60 ng/mL (75 - 150 nmol/L), with intoxication occurring over 150 ng/mL (>375.5 nmol/L). [76-80]

Recently concerns with the statistical methods used to adjust for seasonal variation in 25(OH)D concentrations in case-control studies have been raised.[172] In many studies blood samples are collected on study subjects at different points in time, requiring the data be adjusted for seasonal variation in 25(OH)D concentrations prior to comparison.[172] A two-step method has typically been used but it is now clear that this can lead to misleading results if the variation arising from the first step is not taken into account, resulting in inflated type I or type II errors depending on the situation.[172] It has yet to be addressed if other epidemiological study designs using similar methods share these concerns.

4. Factors affecting the synthesis, bioavailability and metabolism of vitamin D

(a) Geographic location and season

A number of factors can influence the cutaneous synthesis and bioavailability of vitamin D in the body. First, the amount of vitamin D-effective UV radiation varies with geographic location, which depends in part upon latitude. Surface UV radiation, usually expressed in joules per square meter (J m^{-2}), increases as latitude decreases with the highest amount found at the equator. It also depends upon solar zenith angle, which changes over the course of a day and the year, as well as ozone, elevation, cloud coverage, surface albedo and aerosol pollution.[32,33,37,92,93,163] Given these factors, seasonal changes in levels of vitamin D-effective UV are dramatic at most locations over the course of the year. (See Figure 1, as well as Figures 2 (a) and (b)).

In the northern hemisphere the highest levels of vitamin D-effective UV are available in June, July and August, which typically result in higher circulating 25(OH)D concentrations in northern latitude populations a month or so later. [60,92,93,163,164] Several studies have documented that "vitamin D winter" occurs in higher latitudes (e.g., greater than 42˚ N or 45˚ N) between November to February, when seasonal changes in solar zenith angle and increasing cloud coverage make it difficult or perhaps impossible [163] to absorb adequate UV light for cutaneous synthesis. [32,76,108] Additional research suggests that vitamin D winter may extend much further south and depends in part upon individual factors. [37,76,79]

Figure 3 illustrates seasonal changes in UV levels and the lag in their corresponding effect on circulating concentrations of 25(OH)D using data from Norway, a northern European country located between 58˚-71˚N, that has been heavily studied on this topic. The 2-to-3 month lag commonly observed in populations is due in part to the time needed to synthesize vitamin D through the skin and also reflects its duration circulating in the serum. [136,142] This data also illustrates a decline in circulating 25(OH)D concentrations during winter that results in borderline vitamin D deficiency ≤ 20 ng/mL (≤ 50 nmol/L) in a heavy fish-eating population with an optimal summer time vitamin D status. [142]

Comparable seasonal fluctuations in the circulating 25(OH)D concentrations have also been observed in the U.S., where winter values are typically 25-30% lower than summer values. [i.e., 10; see also summary in 60] Figure 4 illustrates data from a current U.S. cohort study and compares seasonal changes in circulating 25(OH)D concentrations between subjects by sex and dietary supplementation use.[10] As in Norway, all subjects show a

seasonal decline in circulating 25(OH)D concentrations that results in insufficiency or deficiency during winter and spring months. Unlike Norway, circulating 25(OH)D concentrations in this U.S. population are rarely optimal during summer, with most below 30 ng/mL (75 nmol/L). Less variability is displayed by females taking a vitamin D supplement than by any other group. The same effect has been noted in other U.S. studies [i.e., 18] and is likely due to the higher amounts of calcium with vitamin D consumed by aging females compared to the amount of vitamin D present in multivitamins consumed by males. [34,52,87,114] It should also be noted for reasons that will be discussed shortly that this cohort is 94% White, with an average age of 63 ± 5 years, and reside in areas across the United States.[10]

(b) Age and sun-reactive Skin Type

Several factors work in conjunction with season to modify the synthesis of vitamin D through the skin, chiefly age and sun-reactive Skin Type. Aging leads to changes in the skin that reduce the ability to synthesize D from solar radiation exposure by approximately 75% by the age of 70, greatly contributing to the high levels of vitamin D deficiency often found in the elderly.[74,79,116,154] The amount and type of the photo-absorbent skin pigment called melanin, which results in differences in sun reactivity as well as skin coloring, also substantially changes the amount of exposure time needed to absorb enough UV light sufficient to synthesize vitamin D.[28,37,39,76,163] The range of human skin sun reactivity was arranged into six categories or Types by Fitzpatrick based on their initial reaction to sunlight.[39] Subsequent studies indicate that individuals with sun-reactive Skin Type II require 20% more exposure to vitamin D-effective UV radiation than Skin Type 1 individuals in order to achieve 1 standard vitamin D dose (1

SDD), approximately equivalent to an oral dose 1000 I.U. vitamin D.[37,108,163] Individuals with Skin Type VI, the least sun-reactive type, require approximately 400% more exposure than Type II individuals.[37,108,163] The actual amount of exposure time needed by all sun-reactive Skin Types also varies as a function of latitude, month, and time of day.

Table 2 compares these values for Fitzpatrick's six sun-reactive Skin Types at two different latitudes at 12:00 noon during the solstice months of June and December. The exposure times provided in this table are estimates based on laboratory experiments exposing the hands, face and arms, which assumes that ¼ Minimal Erythemal Dose (¼ MED) to achieve 1 SDD.[37,163] The actual times needed to obtain 1 SDD in natural sunlight may be up to 30% less, though the relative differences between skin types remains the same and other factors (e.g., age, BMI, body position) may necessitate significantly longer exposure times.[28] Finally, the values in this table were calculated using clear-sky ideal conditions; cloudy skies or heavily polluted areas would increase the minimum exposure time needed by as much as 50%, while necessary exposure times would be decreased at higher altitudes (e.g., 7%) or with greater surface albedo (e.g., 31%).[28] U.S. cities with latitudes comparable to those presented in the table include Houston (29°45'N), Tampa, (27°58′N), Boston (42°21′N), Chicago (41°50′N), and Buffalo (42°54′N).

As illustrated in Table 2, a person with Skin Type I (most sun-reactive) only needs approximately 8 minutes to gain 1 SDD at 12:00 noon at 42.5˚ N on March 21st, while a person with Skin Type VI (least sun-reactive) in the same conditions requires at least 41 minutes.[37,163] At the same latitude, the number of minutes required to

obtain 1 SDD on December 21st is approximately 6 to 10 times longer those needed in March.[37,163] Moreover, if the sun exposure occurrs earlier or later in the day (data not shown), the amount of time required increases 2 or 3 fold.[37,163] The practical implications of this during winter months would be prohibitive for many people, especially since one is advised to obtain 1 SDD every other day outdoors in order to maintain adequate circulating 25(OH)D concentrations.[26,75,76,78,163,164] The correlation between Fitzpatrick sun-reactive Skin Types and self-described race-ethnicity has been explored in two recent U.S. studies,[18,91] which found 90-93% of non-Hispanic Whites fall into the Skin Types I-III, while 90-100% of non-Hispanic Blacks fall into Skin Types IV-VI. Hispanics Americans, who may be of any race but largely identify as White, are far more heterogeneous in sun-reactive Skin Type but tend to center around Types III or Type IV.[18,91,143]

Figure 5 from Fioletov *et al.* 2010b illustrates the approximate northern boundaries where the six sun-reactive Skin Types described in Table 3 can obtain 1 SDD using ¼ MED within one hour during January around noon. In many areas of the country requiring 1 hour per day with even hands, arms and face exposed is unlikely during winter months. One of the implications of the gradient presented by Fioletov *et al.* (2010b) is that U.S. studies that have characterized "vitamin D winter" using latitudinal cut-points of 40˚ N or 42˚ N are capturing this effect for sun-reactive Skin Types I to III (i.e., most non-Hispanic Caucasians); individuals with Skin Types IV, V, and VI (i.e., most non-Hispanic African Americans) would likely experience vitamin D winter and its accompanying seasonal decline in circulating concentrations of 25(OH)D starting at much lower latitudes. Vitamin D winter, then, may be best thought of as an

individual phenomenon based on the joint effects of sun-reactive Skin Type and geographic location, rather than as one common latitudinal marker for all populations. The implications of this observation when evaluating and designing U.S. studies will be discussed in more detail shortly.

(c) Additional factors including sun protection, supplement use and adiposity

Sun avoidance behaviors, such as the use of sun hats or sun screens can prevent the synthesis of vitamin D through the skin. Sunscreens in particular have the potential to completely block cutaneous synthesis (i.e., SPF 8= blocks 92.5%; SPF 15 = blocks 99%),[76] though studies indicate that most individuals do not apply sunscreen to all exposed areas or reapply it as recommended in order to block this route completely.[76,102,127,167] Conversely, individuals may increase their circulating 25(OH)D levels by eating more foods containing D_2 or D_3 or by taking dietary supplements, though the amount required of either to achieve optimal serum levels appears to be substantially more than is routinely consumed.[75,76,77,79,114] Studies on adults have shown that taking a vitamin with 400 I.U. per day of vitamin D has little effect on circulating 25(OH)D concentrations and is not likely to raise concentrations to the desired 30 ng/mL.[23,69,137] A minimum dose of 1,500 to 2,000 I.U. per day are likely to be required to achieve a desirable vitamin D status in an otherwise healthy adult.[69,80] There are also questions as to whether supplements containing D_2, which is manufactured by the UV irradiation of ergosterol in yeast, works as effectively as D_3. The latter, which is manufactured by the UV irradiation of 7-dehydrocholestrol in lanolin, comes closest to that synthesized through the skin.[79,127] As mentioned earlier in this paper, it is also unclear if D_3 obtained from dietary supplements lasts as long in the bloodstream as D_3 obtained from cutaneous

synthesis.[76,79] Sex differences in vitamin D levels have sometimes been observed in various populations, though it is unclear if these reflect biological factors or social behaviors that effect cutaneous synthesis, such as use of sun hats, sun screens or dietary supplements.[8,10,56,58,59] The use and effect of sunscreens and dietary supplements in U.S. populations will be discussed in more detail in the following section.

Finally, several factors may reduce the bioavailability of D_3 or its conversion into 25(OH)D in the liver. Shortly after its conversion in the skin D_3 may sequester in body fat, thus reducing its bioavailability for metabolic conversion in the liver and kidneys or in extra-renal organs.[76,79,168] There is an inverse relationship between circulating 25(OH)D concentrations and body mass index (BMI), with vitamin D status decreasing as adiposity increases. Studies have found that obese individuals (BMI $\geq$30 kg/m^2) have circulating 25(OH)D concentrations that were at least 50% lower than their normally weighted counterparts.[76,79,168] In addition, the use of certain medications such as anticonvulsants, glucocorticoids, Highly Active Antiretroviral Therapy for AIDS treatment and a number of medical conditions including liver failure, chronic kidney disease, and hyperthyroidism can decrease the metabolism of vitamin D into 25(OH)D or calcitrol.[76,79]

C. The vitamin D status of the U.S. population

1. Current estimates from NHANES

National estimates for the vitamin D status of the U.S. population have typically come from the National Health and Nutrition Examination Survey (NHANES), which began collecting circulating 25(OH)D serum samples and documenting vitamin D supplement use beginning with NHANES III in 1988.[103,169] Based on the recently

released NHANES 2005-2006 data, the overall prevalence of vitamin D deficiency (≤ 20ng/mL) in U.S. adults is estimated to be 41.6% (95%CI 36.6%-46.8%), with the highest prevalence observed among non-Hispanic African Americans (82.1%, 95% CI: 76.5%-86.5%) and Hispanic Americans (62.9%, 95% CI: 53.2%-71.7%) and lowest among Non-Hispanic Whites (30.9%, 95%CI: 26.2-36.2).[41] The relative differences in deficiencies between racial and Hispanic ethnicity groups (1:2 ratio for non-Hispanic Whites to Hispanics, and 1:2.7 for non-Hispanic Whites to non-Hispanic African Americans) is consistent with our understanding of the relative difficulties individuals with different sun-reactive Skin Types may have in the U.S. in obtaining adequate vitamin D through solar exposure (Table 3). It also suggests the need to consider race and Hispanic ethnicity as modifying factors when considering the effects of exposure.

Although NHANES is the best national source for vitamin D status, many scientists think the data underestimates the prevalence of vitamin D deficiency in the U.S., since it does not include institutionalized populations who are approximately 70-100% deficient[75,76,79,103] nor draw serum samples from populations in northern states during winter months when circulating 25(OH)D concentrations are at their lowest. [i.e., 10, 60] Furthermore, since NHANES only collects samples once annually, drawing serum at the same time in southern areas during cooler months (November to March) and in northern areas during warmer months (April to October), it is not possible to examine an individual's seasonal variation in circulating 25(OH)D concentrations or estimate their annual average.[44,52,169] Some releases of NHANES data also suppress the month of draw in order to protect patient confidentiality,[52] further obscuring the seasonal relationship of this data and greatly limiting its utility for research in this area of study.

2. Changes in the U.S. population over time

The problems discussed earlier with lab assay methods used to measure circulating 25(OH)D concentrations have also affected the NHANES data, making changes in the vitamin D status of the U.S. population over time somewhat difficult to assess.[52,103,169] Even so, the same rank order and relative differences in vitamin D status between racial and Hispanic ethnicity groups, as well as between age groups, was observed from 1988/1994 to 2004/2006.[103,169] Non-Hispanic African Americans consistently have lower mean serum 25(OH)D concentrations than Hispanics, whose concentrations are in turn lower than non-Hispanic Whites.[41,52,103,169] Older children have lower mean serum 25(OH)D concentrations than younger children, and concentrations in adults continue to decline with increasing age.[52,103,169] The differences between age groups also preserve the same relative differences between racial/ethnic groups previously described, with non-Hispanic African Americans having the lowest circulating 25(OH)D concentrations at any age. [52,103,169]

Additional analyses of the NHANES data suggest that after trying to adjust for changes in lab assay methods, a true decline in population serum levels may have occurred between 1988/1994 to 2004/2006.[103] Males in particular may have experienced a slight decline in circulating 25(OH)D levels, which is attributed to increasing levels of obesity, declining milk consumption and the increasing use of sun protection, particularly among non-Hispanic Whites.[103] Multi-vitamin use (typically containing 400 I.U. of vitamin D during this period of time) also increased between 1988/1994 to 2006/2006 among both sexes, but as noted earlier had no effect on mean circulating 25(OH)D concentrations.[103,169] Overall, NHANES data indicate that women use sun protection

more often than men and also have a slightly higher vitamin D supplement use. [103,169] Inadequate intake levels of vitamin D were found for most males and females over 51 years regardless of race and ethnicity,[103,113,114,169] indicating that individuals of this age or older continue to depend largely upon solar radiation exposure to obtain vitamin D.[79,80] Typically, males have higher circulating 25(OH)D levels than females in NHANES data, though this is not always consistent depending on the subpopulation or time period examined.[41,52,103,169]

3. Current dietary recommendations for the U.S. population

Recommendations to address vitamin D deficiencies in the U.S. population are currently being discussed and the recommended dietary allowances (RDA) needed for optimal health remains a matter of intense scientific debate. In 2010, the Institute of Medicine recommended an RDA for healthy adults that ranges from 600 to 800 I.U.[84] These values are considerably lower than those recently proposed in the Endocrine Society Clinical Practice Guidelines, which recommend 1,500-2000 I.U. in healthy adults to maintain circulating 25(OH)D concentrations of at least 30 ng/mL.[80] These guidelines also estimate that obese adults and individuals on medications or those individuals with conditions that reduce the bioavailability of vitamin D may need approximately 2 to 3 times this amount to achieve a healthy vitamin D status.[80] At present there are no current or specific recommendations for the RDA of vitamin D for chronic disease prevention.[80,84]

D. The epidemiology of colorectal and prostate cancers among males in the U.S.

1. Historical trends and international comparisons

In the U.S., prostate cancer is the leading incident cancer for men of all races and Hispanic origin and second in mortality for most, while colorectal cancer typically ranks second in incidence and third mortality.[17] Once uncommon, the incidence of colorectal cancer rose dramatically during 20th century in the U.S. and in other Western countries that underwent similar social and economic changes.[54] Similarly, the incidence of prostate cancer also rose in Western countries during the 20th century, with the sharpest apparent increase following the introduction of Prostate Specific Antigen (PSA) testing in 1986.[117,134] There are still very large geographic differences in the age-adjusted incidence of colorectal and prostate cancers between countries, with lower rates found in populations near the equator and higher rates in populations of increasing latitude.[63,86] This latitudinal gradient was instrumental in generating the vitamin D hypothesis for both cancers.[i.e.,46,71,146] At present, the highest incidence rates for both colorectal and prostate cancers are in Australia, New Zealand, Europe, and North America, whereas the lowest rates are found in South-Central Asia and parts of Africa.[86] There is a 7-fold difference in the age-adjusted incidence rate of colorectal cancer between the highest and lowest ranked countries (45.7 Australia/New Zealand vs. 4.3 Middle Africa per 100,000), while there is more than a 25-fold difference for prostate cancer (104.2 Australia/New Zealand vs. 4.1 South Central Asia per 100,000).[86] The use of PSA screening in Western countries is responsible in part for the current magnitude of difference observed between Western and non-Western countries, although the rank order by country was comparable in the pre-PSA era.[117,134]

2. Current demographic and geographic patterns in the U.S.

As illustrated by Table 3, considerable differences by race and Hispanic ethnicity exist for colorectal and prostate cancers within the U.S., with non-Hispanic African Americans having the highest incidence and mortality in both.[123,124] Based on 2004-2008 data for the 17 SEER geographic areas, the age adjusted incidence rates for colorectal and prostate cancers in Black males were 24.5% and 47.3% higher respectively than the same rates in White males.[124] The differences reported in Black-White mortality are equally substantial and partially reflect a later stage of diagnosis for African Americans. The 5-year relative survival is also lower for Black males than it is for White males for either cancer. At present these rates are 55.0% for colorectal and 96.2 % for prostate among Black males, compared with 65.5% and 99.7% respectively for White males.[70,123,124,162] American Indians and Alaskan natives have some of the lowest incidence and mortality rates for either cancer in the U.S.[70,123,124,162] Hispanic Americans also have a much lower incidence and mortality than White Americans, which is interesting to contemplate given their higher rate of vitamin D deficiency in the NHANES data.

Within the U.S., there is considerable geographic variation in both the incidence and mortality of colorectal cancer and prostate cancer, depending on the location as well as the racial and ethnic composition of the population.[54,138] There are some interesting similarities, as well as some notable differences, between the geographies of these two cancers, which are illustrated by the maps in Figures 6 and 7. Figure 6a illustrates the current incidence rates for colorectal cancer among all males, with the highest rates in the eastern portion of the U.S. Although the rates are suppressed or unstable in some areas, higher rates may be observed in some northern counties as well as in some southern

counties. The mortality maps, which are stratified by Black and White race, show a more interesting pattern. White males (Figure 6b) residing in northern counties have a much higher mortality (i.e., dark red in this map) than White males residing in southern counties (i.e., light pink), with the highest rates in the northeast. Similarly, mortality rates for African Americans (Figure 6c) from colorectal cancer are also higher in northern counties compared to those in the south. Note that considerably fewer African Americans reside in northern counties than live in the south, hence the sparseness of data in many areas. The maps in Figure 8 depict the current population distribution of non-Hispanic Whites, non-Hispanic Blacks and Hispanics in U.S. counties and may be useful for comparison.

The geographic patterns displayed by prostate cancer are similar, though not identical, to those observed for colorectal cancer. In terms of incidence (Figure 7a), higher rates may be observed across all northern counties, as well as in some south-eastern states. When considering mortality, Whites (Figure 7b) residing in northern counties have higher mortality rates from prostate cancer than those residing in southern counties. Unlike colorectal cancer, the concentration appears to be greater in the northwest than in the northeast, and counties with high mortality rates also include states with high UV levels, such as Utah and New Mexico. The geographic pattern for Black mortality from prostate cancer (Figure 7c) is harder to discern visually, suggesting what appears to be higher rates throughout much of the southeast. These within-country differences between geographic areas and racial/ethnic groups for the two cancers indicate that there are likely to be important differences, perhaps highly dependent on

other risk factors, in any role that vitamin D may play in the etiology and progression of colorectal and prostate cancers.[56,58,62,63]

3. Colorectal cancer biology

Most colorectal cancers arise from epithelial cells and are preceded by polyps, the most common of which are adenomas or adenomatous polyps that result in adenocarcinomas after a lag of at least 10 years.[54,138] More colorectal tumors arise in the colon (70%) than in the rectum (20%) or rectosigmoid junction (10%).[54,138] The incidence rate also differs by subsite within the colon, with cancer developing most often in the sigmoid colon (~25%), cecum (~20%), transverse colon (~15%) and ascending colon (~10%).[54,138] Colorectal tumors become symptomatic when they obstruct the bowel and produce a change in bowel habits, or when they bleed and either leave blood in the stool or cause anemia.[54,138] Contemporary diagnostic tools include barium enema, sigmoidoscopy, colonoscopy, virtual colonoscopy (also known as CT or MRI colonography), with biopsy.[54,126,138,160] Currently, a fecal occult stool sample, sigmoidoscopy and colonscopy are used as routine screening tools; virtual colonoscopy is less widely available at present than conventional colonoscopy but has greater patient acceptability because it is non-invasive, has a shorter test time and does not require sedation.[54,68,72,126,138] Treatment typically involves the surgical removal of the primary lesion and may be accompanied by chemotherapy depending on the stage of cancer.[54,138]

Table 4 illustrates that colorectal cancers that are diagnosed and treated when still localized have a much better 5-year relative survival (90%) compared to the general population than those diagnosed at the regional (70%) or distant (12%) stages. Pre-operative and post-operative radiotherapy are often used in conjunction with the surgical

removal of rectal cancer, lowering the risk of local recurrence and improving long-term survival.[54,138]

4. Prostate cancer biology

The Prostate, which is a walnut-sized gland located below the bladder and in front of the rectum, consists of the central, transitional and peripheral zones, with more tumors typically occurring in the latter.[117,134] Most prostate cancers (99%) arise from epithelial cells and result in adenocarcinomas, which unlike many other solid tumors tend to be multifocal.[134] Although the average age of diagnosis in the U.S. is currently 67 years of age,[124] autopsies have revealed that many middle-aged men have a high prevalence of malignant precursor prostatic intraepithelial neoplasia and small invasive cancers, indicating that progression to disease starts much earlier in life.[117,134] Many prostate tumors are slow growing "indolent" cancers, while others are more aggressive in nature and, therefore, of clinical concern.[117,134] In the U.S., PSA testing was introduced starting in 1986 to monitor disease progression in males and increased the apparent incidence of the disease shortly thereafter.[117,134]

As with colorectal cancer, the current staging for prostate cancer is classified using the TNM system, which is based on the extent of the tumor (T)**,** the extent of spread to the lymph nodes (N)**,** and the presence of distant metastasis (M)**.** [See 120] Histological grading for prostate cancer, however, uses the Gleason scoring system. This system identifies both the dominant primary and secondary patterns of glandular distortion, which are each scored from 1 (least disarrayed) to 5 (most disarrayed) then summed to form a total score that ranges from 2 to 10.[134] The treatment for prostate cancer is controversial and varies based on the stage and grade of cancer, the age and

overall health of the patient, and personal preference.[117,134] Currently, patients with localized disease and Gleason scores under 7 may be treated with a wide range of options that include radical prostatectomy, curative external beam radiation therapy, brachytherapy or active surveillance.[117,134] Patients with Gleason scores of 7 or higher are considered to have histologically poor disease and generally receive one of the more aggressive treatment options listed above (e.g., radical prostatectomy or radiotherapy).[134] Treatment for advance disease can include local radiotherapy and endocrine manipulation.[117,134] The prognosis for prostate cancer has varied greatly among time periods and between countries. At present in the U.S., most tumors that are diagnosed in the localized (81 %) or regional stages (12%) each have a 5-year relative survival of 100%.[124]

5. Common risk factors and their relationship to vitamin D

Colorectal and prostate cancers have both been heavily studied for risk factors. The risk factors which are common to both cancers that also have an established or suspected relationship to vitamin D are summarized in Table 5 and are discussed in detail in the next paragraph. Many additional risk factors including rare genetic syndromes have also been heavily studied for both cancers, but a detailed discussion of these is largely beyond the scope of this paper. Colorectal cases diagnosed before the age of 40 are usually rare and are strongly associated with genetic syndromes such as Familial adenomatous polyposis and Hereditary nonpolyposis colorectal cancer, also referred to as Lynch syndrome.[54,138] There is also evidence for differences in the genetic etiology of colorectal cancer by subsite, in particular for cancers occurring in the proximal versus distal regions.[54] Similarly, genetic components have also been studied extensively for

prostate cancer, which appears to have a strong inherited susceptibility particularly for early onset disease.[117]

As presented in Table 5, the most common risk factors that also have a relationship to vitamin D are age, race, geographic location, BMI, a Western diet and lifestyle, and smoking. As discussed earlier, both colorectal and prostate cancers are age-related, typically slow growing and diagnosed later in life.[54,117,134,138] They also occur with higher frequency in northern areas of the country and have a much higher incidence among African Americans.[54,117,134,138] The decline in the synthesis of D_3 with increasing age, lower levels of vitamin D-effective UV in northern areas during the winter, and longer amounts of time required for less sun-reactive Skin Types to absorb enough radiation to synthesize 1 SDD have been previously discussed in this paper. Numerous factors associated with a Western diet and Western lifestyle have also been heavily studied for both cancers, together encompassing a spectrum of exposures that include decreased outdoor physical activity or work, a more sedentary urban lifestyle, increased levels of obesity, and higher consumption of animal fat and dairy products.[54,117,134,138] Many of these factors are also strongly associated with a decline in vitamin D status, particularly increased BMI, increased time spent indoors, increased amounts of environmental pollution, high calcium intake and low intake of fish.[76,79] The relative importance of these factors, however, varies between cancers and most likely between different pathways leading to disease.[54] For example, low levels of physical activity and increased BMI are strongly associated with increased risk for colorectal cancer, but the association is less clear or weaker for prostate cancer.[106,117,138,140,148] The relationship with calcium is particularly complex and appears somewhat contradictory between

cancers. Lower intakes or lower circulating concentrations of calcium are associated with an increased risk for disease that varies by stage or subsite of colorectal cancer,[54,117] while higher intakes or circulating concentrations are associated with an increased risk for prostate cancer, particularly for advanced or fatal disease.[54,117,134,152] Since intestinal calcium absorption is regulated by vitamin D, these findings suggest an interaction between the two in determining risk that may differ for each cancer or require an intermediate range that would best serve both. [20,117,138,152]

Currently, there is much research being conducted at the cellular level to better understand the relationship between colorectal cancer, prostate cancer, and vitamin D. As briefly discussed earlier, vitamin D receptors mediate the biologic actions of vitamin D metabolites on cells with pro-apoptosis, pro-differentiation, anti-proliferation effects.[3,40,83,94,104,107] Both colorectal and prostate cancers typically arise in epithelial cells possessing VDRs, and certain polymorphisms in these VDRs are hypothesized to interact with the environment and increase the risk for each cancer.[12,54,107,117,152] Furthermore, prostate cell division is strongly influenced by certain steroid hormones,[117] and hormone response targets in colorectal cells are also thought to play a role in carcinogenesis.[54] Consequently, complexities in the hormonal relationship to vitamin D are now areas of intense investigation for both cancers.[i.e.,4,151] The role that vitamin D plays in mediating the chronic inflammation that contributes to the pathogenesis and progression for either disease is also of particular interest.[12,24,96] Finally, higher levels of IGF-I (Insulin like growth factor), which has anti-apoptotic properties, is associated with an increased risk for both prostate and colorectal cancers.[4,54,117] Current research

indicates that healthy levels of IGF-I are associated with high vitamin D concentrations in healthy subjects, suggesting yet another aspect of this complex relationship.[7,42]

E. Summary of evidence and pending research questions on the vitamin D hypothesis

1. Colorectal and prostate cancer incidence and mortality

To date, the strongest and most consistent support for the vitamin D hypothesis is for colorectal cancers, where studies using a range of designs and measures of exposure (e.g., solar UV levels, circulating 25(OH)D concentrations, and dietary supplement intake) largely support a protective association for both incidence and mortality.[45,56,57,58,141] Solar UV studies have typically found a 10-20% reduction in incidence and 20-30% reduction in mortality from colon cancer when comparing populations residing in highest exposure area to residents in the lowest exposure areas.[8,43,63] Several studies have examined rectal cancer separately from colon cancer and found a comparable or stronger association.[8,61] Most geographic studies have been conducted in Nordic areas or other European populations, which tend to be more ethnically homogenous than the U.S. [See summary in 63] Black populations have been included in only a handful of U.S. solar radiation studies on colorectal cancer, where they have typically shown a much weaker relationship to north-south gradients in exposure than Whites. [8,19] This is no surprise once one recognizes that the original purpose of the exposure data used in these studies was to estimate the potential damage (i.e., sunburn, DNA) from UV radiation for Caucasian populations.[i.e.,8,59] The protective effect of vitamin D for colorectal incidence is supported for the population more generally by two recent meta-analyses of prospective studies. In Ma *et al.* 2011, both circulating 25(OH) D concentrations (RR 0.67, 95% CI: 0.54 to 0.80) as well as Vitamin D intake (RR 0.88,

95% CI: 0.80 to 0.96) were inversely associated with the risk of colorectal cancer when comparing high versus lowest exposure categories.[105] Overall, a 10 ng/mL increment in circulating 25(OH) D concentration was estimated to confer a 25% reduction in risk (RR 0.74, 95% CI: 0.63 to 0.89),[105] which is fairly comparable to that reported in a slightly earlier meta-analysis conducted by Gandini *et al.* 2011 (RR 0.85, 95%CI: 0.79-0.91).[45]

Although supported in animal studies, the evidence for a protective effect between vitamin D and prostate cancer incidence is less consistent and generally weaker than that observed for colorectal cancer with the exception of a moderate protective association for progression to or mortality from advanced stage disease.[50,51,67,151,154] Solar radiation studies have often found a considerably weaker and more variable protective association for both prostate cancer incidence and mortality than for colorectal cancer when only current UV exposure is considered.[22,66,59,71,146] Solar radiation studies that reported a 20-40% reduction in incidence[90] or a 10 % reduction in mortality[43] estimated current residential exposure in conjunction with UV levels in state of birth or state of longest residency. Prospective cohort studies measuring circulating 25(OH)D concentrations have often failed to find a protective effect on prostate cancer incidence, or when doing so find weaker or inconsistent associations. Two recent meta-analyses of prospective cohorts both failed to find any association with a 10 nm/mL increase in circulating 25(OH)D concentrations and prostate cancer incidence (RR 0.99, 95%CI: 0.95,1.03;[45] OR 1.04, 95%CI: 0.99, 1.10[51]). One noteworthy exception to this is the study by Ahonen *et al.* 2000 conducted in Finland, which found that younger men (less than 52 years of age) with circulating 25(OH)D concentrations less than 40 nmol/L had a 60% or higher increase in risk for the development of aggressive prostate cancer compared with other

males, after adjustment for smoking status, BMI, cholesterol and blood pressure.[1] A much discussed U-shaped association between circulating 25(OH)D concentrations and prostate cancer incidence in a large Nordic nested case control study was reported by Tuohimaa *et al.* 2004, which found that males with low (<19 nmol/L; as well as high (>80 nmol/L) circulating 25(OH)D concentrations were associated with higher prostate cancer risk (e.g., OR 2.4, 95% CI: 1.1 - 5.1; OR 1.7, 95% CI: 1.1 - 2.4, respectively).[155] Prospective studies conducted on vitamin D intake and prostate cancer risk have been largely negative; for further information see the review and extensive summary tables presented in Gupta *et al*. 2009.

Researchers have proposed an explanation for the differences observed between solar and serum prostate cancer studies which may also explain why they differ from those observed for colorectal cancer. It is possible that long-term vitamin D status is more important for preventing prostate cancer than for colorectal cancer, and solar radiation studies have been better able to capture this than prospective serum studies, which are based on relatively recent circulating 25(OH)D concentrations.[51,53,56,58,62,67] Biological differences between colorectal and prostate cancer seem to support this. Colorectal cells, both normal and neoplastic, are able to locally synthesize and/or utilize calcitriol after the advent of cancer, while neoplastic prostate cells apparently cannot.[53,56,62] Since the progression to disease appears to start earlier in life for prostate cancer than it does for colorectal,[54,117] early life and/or long-term exposure to vitamin D may be most critical for the prevention of prostate cancer. [53,56,58,62,67]

2. Season of diagnosis and survival

Questions have been raised by researchers about the role vitamin D may play with respect to the timing and stage of cancer for both colorectal as well as prostate cancer survival.[56,57,58,62,144] A handful of studies conducted in Norway have shown that the prognosis of colorectal [i.e.,110,111,142] and prostate [i.e.,97,142] cancer are best when diagnosis and therapy begin in the late summer and fall months, presumably when a patient's vitamin D status is at its highest. Since the timing and bioavailability of vitamin D are known to be important factors for controlling cell proliferation and maintaining apoptosis, researchers assert the seasonal relationship is biologically plausible.[40,83,109] The observed protective association of a summer or autumn diagnosis also appears to be slightly stronger for younger patients, which is consistent with the decline in the cutaneous synthesis of D_3 that occurs with age.[97,110-112]

In one of the largest studies conducted using data from the Norway Cancer Registry, case fatalities for fall diagnoses were consistently 20-40% lower compared with cases diagnosed in winter months with no change in the reported effect after adjustment for age at diagnosis, birth cohort, period of diagnosis, stage of disease at diagnosis, and various other factors.[142] Table 6, adapted from Robsahm *et al.* 2004, illustrates this data. Not that the observed protect effect was slightly higher for deaths occurring during the first three years after diagnosis compared with deaths occurring during all follow-up years. None of the studies conducted in Norway reported a difference in the number of cases diagnosed per season or in a protective association between geographic regions in Norway.[110,142] Since Norway is located above 58˚ N latitude and is fairly homogenous in racial and ethnic composition, it is probable that all residents undergo a seasonal drop in

vitamin D levels at roughly the same time during winter months which is strongly reflected in this seasonal pattern.

A subsequent study conducted by Lim *et al.* 2006 in the United Kingdom (U.K.)[101] found a much weaker protective association for either cancer in males, with the greatest benefit in survival observed in individuals residing in areas that had 3 months of sunshine prior to a summer diagnoses. Using winter as a referent, the relative risks were 0.92 (95% CI 0.85, 0.98) for Prostate cancer fatality and 0.93 (95% CI 0.85, 0.98) for Colorectal cancer fatality, adjusted for age and period of diagnosis.[101] There were a number of substantial differences between the Norway and U.K. studies (e.g., geographic, adjustments for various confounders) that make a more detailed comparison somewhat difficult.

To date, the key studies examining the effect of season of diagnosis on colorectal and prostate cancer survival have all been conducted in small northern counties (e.g., United Kingdom and Norway, both above 50˚ N latitude) on populations that all experience vitamin D winter.[97,101,110,111,135] It is unclear if this same protective association will be found at lower latitudes or if other factors such as race modify it.[56,57,104] Of related interest, several studies have found that vitamin D enhances the effectiveness of radiation treatment for prostate cancer,[29,49] raising the question if radiotherapy treatment may work in conjunction with the seasonal effect described above since it is typically undertaken shortly after diagnosis.[3,110,142,154] Further work is needed in geographic areas with a greater range of solar radiation exposure to better understand the possible association between season of diagnosis, background vitamin D-effective

UV radiation levels, concurrent radiotherapy treatment, stage or grade of cancer, race and ethnicity on disease progression and survival.[3,51,56,58,63,65]

3. Criticisms of U.S. solar radiation studies

One of the most frequent criticisms of solar radiation studies is their heavy reliance on purely ecologic designs that are prone to confounding[161] and their failure to use an estimate of exposure that estimates vitamin D-effective UV radiation considering the many factors that modify it [i.e.,92,93] The U.S. has been the site of the earliest and most numerous solar radiation studies examining the vitamin D hypothesis for both colorectal or prostate cancers, which are summarized in Tables 8 and 9. Only two of these studies have used an analytic observational design: the study by Freedman *et al.* 2002 examined the association between solar radiation and colorectal and prostate cancer mortality using a case control design,[43] while the study by John *et al.* 2004 [88] (including its subsequent follow-up in 2007) [90] used a cohort design to examine solar radiation and prostate cancer incidence. To date, all other studies examining the relationship between solar radiation exposure and colorectal or prostate cancer incidence or mortality rates in the U.S. using a national sample of exposures have been purely ecologic.

Table 7 summaries the exposure data used in U.S. studies that have examined the association between solar radiation and prostate or colorectal cancer incidence or mortality. There is notable range in the size of the geographic unit and complexity of the UV data used to estimate exposure. The two ecologic studies that generated the vitamin D hypothesis (i.e., Garland and Garland 1980; Schwartz and Hulka 1990) have been criticized for using too large a geographic unit as their unit of analysis or a simplistic measure of exposure.[92,93,161] In general, county rather than state or larger region is

considered a more desirably-sized geographic unit for capturing an area's UV level.[132,171] Latitude alone is generally considered insufficient as a measure of exposure since numerous factors including elevation, cloud coverage, ozone, aerosol pollutants and surface albedo substantially modify the amount or type of UV light reaching the ground.[33,36,37,92,93,171] Several subsequent ecologic studies tried to address these issues by conducting their analyses using county as the geographic unit rather than state (i.e., Hanchette and Schwartz 1992; Boscoe and Schymura 2006). Several studies have also included climatological and geophysical factors modifying ground levels of UV radiation (i.e., Grant 2002; Grant and Garland 2006; Boscoe and Schymura 2006), but used NASA's space-based Total Ozone Mapping Spectrometer (TOMS) estimates of UV-B radiation, which were later found to significantly underestimate the reduction of UV light due to aerosols in the northeastern U.S.[59]

A few recent have used county or state UV-Index (i.e., Schwartz and Hanchette 2006; Colli and Grant 2008), which is a simple composite scale based on ground-level UV radiation, elevation, projected ozone and cloud coverage.[36,108] As with most of the exposure data used to date in US studies, however, the UV Index is intended to estimate the portion of the UV spectrum that can cause erythemal damage (sunburn) rather than portion of the spectrum needed for vitamin D synthesis. The range of wavelengths capable of producing erythemal damage is much wider the vitamin D action spectrum and can differ from it by as much as a factor of 5, depending on latitude and the season of the year.[30,35,36,37,108] Figures 9 and 10 attempt to illustrate this difference. An algorithm making it possible to weight the UV Index to more accurately reflecting the

vitamin D spectrum is available but is rarely used.[35,36,108] It does not appear to have been used in any of the U.S. solar radiation studies examined for this review.

Finally, it is worth noting that UV data estimating erythemal damage was often calculated for Fitzpatrick Types I or II (i.e., Caucasians) to capture their risk for melanoma,[8] and may not adequately estimate the exposure for other sun-reactive Skin Types. None of the studies examined for this review addressed this concern, which may explain why some finding a strong association for Whites failed to find a comparable association for Black populations (i.e., Grant 2002; Boscoe and Schymura 2006; Colli and Grant 2008). Rather than regard these findings as counter to the vitamin D hypothesis, we suggest that the exposure gradient in the U.S. for Blacks is different than it is for Whites particularly during winter months and consideration must be given to this when accessing regional differences in UV levels.[39,163]

In late 2010, a Vitamin D Action Spectrum-Weighted UV climatology based on 1957-2005 data became available for all of North America from Environment Canada, offering the most direct estimates to date of vitamin D-effective UV for the U.S. and Canadian populations. [37] Figures 2 (a) and (b), which were presented earlier in this paper, illustrate some of this data. Similar to the UV Index, the Vitamin D action spectrum-weighted UV Climatology incorporates numerous factors such as ozone, cloud coverage and albedo.[37] It also offers monthly estimates for the relative differences in exposure time needed for the six different skin types that were discussed earlier in this paper to obtain 1 SDD. This data was also presented earlier in Figure 5. [37] This dataset also has yet to be used in an analysis examining solar exposure and colorectal or prostate cancer data.

F. Implications for a population-based observational study and concluding comments:

Our review has attempted to illustrate the complexities of interpreting and comparing levels of circulating concentrations of vitamin D and various measures of solar radiation that have been commonly used in epidemiologic studies. We spent a considerable amount of time reviewing the main issues with solar radiation since these measures were both instrumental in generating the vitamin D hypothesis and continue to be of interest for observational studies. While circulating concentrations of vitamin D continue to be the optimal measure, these studies also have notable shortcomings. Of particular concern, there are questions as to if these measures have been adequately adjusted for fluctuations due to seasonal variation that may be associated with the development and progression of cancer. Few of the studies reviewed for this paper measured both the circulating concentrations of vitamin D and solar radiation levels. One study using a smaller, climatologically homogenous area adjusted for cloud cover successfully predicted up to 40% of the observed variation in serum 25(OH)D levels among a cohort of pregnant, White females.[145] Based on data collected in other studies, it appears that solar radiation levels may be a an even better predictor for male (both Black and White) 25(OH)D concentrations than it is for White females due to sun behavior and/or dietary supplementation practices.[19,31,164]

Scientists have long recognized the incredible spectrum of UV light in the continental U.S., making it a very desirable landscape to study the association between solar radiation exposure and chronic diseases. Numerous well-cited population-based cohort studies have used the National Cancer Institute's *Surveillance, Epidemiology and End Results* (SEER) data to examine the association between UV light and skin or

salivary gland cancers, and estimated patient exposure based on county or state of residency at time of diagnosis sometimes in conjunction with state of birth to capture long-term exposure.[i.e.,73,131,149,171] To date, no comparable studies have been conducted using SEER data to test the vitamin D hypothesis for colorectal or prostate cancers. We suggest that by addressing the concerns raised it this paper for the proper assignment of the vitamin D spectrum as an area-based measure it should be possible to design and conduct population-based observational studies that could be used to address some of the pending research questions for these cancers in the absence of serum measures. This design would have particular utility for the investigation of the possible differential effects of solar radiation exposure to the vitamin D spectrum on diverse populations on the progression and survival for colorectal and prostate cancers.

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Table 1: Comparative sources of vitamin D in the U.S. population.

Source	Approximate Vitamin D_3 Content	Notes
Cutaneous synthesis of UV light containing the vitamin D spectrum (during peak exposure, 10 AM to 3 PM)	3,000 I.U./ 0.5 MED (e.g., 5 to 10 minutes with arms and legs exposed) to 20,000 I.U./1 MED (e.g., 20 to 30 minutes in a bathing suit)	Dose varies considerably with season, latitude, time of day, sun-reactive, skin type, age, and other factors; must be direct exposure to UV light, not through window glass.[76,127]
Cod liver oil	400-1000 I.U./1 teaspoon	natural food source[76,79]
Salmon, Fresh Wild	600-1000 I.U./3.5 ounces	natural food source[76,79]
Salmon, Fresh farmed	100-250 I.U./3.5 ounces	natural food source[76,79]
Tuna, canned	230 I.U./3.6 ounces	natural food source[76,79]
Fortified milk, orange juice or yogurt	100 I.U./8 ounces, usually vitamin D_3	Amount in fortified food may be considerably less than label indicates [19,76,79]
Multivitamin supplement	Through 2007: 400 I.U. most common; Since 2007: varies from 400 – 1000 I.U.; may be either D_2 or D_3	Approximately 40% of US population currently take a supplement including vitamin D; more women take supplements than men; trend started in mid-90s with aging female baby boomers as main consumers of calcium with vitamin D[27, 34, 52,103,127,169]
Vitamin D_3 supplement	Through 2007: 400 – 2,000 I.U. commonly available; Since 2007: 400- 50,000 I.U. available.	Mega-dose vitamin D not a big seller until mid-2000s; sales increased 30 % year from 2007 between 2010.[87]

Notes: MED= Minimal Erythemal Dose.

Sources: Adapted from Holick 2007[76] and Holick 2011[79] with additional sources as indicated.

Table 2: Estimated minimum minutes of exposure needed for one standard dermal dose of vitamin D using hands, face and arms at 12:00 noon under clear skies during solstice months.

Fitzpatrick Sun-reactive Skin Type	**Typical reaction to sun**[163]	**Adjustment factor relative to Skin Type II**[37,163]	**29° N.**	**29° N.**	**42.5° N.**	**42.5° N.**	**†Association with self-described race/ ethnicity in NHANES 2003-2004**[91] n=2691
			On 21st December[163]	**On 21st June**[163]	**On 21st December**[163]	**On 21st June**[163]	
I	Always burns easily, never tans; most photo-reactive	0.8	16	3	70	4	White, Non-Hispanic <5%
II	Usually burns easily, tans with difficulty	1.0 (referent)	20	4	94	5	White, non-Hispanic ~40%
III	Burns moderately, tans gradually	1.2	23	5	127	6	White, non-Hispanic ~50%
IV	Rarely burns, always tans well	1.8	35	7	(179*)	8	Black, non-Hispanic <10%
V	Very rarely burns, tans very easily	2.4	48	10	(225*)	11	Black, non-Hispanic ~20%
VI	Never burns, deeply pigmented; least photo-reactive	4.0	85	16	(376*)	19	Black, non-Hispanic ~70%

Notes: ( ) = Beyond the limit of simulation tool; * = times estimated based on adjustment factors relative to type II skin for purposes of comparison only. †In comparison, Chan *et al.* 2005[18] found the following distribution in her sample: Whites, non-Hispanic (n=304): 32.6% Type 1, 28.3% Type 2, 29.3 % Type 3, 6.2% Type 4, 3.6% Type 5, 0% Type 6; Blacks, non-Hispanic (n=36): 0 % Type 1, 0 % Type 2, 0% Type 3, 25% Type 4, 33.3% Type 5, 41.7 % Type 6.

Sources: Adapted from Webb *et al.* 2006[163], Fioletov *et al.* 2010b[37] and Keiser *et al.* 2012.[91]

Table 3: Age-adjusted incidence and mortality rates per 100,000 by race/ethnicity for colorectal and prostate cancer in males, U.S. SEER data 2004-2008.

SEER 2004-2008, Males only, Age-adjusted rates per 100,000	**Colorectal Cancer**		**Prostate Cancer**	
Race/Ethnicity	**Incidence**	**Mortality**	**Incidence**	**Mortality**
All Races	55.0	20.7	156.0	24.4
White*	54.4	20.1	149.5	22.4
Black	67.7	30.5	233.8	54.9
Asian/Pacific Islander	45.4	13.3	88.3	10.5
American Indian/Alaska Native	42.7	19.8	75.3	20.7
Hispanic *	39.9	15.5	107.4	18.5

Notes: *Hispanic cases in California registries incorrectly coded to non-Hispanic. Correction from SEER is forthcoming.

Source: National Cancer Institute. Surveillance Research Program. [123,124]

Table 4: Stage distribution and 5-year relative survival by stage for colorectal and prostate cancers, all races, U.S. SEER data 2001-2007.

SEER 2001-2007, 5-Year Relative Survival by Stage at Diagnosis, All Races	**Colorectal Cancer* (both sexes)**		**Prostate Cancer (males)**	
Stage at Diagnosis	**Stage Distribution (%)**	**5 – Year Relative Survival (%)**	**Stage Distribution (%)**	**5 – Year Relative Survival (%)**
Localized (confined to primary site)	39	90.1	81	100.0
Regional (spread to regional lymph nodes)	37	69.2	12	100.0
Distant (cancer has metastasized)	20	11.7	4	28.7
Unknown (unstaged)	5	33.3	3	69.9

Source: National Cancer Institute. Surveillance Research Program. [123,124]

Table 5: Risk factors common to both colorectal and prostate cancers, and their relationship to vitamin D.

Risk factor	Effect on Colorectal cancer	Effect on Prostate cancer	Effect on Vitamin D synthesis or metabolism
Age	Risk increases with age; median age at diagnosis: 70; median age at death: 75, in U.S. SEER data[123]	Risk increases with age; median age at diagnosis: 67; median age at death: 80, in U.S. SEER data [124]	Synthesis declines substantially with age, e.g., individuals aged 62-80 years synthesis 75% less than individuals aged 20-30 year. [74]
Race	African Americans have higher age-adjusted rates per 100,000 than Whites: incidence: 67.7 vs. 54.4; mortality: 30.5 vs. 20.1, in U.S. SEER data [123]	African Americans have higher age-adjusted rates per 100,000 than Whites: incidence 233.8 vs. 149.5; mortality 54.9 vs. 22.4, in U.S., SEER data [124]	Melanin is a photo-absorber; sun-reactive skin type determines the time needed to absorb enough UV to synthesize a dose of vitamin D; less photo-reactive skin requires 4 or more times the length of exposure than white skin to achieve 1 SDD.[37,163]
Geographic location	Greater incidence and mortality in northern areas of the U.S., particularly among Whites in the Northeast.[118,119]	Greater incidence and mortality in northern areas of the U.S., particularly among Whites in the Northwest.[118,119]	Vitamin D-effective UV shows considerable seasonal variation and declines as you move north; it is difficult for many individuals living in northern areas to synthesis adequate amounts of vitamin D during winter months.[60,163]
Western diet; see below for Dairy/Calcium	Increased risk has been associated with increased consumption of red meat, animal fat and decreased consumption of fruits, vegetables and fiber.[54,138]	Increased risk associated with a higher intake of animal fat; reduced risk associated with higher fish intake. [117,134]	Western diet is typically low in fish, which often contain higher natural levels of D_3 than fortified food.[76,79]
Dairy and Calcium	Increased risk associated with lower intake of dairy, lower intake or circulating levels of calcium, (particularly without adequate vitamin D); risk may differ by stage or subsite. [54,138]	Increased risk associated with higher consumption of dairy, with highest levels of calcium through intake or supplementation associated with advanced or fatal cancers.[117,134]	The Western diet is high in calcium through dairy consumption; high levels of calcium may suppress circulating levels of calcitriol, the bioactive metabolite of vitamin D;[117] conversely, low circulating concentrations of calcium are associated with low circulating levels of vitamin D.[20]

Western lifestyle; see below for BMI	Risk increases with sedentary life, low physical activity, white collar jobs; risk increases for Asian migrants with migration to the U.S. [54,138]	Risk may increase with urbanization or with urban occupations; risk increases for Asian migrants with migration to the U.S.[117,134]	Indoor living and urban areas decrease access to vitamin D-effective UV radiation; institutionalized populations 70-100% vitamin D deficient;[76,79,127] air pollution reduces availability of vitamin d spectrum (e.g., 50% less in heavily aerosol polluted urban areas vs. clean rural areas).[37,92,93]
BMI	Risk increases with increasing BMI; obesity doubles risk; appears to be a stronger risk factor for males than females.[54,138]	Risk may increase with BMI; unclear if due to adiposity vs. muscle mass (hormones)[106,117,134]	Vitamin D sequesters in fat and obesity decreases vitamin D metabolism (e.g., individuals with BMI $\geq 30/m^2$ have circulating levels that are 50% less than individuals with BMI $<26/m^2$.[98,158,168]
Smoking	Increases risk for cancer of the rectum; highest risk observed in long-terms (≥30 years) smokers.[9,54,138]	Increases risk for fatal or metastatic prostate cancer ; highest risk observed in heaviest smokers compared with nonsmokers.[82,117,134]	Smoking reduces circulating 25(OH)D concentrations; 25(OH)D concentrations were 13-26% lower in smokers compared with non-smokers with the same frequency of sun exposure.[11]

Sources: Various, as indicated above.

Table 6: The Relative Risk (RR) of cancer death in males with colon or prostate cancer in Norway by season of diagnosis.

Season of Diagnosis	Colon Cancer Crude RR (95% CI)	Colon Cancer Adjusted RR (95% CI)	Prostate Cancer Crude RR (95% CI)	Prostate Cancer Adjusted RR (95% CI)
	Risk of fatality at any time after diagnosis	Risk of fatality at any time after diagnosis	Risk of fatality at any time after diagnosis	Risk of fatality at any time after diagnosis
Winter†	1.00	1.00	1.00	1.00
Spring	0.94 (0.88,1.00)	0.93 (0.87,1.00)	1.01 (0.96,1.05)	0.96 (0.92,1.01)
Summer	0.94 (0.89, 1.01)	0.90 (0.84,0.96)	0.97 (0.93,1.02)	0.88 (0.86,0.84 *sic*)
Fall	0.84 (0.79,0.90)	0.78 (0.72,0.82)	0.83 (0.79,0.86)	0.80 (0.77,0.84)
	Risk of fatality within 3 years of diagnosis	Risk of fatality within 3 years of diagnosis	Risk of fatality within 3 years of diagnosis	Risk of fatality within 3 years of diagnosis
Winter†	1.00	1.00	1.00	1.00
Spring	0.93 (0.86,0.99)	0.92 (0.86,0.99)	0.98 (0.93,1.04)	0.93 (0.89,0.99)
Summer	0.91 (0.86,0.98)	0.85 (0.80,0.92)	0.86 (0.82,0.92)	0.80 (0.75,0.84)
Fall	0.80 (0.73,0.84)	0.71 (0.66,0.77)	0.73 (0.68,0.78)	0.70 (0.66,0.74)

Notes: Estimated relative risks are adjusted for age at diagnosis, birth cohort, period of diagnosis, stage of disease at diagnosis, level of education, and residential and occupational sun exposure. The data is from the Norway Cancer Registry, 1964-1992.
† = referent

Source: Adapted from Robsahm *et al.* 2004.[142]

Table 7: Solar radiation data used in U.S. prostate or colorectal cancer incidence or mortality studies.

Exposure Data	***Latitude***	***Solar radiation***	***"Epidemiologic Index"***	***DNA weighted UV-B radiation***	***Erythemally-weighted UV-B radiation***	***UV Index***
Source of UV measurement	--	Ground measurements published by U.S. Weather Bureau	Urback, Berger and Davies field measurements of mean UV radiation published in NTIS document	Solar irradiance from NASA's Total Ozone Mapping Spectrometer (TOMS)	Solar irradiance from NASA's Total Ozone Mapping Spectrometer (TOMS)	Ground level UV from monitoring stations; adjusted dataset from NOAA
Adjusted for geophysical factors	no	no	cloud cover, latitude, altitude	length of day, cloud cover, ozone, latitude, % urban	length of day, cloud cover, ozone, latitude, air quality	elevation, projected ozone, cloud coverage
Original purpose of data	geographic	estimate total UV radiation at ground level	estimate potential for erythema from UV (Caucasians)	estimate UV reaching the earth's surface that directly alters DNA	estimate UV reaching the earth's surface that causes erythema (Caucasians)	monitor and forecast potential erythema; (recommend-ations for type sun-reactive Skin Types I and II)
Metric and range	24 to 48 degrees North	300-500 gm-cal/cm^2	12 to 40	3.4 to 10 kJ/m^2	650-1540 kJ/m^2	0 to 16
Annual average	N.A.	1974	1974	--	1996-2003	1995-2001
July average	N.A.	--	--	1992	--	1995
January average	N.A.	--	--	--	--	1995
Geo unit used in one or more study	county centroid	state; region	county; state	state economic areas	county	county; state
SES factors included in some or all of the studies	none	race; SES status based on occupation	none	% urban; % Hispanic; % poverty; lung deaths; alcohol sales	% rural; % poverty; median household income; lung cancer mortality rate; 20% +migration excluded	none
Key studies†						
Prostate	Hanchette and Schwartz 1992[71]	Freedman 2002[43]; John et al. 2004,[88] 2005,[89] 2007[90]	Schwartz and Hulka 1990[146]; Hanchette and Schwartz 1992[71]	Grant 2002[59]; Grant and Garland 2006[61]	Boscoe and Schymura 2006[8]	Schwartz and Hanchette 2006[147]; Colli and Grant 2008[22]
Colorectal		Garland and Garland 1980[46]; Freedman 2002[43]		Grant 2002[59]; Grant and Garland 2006[61]	Boscoe and Schymura 2006[8]	

Notes: † To convert kilojoules (kJ) to Joules (J), multiply by 1000.

Sources: As indicated, above.

Table 8: Major U.S. studies examining solar radiation exposure and colon or rectal cancers.

Study	***Design, Study Population and Outcome Data***	***Exposure***	***Other Factors/Notes***	***Findings (males only)***
Garland and Garland 1980[46]	Ecologic (state, all); White males, age-adjusted mortality rates for 1959-1961	Annual mean daily solar radiation per state	Stratified into metropolitan (17) and non-metropolitan states (32)	Pearson Correlation, **Colon cancer mortality, white males:** r = -0.9 metropolitan states , r = -0.6 non-metropolitan states
Freedman *et al.* 2002 [43]	Case-control (death certificate in 24 states); Whites and Blacks; mortality 1984-1985.	Residential exposure estimated as solar radiation in state of birth/residence, categorized into Low, Medium and High regions	Also examined occupational exposure, physical activity, and socioeconomic status; occupational exposure not associated with mortality.	OR and 95% CI adjusted for age, race and sex **Colon cancer mortality, whites and blacks:** Low = 1.0 referent Medium: OR =0.90 (0.88-0.92); High: OR= 0.73 (0.71-0.74); Note: risks consistent for blacks and whites
Grant 2002[59]	Ecologic (506 state economic areas, other data from 3053 counties; Whites and Blacks; mortality 1970-1994; 1950-1996 data also examined.	(a) DNA weighted TOMS UV-B for July 1992; (b) UV-B from ground monitoring stations for July and September 1992	Omitted data from states with large population increases (AK, AZ, CA, FL, NV) or with other data issues (HI); (a) underestimate aerosols, while (b) includes aerosols plus elevation	Regression coefficients, 1970-1994 **Colon cancer mortality, white males:** (a) r = -0.62, p<0.001; (b, July) r = -0.80, p<0.001; (b, Sept.) r = -0.84, p<0.001; **Rectum cancer mortality, white males:** (a) r = -0.69, p<0.001; (b, July) r = -0.83, p<0.001; (b, Sept.) r = -0.86, p<0.001; **Colon cancer mortality, black males**: (a) r = -0.34, p< 0.001; (b) not reported **Rectum cancer mortality, black males**: (a) r = -0.29, p< 0.001; (b) not reported
Boscoe and Schymura 2006 [8]	Ecologic (county) ; Incidence: counties in all or part of 32 states; Mortality: counties in all states except AK, HI plus DC; Non-Hispanic Whites,	Annual average of Erythemally – weighted TOMs UV-B for 1996-2003 period; categorized into areas by	Excluded counties with >20% migration; North annual average UV-B 650 kJ/m^2 (e.g., far north such as ME, MN, WA); South annual average	RR and 95% CI adjusted for (county): age, % in poverty, median household income, lung cancer mortality rate, workers in outdoor occupation, % rural, Air quality; (state): alcohol, exercise.

	Blacks;; incidence 1998-2002 and mortality 1993-2002	kJ/m^2 (exposure correlated closely with latitude)	UV-B: 1540 kJ/m^2 (e.g., TX, FL, AZ); Mid-U.S. UV-B 1100kJ/m^2; RR in between North and South (to be assumed, as per paper)	**Non Hispanic white males, using** South as Referent (RR=1): **Colon cancer incidence:** North RR 1.11(1.08-1.13) **Rectum cancer incidence:** North RR 1.27(1.23-1.32) **Colon cancer mortality:** North RR 1.27 (1.24-1.30) **Rectum cancer mortality:** North RR 1.53 (1.45-1.60) **Black males: No north-south gradient found for these cancers**
Grant and Garland 2006[61]	Ecologic (states) Whites; mortality 1970-1994; 1950-1969 also examined	DNA weighted TOMS UV-B for July1992 (kJ/m^2)	% urban 1970, % Hispanic 1980, % Poverty 1969, Smoking=lung deaths per year/100k, 1970-1994; alcohol=gallons/year per person; latitude (interpreted as an index of winter UVB)	Regression coefficients, **Colon cancer mortality, white males only,** 1970-1994: UVB -0.71, $p<0.001$, adjusted for smoking, alcohol, urban , Hispanic, poverty; Adj $R^2= 0.74$ **Rectal cancer mortality, white males only**, 1970-1994 : UVB -0.75, $p<0.001$, adjusted for smoking, alcohol, urban , Hispanic, poverty; Adj $R^2= 0.79$

Notes: TOMS = Total Ozone Mapping Spectrometer (satellite measured). The UV Index is the erythema dose calculated from forecasted UV radiation expected to reach the Earth's surface when sun is highest in sky (ozone, cloud coverage, elevation included). *Values have been summarized for males only, unless otherwise indicated.

Table 9: Major U.S. studies examining solar radiation exposure and prostate cancer.

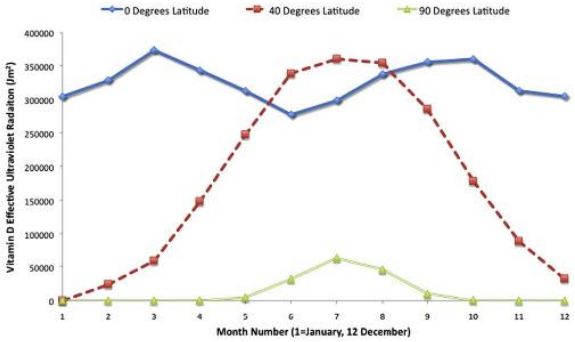
Study	***Design, Study Population and Outcome Data***	***Exposure***	***Other factors/notes***	***Findings (males only)***
Schwartz and Hulka 1990 [146]	Ecologic (48 contiguous state) ; White and Black males, mortality 1950-1969	Mean UV radiation by state	States with <than 100,000 males excluded ; 25 Central and Mountain states excluded for Black males, none for White.	Correlation coefficients, **Prostate cancer mortality:** **White males**: r = -0.53, p<0.001; **Black males**: r = -0.54, p<0.01
Hanchette and Schwartz 1992[71]	Ecologic (county, all in 48 contiguous states) ; White males, mortality 1970-1979	(a) UV radiation, cloud cover, latitude; (b) UV count including latitude and altitude; (c) latitude	Trend surface analysis; (a) limited to 220 counties that had cloud cover available ; other analyses used 3069 counties (b) or 3073 counties (c)	Correlation coefficients, **Prostate cancer mortality, white males**: (a) r = -0.25, p <0.0002; (b) r = -0.15, p <0.0001; (c) r = -0.19, p <0.0001;
Freedman *et al.* 2002[43]	Case-control (death certificate in 24 states); Whites and Blacks; mortality 1984-1985	Residential exposure estimated as solar radiation in state of birth/residence, categorized into Low, Medium and High regions	occupational exposure, physical activity, socioeconomic status also examined; occupational exposure not associated with mortality	OR and 95% CI adjusted for age, race, **Prostate mortality, white and black males**: Low = 1.0 referent Medium: OR=0.89 (0.86-0.91); High: OR=0.90 (0.87-0.93); Note: **black males had higher risk in high region than whites.**
Grant 2002[59]	Ecologic (506 state economic areas, other data from 3053 counties; Whites and Blacks; mortality 1970-1994; 1950-1996 data also examined.	(a) DNA weighted TOMS UV-B for July 1992; (b) UV-B from ground monitoring stations for July and September 1992	Omitted data from states with large population increases (AK, AZ, CA, FL, NV) or with other data issues (HI); (a) underestimate aerosols, while (b) includes aerosols plus elevation	Regression coefficients, **Prostate mortality, white males**: (a) r = -0.32, p<0.001; (b, July) r = -0.44, P<0.061; (b, Sept.) r = -0.63, P<0.012
John *et al.* 2004[88]	Cohort (NHANES I Follow-up study, n=3414); White males; incidence, 1971-1975 to 1992 (n=153)	(a) Region of residence at baseline (b)Average solar radiation level in state of birth	Between 28-46 prostate cancer cases per region; high solar radiation at longest residence associated with decreased risk	RR and 95% CI adjusted for age, family history of prostate cancer, fat intake, calcium intake **Prostate cancer incidence, white males:** (a) Northeast RR=1.0 referent Midwest RR=1.05 (0.66-1.67) West RR= 0.94 (0.60-1.48) South RR= 0.68 (0.41-1.13) (b) Low: 1.0 referent Medium: 0.75 (0.51-1.09) High: 0.49 (0.30-0.79)

John *et al.* 2005[89]	Case-Control, San Francisco Bay area (case=450,control=455); Non-Hispanic white males age 40-79, Advanced prostate cancer **incidence,** July 1997-February 2000.	Solar radiation in state of birth, in low, medium and high regions	All men had medium or high solar radiation; Lifetime outdoor activities, lifetime outdoor jobs not associated with outcome.	OR and 95% CI adjusted for age **Advance prostate cancer incidence, non-Hispanic white males**: Low: OR= 1.0 referent Medium: OR=1.01 (0.69-1.50) High: OR= 1.01 (0.74-1.39)
Boscoe and Schymura 2006 [8]	Ecologic (county) ; Incidence: counties in all or part of 32 states; Mortality: counties in all states except AK, HI plus DC; Non-Hispanic Whites, Blacks; incidence 1998-2002 and mortality 1993-2002	Annual average of Erythemally – weighted TOMs UV-B for 1996-2003 period; categorized into areas by kJ/m^2 (exposure correlated closely with latitude)	Excluded counties with >20% migration; North annual average UV-B 650 kJ/m^2 (e.g., far north such as ME, MN, WA); South annual average UV-B: 1540 kJ/m^2 (e.g., TX, FL, AZ); Mid-U.S. UV-B 1100kJ/m^2; RR in between North and South (to be assumed, as per paper)	RR and 95% CI adjusted for (county): age, % in poverty, median household income, lung cancer mortality rate, workers in outdoor occupation, % rural, Air quality; (state): alcohol, exercise. **Non Hispanic white males, using** South as Referent (RR=1): **Prostate Cancer Incidence** RR 1.20 (1.19-1.22) **Prostate Cancer Mortality** RR 1.17 (1.15-1.19)
Grant and Garland 2006 [61]	Ecologic (states) Whites; mortality 1970-1994; 1950-1969 data also analyzed	DNA weighted TOMS UV-B for July1992 (kJ/m^2)	% urban 1970, % Hispanic 1980, % Poverty 1969, Smoking=lung deaths per year/100k, 1970-1994; alcohol=gallons per year per person; latitude (interpreted as an index of winter UVB)	Regression coefficients, **Prostate cancer mortality, Whites** (1970-1994): UVB: 0.38, p=0.04, adjusted for smoking, urban, poverty, alcohol, Hispanic; and latitude (0.045, p<0.01); Adj R^2=0.59
Schwartz and Hanchette 2006 [147]	Ecologic(>2,500 counties and 505 State Economic Areas); White males, mortality , 1950-1969, 1970-1994	Annual average UV Index for 1995 (interpolated from 55 cities); January and July UV Index also examined.	Methods include a trend surface analysis and regression analysis; Northern counties: >40 degrees N; Southern counties: =<40 degrees N	Correlation coefficients, **Prostate cancer mortality, white males 1970-1994:** Annual UV-Index All counties: -0.23, p<0.0001 Northern: -0.16, p<0.0001 Southern: -0.7044, p=0.7044 January -0.28, p<0.001 July -0.25, p<0.001

John *et al.* 2007*[90]	Cohort (NHANES I Follow-up study, n=3528); Non-Hispanic white males, incidence, stratified into non-fatal and fatal cases, 1971-1975 to 1992 (n=161)	(a) Average solar radiation level in state of birth (b) Average solar radiation in state of longest residence	Subjects with high solar radiation and high in state of longest residency have decreased risk (RR 0.66, 95% CI 0.47-0.93); frequent sun exposure associated with reduced risk for fatal prostate cancer only (RR 0.47, 95% CI 0.23-0.99)	RR and 95% CI adjusted for age, **Prostate cancer incidence, non-Hispanic whites**: (a) Low: 1.0 referent Medium: RR 0.75(0.52-1.07) High: RR 0.52(0.33-0.81) (b) Low: RR 1.0 referent Medium: RR 0.72(0.50-1.05) High: RR 0.59 (0.39-0.88)
Colli and Grant 2008 [22]	Ecologic (state) ; White and Black males; incidence 2003-4; mortality 1992-2001.	UV Index in (kJ/m^2) averaged over 1995-2001; annual and seasonal averages	For Whites: the inverse correlation of PC Incidence (R -0.42 p<0.01), PC Mortality (R-0.53, p<0.001), was strongest for fall/winter UVI; For Blacks, the inverse correlation with PC Incidence (R-0.40, p<0.05) only, and strongest for summer UVI.	**Correlation coefficients,** **Prostate cancer incidence, Whites:** Annual -0.36, p<0.05 Winter -0.42, p<0.01 Spring -0.38, p<0.05 Summer -0.23, p>0.05 Fall -0.40, p<0.01 **Blacks:** Annual -0.30, p>0.05 Winter -0.20, p>0.05 Spring -0.27, p>0.05 Summer -0.40, p<0.05 Fall -0.26, p>0.05 **Prostate cancer mortality**, **Whites:** Annual -0.46, p<0.01 Winter -0.53, p<0.001 Spring -0.48, p<0.01 Summer -0.31, p>0.01 Fall -0.50, p<0.001 **Blacks:** Annual 0.15, p>0.05 Winter 0.24, p>0.05 Spring 0.18, p>0.05 Summer 0.03, p>0.05 Fall 0.18, p>0.05

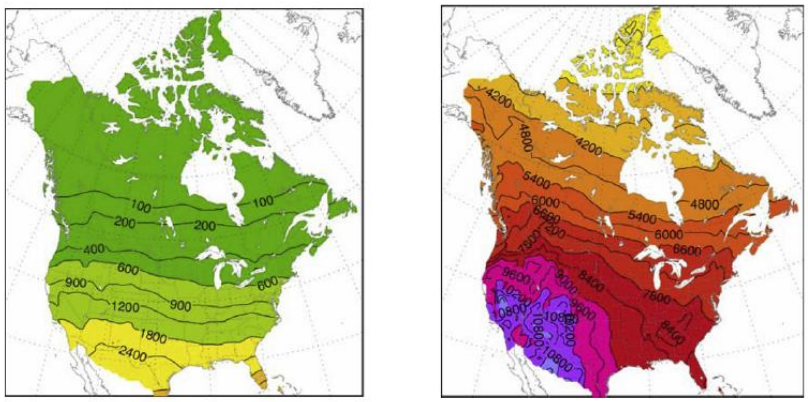
Notes: TOMS = Total Ozone Mapping Spectrometer (satellite measured); the UV Index is the erythema dose calculated from forecasted UV radiation expected to reach the Earth's surface when sun is highest in sky (ozone, cloud coverage, elevation included). *Reanalysis and expansion of John *et al.* 2004.

Figure 1: Impact of latitude on total monthly vitamin D-effective ultraviolet radiation in Joules per square meter.



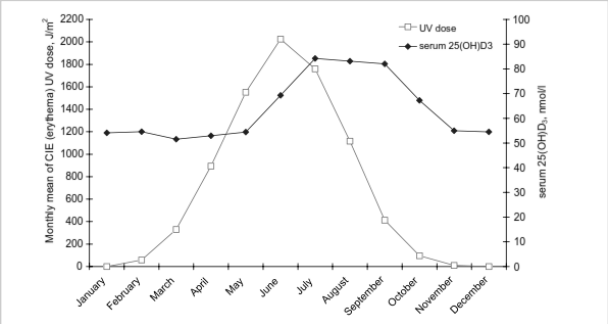
Source: Reprinted from *Molecular Aspects of Medicine*, 29(6), Kimlin, M. G., Geographic location and vitamin D synthesis, pages 453-461, Copyright (2008), with permission from Pergamon.[93]

Figure 2: Mean monthly values from the *Vitamin D action spectrum-weighted UV climatology for North America* in Joules per square meter for (a) January and (b) July.



Source: Reprinted from *Journal of Photochemistry and Photobiology B-Biology*, 100(2), Fioletov, V.E., McArthur, L. J. B., Mathews, T. W., & Marrett, L., Estimated ultraviolet exposure levels for a sufficient vitamin D status in North America, pages 57-66, Copyright (2010), with permission from Elsevier S.A.[37]

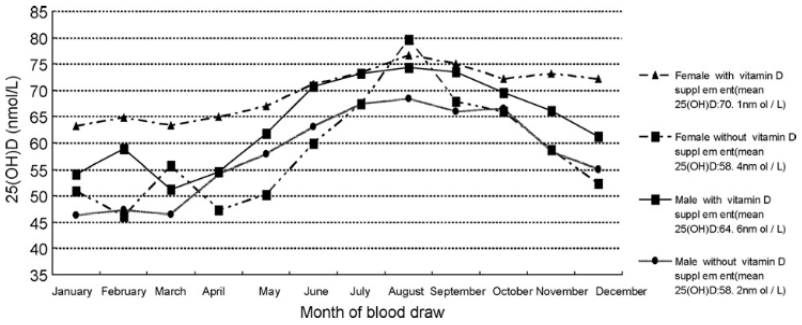
Figure 3: The monthly variation in circulating 25(OH)D in northern Norway (68-71˚ N) together with monthly values of erythemogenic UV radiation, averaged over the years 1996–1999.



Note: To convert to ng/ml, divide by 2.496.

Source: Reprinted from *Cancer Causes & Control*, 15(2), Robsahm, T. E., Tretli, S., Dahlback, A., & Moan, J., Vitamin D-3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway), pages 149-158, Copyright (2004), with permission from Springer-Verlag Dordrecht.[142]

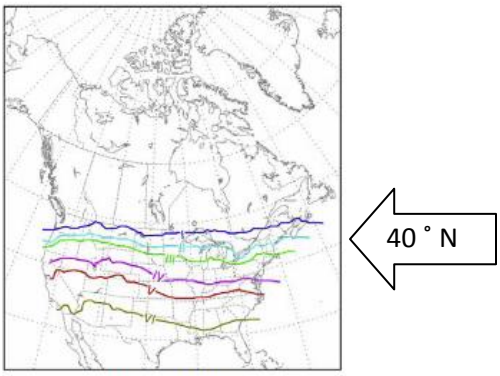
Figure 4: Seasonal variation in serum 25(OH)D concentrations in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) cohort comparing levels by sex and intake or not of vitamin D supplement use.



Note: The composition of this cohort is 94% White, with an average age of 63 ± 5 years, and reside in areas across the United States. [10] To convert to ng/ml, divide by 2.496

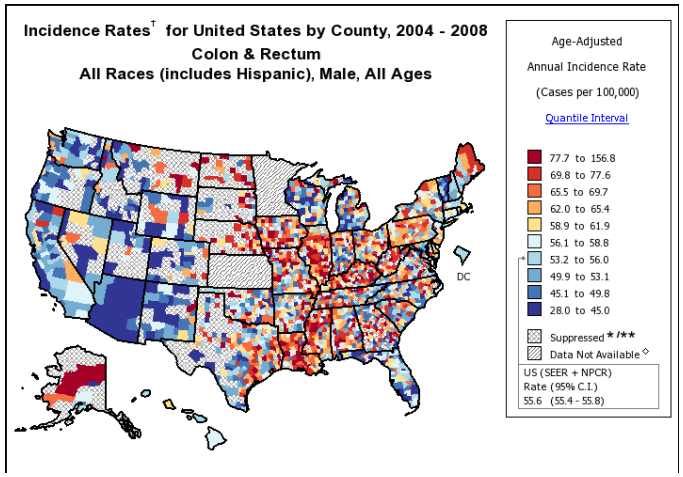
Source: Reprinted from *Journal of Steroid Biochemistry and Molecular Biology, 121* (1-2), Brock, K., Huang, W. -., Fraser, D. R., Ke, L., Tseng, M., Stolzenberg-Solomon, R., . . . Graubard, B. , Low vitamin D status is associated with physical inactivity, obesity and low vitamin D intake in a large US sample of healthy middle-aged men and women, pages 462-466, Copyright (2010), with permission from Pergamon. [10]

Figure 5: The northern borders of the areas where 1 SDD can be obtained within 1 hour near noon for the six Fitzpatrick sun-reactive Skin Types.

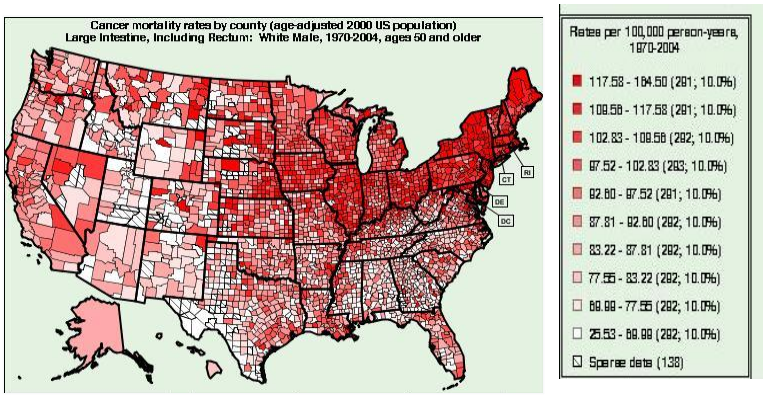


Source: Reprinted from *Journal of Photochemistry and Photobiology B-Biology*, 100(2), Fioletov, V.E., McArthur, L. J. B., Mathews, T. W., & Marrett, L., Estimated ultraviolet exposure levels for a sufficient vitamin D status in North America, pages 57-66, Copyright (2010), with permission from Elsevier S.A. [37]

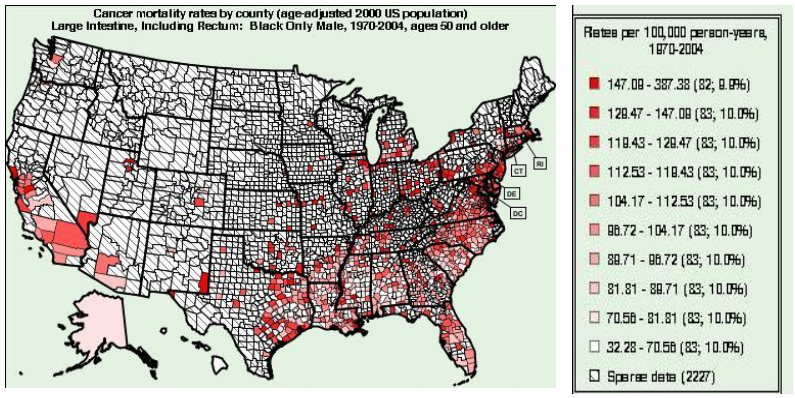
Figure 6: Age-adjusted colorectal cancer incidence (a) and mortality in (b) White and (c) Black males (per 100,000 males).



(a)



(b)



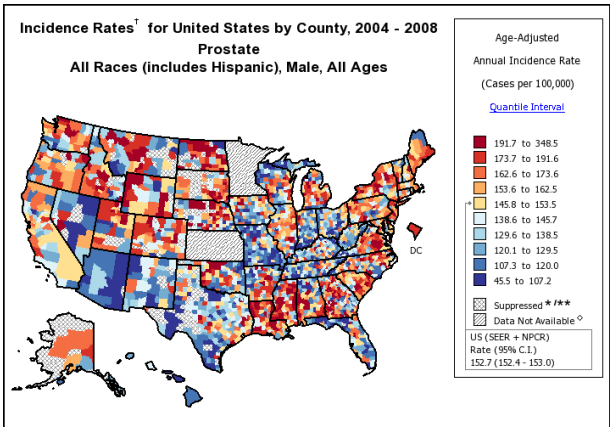
(c)

(a) Age-adjusted annual colorectal cancer incidence rates for U.S. males of all races by county for 2004-2008. Each category contains 10% of cases, which range from an incidence of 28.0 - 45.0 (darkest blue) to 77.7 - 156.8 (darkest red) per 100,000 males. Areas with black and white hatch-marks indicate unstable estimates or suppressed data.
Source: Map created by author using the National Cancer Institute's interactive *State Cancer Profiles*. [119]

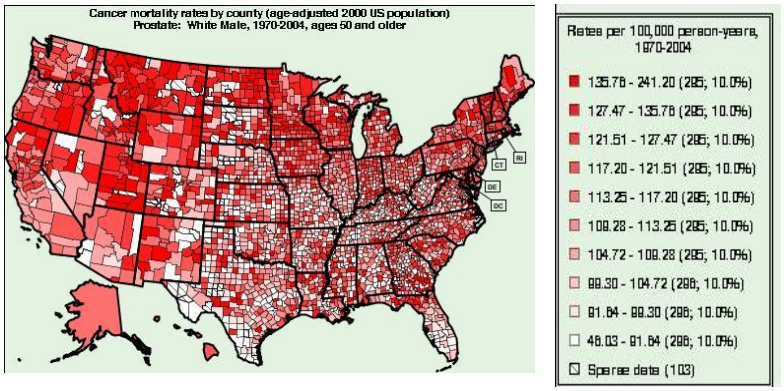
(b) White Male and (c) Black Male age-adjusted mortality rates for cancer of the large intestine including the rectum by U.S. county for 1970-2004, ages 60 and older. Each category contains 10% of cases. Rates for White males range from 25.53 – 89.99 (white areas) to 117.58 - 184.50 (dark red areas) per 100,000 person years. Rates for Black males range from 32.28 – 70.58 (white areas) to 147.09 - 387.38 (dark red areas) per 100,000 person years. Areas with black and white hatch-marks indicate unstable estimates.

Source: Maps created by author using the National Cancer Institute's interactive *Cancer Mortality Maps.* [118]

Figure 7: Age-adjusted prostate cancer incidence (a) and mortality in (b) White and (c) Black males (per 100,000 males).



(a)



(b)

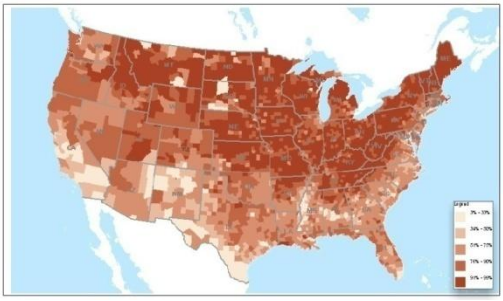
(c)

(a) Age-adjusted annual prostate cancer incidence rates for U.S. males of all races by county for 2004-2008. Each category contains 10% of cases, which range from an incidence of 45.5-107.2 (darkest blue) to 191.7-348.5 (darkest red) per 100,000 males. Areas with black and white hatch-marks indicate unstable estimates or suppressed data.
Source: Maps created by author using the National Cancer Institute's interactive *State Cancer Profiles*. [119]

(b) White Male and (c) Black Male age-adjusted mortality rates for cancer of the prostate by U.S. county for 1970-2004, ages 60 and older. Each category contains 10% of cases.

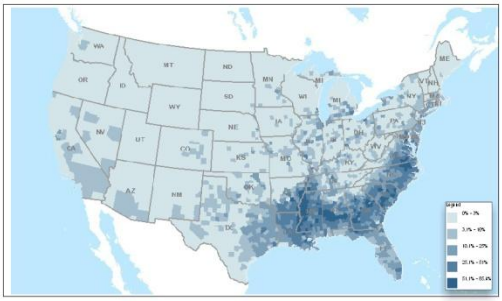
Rates for White males range from 48.03 – 91.84 (white areas) to 135.78 - 241.20 (dark red areas) per 100,000 person years. Rates for Black males range from 82.53 - 182.77 (white areas) to 308.99 - 872.90 (dark red areas) per 100,000 person years. Areas with black and white hatch-marks indicate unstable estimates.
Source: Maps created by author using the National Cancer Institute's interactive *Cancer Mortality Maps*. [118]

Figure 8: U.S. county population concentrations (%) by race and ethnicity based on the 2000 Census. (a) % non-Hispanic White; (b) % Hispanic; (c) % non-Hispanic African American.



(a)

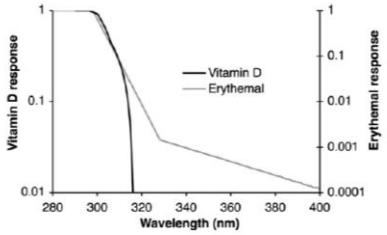
(b)



(c)

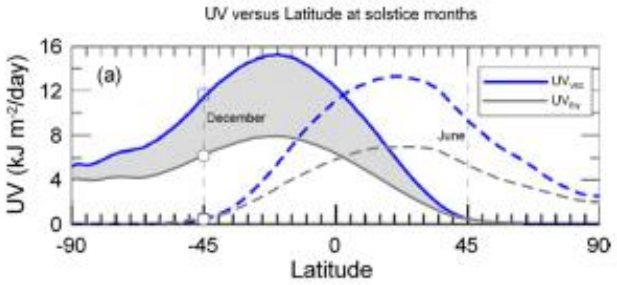
Source: Maps created by author using the Economic Research Service's interactive *Atlas of Rural and Small-town America.* [156]

Figure 9: The difference in wavelengths in the action spectra for vitamin D production and erythemal response.



Source: Reprinted from *Journal of Photochemistry and Photobiology B-Biology*, 86(3), Kimlin, M. G., Olds, W. J., & Moore, M. R., Location and vitamin D synthesis: Is the hypothesis validated by geophysical data?, pages 234-239, Copyright (2007), with permission from Elsevier S.A.[92]

Figure 10: A comparison of erythemally weighted UV (grey line) and vitamin D-effective UV radiation (blue line) during solstice months, in kJm^{-2}/day.



Source: Reprinted with permission from *Photochemistry and Photobiology*, 85(1), McKenzie, R. L., Liley, J. B., & Bjorn, L. O., UV radiation: Balancing risks and benefits, pages 88-98, Copyright (2009), with permission from Pergamon Press.[108]

VITAMIN D ULTRAVIOLET RADIATION, DISPARITIES AND SURIVAL IN COLORECTAL AND PROSTATE CANCER PATIENTS

By AMY E. ABRUZZI

Manuscript 2 of 3 of a dissertation entitled

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In partial fulfillment of the requirements

For the degree of

Doctor of Philosophy

UMDNJ-School of Public Health

Awarded jointly by these institutions and

Written under the direction of

Kitaw Demissie, MD, PhD

ABSTRACT OF MANUSCRIPT 2 OF 3

VITAMIN D ULTRAVIOLET RADIATION, DISPARITIES AND SURIVAL IN COLORECTAL AND PROSTATE CANCER PATIENTS

Dissertation Director

Kitaw Demissie, MD, PhD

ABSTRACT

Numerous studies have reported a protective association between higher levels of vitamin D obtained from ultraviolet B radiation ("environmental D") and decreased prostate and colorectal cancer mortality in the U.S. Few studies, however, have examined this hypothesis in conjunction with Black-White differences in survival which are likely to reflect differences in sun-reactive Skin Type impacting the ability to obtain an adequate amount of vitamin D from the environment. This study examines the association between environmental D and the hazard for death among White and Black non-Hispanic male patients aged 50 years or older who were diagnosed with a non-metastatic prostate, colon or rectal cancers. Patients diagnosed from 1978 to 2003 were drawn from the National Cancer Institute's Surveillance, Epidemiology and End results database and followed for 10-year survival through 2008. Environmental D exposure was estimated based on the patient's county of residence at diagnosis using data obtained from Environment Canada. A strong interaction between vitamin D radiation and urban level was observed in all models. Using a Cox Proportional Hazards model, we found a moderate protective association with increasing levels of vitamin D radiation for prostate and colon cancer patients residing in all-urban areas, after adjustment for age, period,

stage of disease, and county factors including socio-economic deprivation and a proxy for smoking. Contrary to this finding, a modest increase in risk with increasing VDR was also observed among all patients residing in the least-urban areas. A slightly stronger effect was observed among prostate patients than among those with colon or rectal cancers, although our competing risk analysis suggests this effect may be overestimated for the former. In general, our findings also support that Blacks residing in all-urban areas appear to be at greater risk than Whites, and that this risk may be associated with their environmental D exposure needs.

ABBREVIATIONS USED

adj – adjusted

CI – Confidence Interval

I.U. – International Units

J/m^2 – Joules per square meter

KM – Kaplan Meier

MED – minimal erythemal dose

MM – minimum minutes of exposure time

NCI – National Cancer Institute

SD – Standard Deviation.

SDD – standard dermal dose

SEER – Surveillance, Epidemiology, and End Results

UV-B – ultraviolet-B radiation

VDR – vitamin D radiation

VITAMIN D ULTRAVIOLET RADIATION, DISPARITIES AND SURIVAL IN COLORECTAL AND PROSTATE CANCER PATIENTS

Introduction

Among males in the U.S., the incidence of and mortality from colorectal and prostate cancers continues to be higher for Blacks than Whites.[76,77] While socio-economic factors are known to contribute to these disparities,[i.e.15,16,65] it is probable that biologic and/or genetic differences also play an important role.[11,81,94] Recently it has been suggested that vitamin D deficiency may contribute to the racial/ethnic differences observed for these and other cancers.[18,25,41,42] A substantial body of evidence supports the proposition that vitamin D plays an active role in regulating aspects of the cell cycle that mediates the pathogenesis and progression of disease.[27,50,63] U.S. prevalence surveys have also consistently found that vitamin D deficiency levels (typically defined as circulating concentrations of less than 20 nm/ml) are approximately 2.5 to 3 times higher among non-Hispanic Blacks than among non-Hispanic Whites after adjusting for age and other factors. [i.e.,9,18,28,34,44]

While diet and the amount of time spent outdoors contribute to racial/ethnic differences in circulating concentrations of vitamin D, the most striking difference between Blacks and Whites are the relative differences in exposure time needed within the same geographic environment to ultraviolet-B (UV-B) radiation in order to achieve an adequate amount of vitamin D.[9,18,44] Solar exposure to the vitamin D action spectrum contained in UV-B radiation ("environmental D") is the primary source of vitamin D in adults, which is absorbed through the skin and subsequently synthesized through a complex multi-organ pathway into its bioactive form that works by binding with

receptors found in a wide range of organs.[27,48,50] Depending on the latitude, month of the year, cloud cover, pollution and other factors, the relative differences in exposure time among individuals residing in the same environment may be a matter of a few minutes during summer months to several hundred during the winter.[19,20,23,92] Dermatological studies have typically classified individuals by Fitzpatrick[26] sun-reactive Skin Types, which range in values from the most sun-reactive (Type I) to least sun-reactive (Type VI) with Type II commonly used as the referent. [23,92] Studies have found that Type VI individuals need at least 4 times the daily exposure to environmental D than Type II individuals in order to achieve one standard dermal dose ("1 SDD"), which is roughly equivalent to an oral dose of 1000 I.U**.** vitamin D.[23,92] The correlation between Fitzpatrick sun-reactive Skin Types and self-described race-ethnicity was reported in two recent U.S. studies, where approximately 90 to 93% of non-Hispanic Whites fall into the Skin Types I-III, while 90-100% of non-Hispanic Blacks fall into Skin Types IV-VI. [8,56]

For more than 20 years vitamin D has been studied as a protective factor for colorectal and prostate cancers. [31,83] To date numerous studies have found that higher levels of vitamin D, measured either as circulating serum concentrations or as area UV-B level indicative of environmental D, are protective for both colorectal cancer incidence and mortality. [i.e., 30,36,39,40,64] In general the results are less consistent and generally weaker for prostate cancer than for colorectal cancer, [13,30,43,64] but a moderate protective association has been observed for mortality which appears to be stronger among individuals with long-term environmental exposure.[29,32] Although the effects on disease progression and survival for these cancers are just beginning to be evaluated and many questions remain, vitamin D deficiency appears to substantially increase the risk of death

for both colorectal and prostate cancer patients.[35,38,59,89] Most studies have not yet examined the relationship between race, vitamin D and associated risks for these cancers; however, the few ecologic studies that included Black populations have reported inconsistent results, generally concluding that Blacks do not have the same relationship to environmental D as Whites.[25,41,42]

In this paper, a cohort of non-Hispanic White and Black male patients who were diagnosed from 1978 to 2003 with a non-metastatic first primary colorectal or first primary prostate tumor were drawn from a population based cancer registry; these patients were compared by clinical characteristics, county level environmental D and other factors including socio-economic disparities, then followed for 10-year survival through 2008.

Data Sources

Study population

The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database was the source of our patient data. This population based registry was specifically developed for evaluating the incidence and survival from various cancers in U.S. populations.[75] Most cases (95%) have had continuous follow up from diagnosis to November 1, 2008 or the time of death.[75] Since the registries included in SEER span a wide range of UV levels this data set is also highly desirable for examining associations between this exposure and cancer, as documented by previous studies conducted on skin cancers, non-Hodgkin's lymphoma and salivary cancers. [i.e.,17,46,78,86,88,96] The areas in SEER also tend to be urban and include a substantial number of Blacks.

White and Black male patients aged 50 and over were included if they were diagnosed with a histologically confirmed, first primary colon (ICD-O3 210.41 – 210.49), rectal (ICD-O3 210.51-210.52) or prostate (ICD-O3 280.10) cancer between 1978 and 2003. Patients were excluded if they had missing or unknown data on age at diagnosis, race/ethnicity, county of residence at diagnosis or treatment status. Patients were also excluded if they were diagnosed at autopsy or by death certificate only, or did not have survival time greater than zero. Survival time was defined as time from date of the first primary cancer diagnosis to the date of last follow up, or the date of death, whichever occurred first as measured in months. The November 2008 releases of the SEER data no longer makes SEER Historic Stage available for prostate cancer patients diagnosed before 1995, so site-specific SEER Extent of Disease fields[45,71-74] were used to identify and exclude any patients with distant lymph nodes or metastatic cancer from the cohorts, as well as any patients with unknown information. In addition to identifying patients with positive regional lymph node involvement, we identified any colorectal patients with extension into the serosa or prostate patients where the disease had spread beyond the prostate capsule. In addition, we also categorized our colon patients by proximal and distal locations of the tumor since this has been associated with Black-White differences in survival.[94] We defined "proximal" as the cecum, appendix, ascending colon, hepatic flexure, transverse colon and splenic flexure; "distal" was defined as the descending colon, sigmoid colon, and large intestine. Finally, we excluded all patients with Hispanic ethnicity from our main analyses, though these patients were retained for later use as part of a sensitivity analysis. Table 1 summarizes our patient data.

Environmental D

Our environmental D exposure data was estimated based on the *Vitamin D action spectrum-weighted UV climatology for North America,* which was released in late 2010 by Environment Canada.[23] This climatology is based on data covering 1957 to 2005 and was estimated based on the statistical relationship between UV irradiance, global solar irradiance, total ozone, cloud cover (as dew point temperature), solar zenith angle, snow and latitude, and was validated by Brewer spectrophotometer measurements.[23] This dataset was developed for "typical" urban conditions, which may be as higher in less polluted areas and lower in heavily polluted areas. [23] It included mean hourly estimates per month of the spectrum in Joules per square meter (J/m^2) as well as the associated number of minimum minutes needed to achieve 1 SDD using hands, face and arms (¼ personal minimal erythemal dose or "MED") via cutaneous synthesis for the six Fitzpatrick sun-reactive Skin Types.[23] ArcGIS10 was used to interpolate the gridded dataset using Inverse Distance Weighting, one of the most appropriate methods for climate data.[84]

Two types of environmental D exposure characterizations were estimated for each SEER county included in the study and compared in our analysis. The first type was the mean monthly vitamin D radiation (VDR) in J/m^2 at the noon hour, the noon representing the hour of the day when the time needed for exposure is shortest.[23,48] This measure was applied to each patient based on their county of residence at diagnosis. The second type of characterization was constructed in order to better explore the relative differences in exposure requirements between Whites and Blacks residing in the same county. Based on the most common Fitzpatrick sun-reactive Skin Type groupings discussed earlier for

non-Hispanic Whites (i.e., Types I-III) and non-Hispanic Blacks (i.e., Types IV-VI), two averages were created for each county in our data set that represent the minimum minutes of daily exposure required to achieve a standard dermal dose using face, hands and arms for an average person of that race/ethnicity. Minimum minutes (MM), then, are the product of the vitamin D radiation level in that area multiplied by factors required for cutaneous synthesis for those Skin Type groupings, and were applied to each patient based on county of residence at diagnosis in conjunction with their race/ethnicity.

Socio-economic Deprivation Index

We constructed a county-level socio-economic deprivation index from U.S. Census Data[85] to capture socio-economic status. Deprivation indexes are known to be a more robust and stable index over time than any single variable and offer an advantageous data reduction method. [55,66] Following the methods of Messer et al. (2006) and Kachigan (1991), over 50 variables were identified in the 1990 Decennial Census, which were narrowed to 21 after removing variables that measured the same or similar concepts, then standardized for analysis. Our initial principal components analysis using varimax rotation resulted in three factors that explained 78.2% of the variance. Seven variables that loaded with the highest scores were rerun as one factor, which explained 75.04% of the variance with a Kaiser-Meyer-Olkin Measure of Sampling Adequacy of 0.882. This score was retained for use as our 1990 county-level socio-economic deprivation index. The seven variables included in this factor were: percent in occupied housing units with greater than one person per room, percent persons with income in 1989 below federal poverty level, percent unemployed civilian population in labor force 16 years, percent occupied housing units without a telephone, percent households with

public assistance income, percent female householders with one or more persons under 18 with no husband present, and percent of households with interest, dividend or net rental income. The process was then conducted using equivalent variables from the 1980 and 2000 Census, resulting in factors that explained 64.146% and 71.292% of the variance (respectively). These factors were highly correlated (0.90 or higher) with our 1990 index, which was then used in all analyses.

Additional 1990 Census Covariates

An urban/rural indicator ("percent urban") was used in all analyses in conjunction with our environmental D exposure data, as the latter was developed using a typical urban environment and may be higher or lower in more urban or more rural areas depending on pollution level. [23] In addition, we retained "Percent in same house for 5 previous years" and "Percent in the same county for 5 previous years", as a combined measure of county stability for later use in our sensitivity analysis. The 1990 census data for these variables were also highly correlated (0.80 or higher) with the 1980 and 2000 census data and used in our analyses.

Proxy for Smoking

Finally, as a proxy measure for individual smoking, we obtained county-level lung cancer mortality rates for White and Black males aged 50 years and older for 1975-2004 from the National Cancer Institute.[70] Rates for Whites and Blacks were significantly different, so county rates were assigned to each patient based on race as well as county of residency. The 1975-2004 White rate correlated moderately highly with individual decades (0.77-0.85), as did the 1975-2004 Black rate (0.74-0.91) and was used in our analyses.

Finally, we checked for correlations between all of our county level variables. All continuous variables were then centered by their mean and divided by 1 standard deviation prior to our statistical analysis and model checks. This study was approved by the UMDNJ IRB (July 2012).

Statistical Analysis

The primary outcome of our study is survival from prostate, colon or rectal cancers. The primary exposure of interest is environmental D and race, adjusted for other tumor and socio-demographic factors. Two characterizations were used and compared in separate models for environmental D: vitamin D radiation levels with a separate variable for race vs. our race-based minimum minutes of exposure. Our primary hypothesis is that higher levels of vitamin D radiation will have a protective association on survival from both prostate and colorectal cancers. In addition, Blacks will have lower survival than Whites, which is associated with their greater environmental D exposure needs.

We modeled the relationship between outcome and exposure for each cohort by using a multivariate Cox Proportional Hazards model that estimated the hazard ratio (risk) of death. For our final model, we also evaluated the competing risk for all other causes of death. When developing each model, we retained all variables of clinical significance or any coefficient with a P value less than 0.05. Most covariates of interest were highly significant and were included in our final models, with one exception. Season of diagnosis, tested both as four separate seasons as well as grouped in two categories (i.e., Winter/Spring and Summer/Fall), were not significant and eliminated from all final models.

For our initial analyses, continuous variables were centered around their mean and divided by a standard deviation, which offered a satisfactory scale. Since we expected that survival would differ by urban/rural status, we categorized percent urban by level. Initially, quartiles were used, but as the effect estimates for the two middle-urban categories differed little from one another, they were collapsed into one and the following cut-points were used: Least-urban <85%; mostly-urban 85-99%; all-urban 99% or more. Recall that the SEER data is heavily urban, with the greater share of patients residing in the north east. Hence few patients in our cohorts, Blacks in particular, resided in high VDR-low urban areas. These limitations were circumvented, in part, by using our alternative MM model. Highly significant ($p<0.0001$) interactions between our environmental D characterizations and urban level were identified in all models. The assumption of proportional hazards was evaluated in all models by using the score test based on scaled Schoenfeld residuals as well as by running an extended Cox model that checked each variable for a possible interaction with time. In each cohort, the variables for treatment, extent of disease, marital status and grade consistently failed to satisfy the proportional hazards assumption. Since these were not the focus of our investigation and no interactions were found between these variables and others retained in our final models, we handled them using a Stratified Cox Model adjusted for additional factors.[51,58]

Competing risks were evaluated by fitting separate stratified Cox models for death by other causes,[1] after determining that the method of Fine and Gray[24] was not appropriate given the number of time-varying covariates in our models.[3,60] We also explored the data augmentation method of Lunn and McNeill[62] to fit a single Cox

proportional hazard model for each cohort with an indicator by risk type (i.e., death from disease and death from all other causes) and determined after various tests that our data was best handled through a stratified Lunn McNeill model.[2,58] Since in principle this yields results that are identical to fitting separate Cox regressions for each risk, we opted for the latter since it offered us a wider range of options for handling our TVCs and checking the fit of our final models. [2,58] Finally, sensitivity tests and sub-analyses were conducted in order to check the assumptions we made about key variables and estimate the impact these had on results. All analyses were conducted using Stata/MP 12.[87]

Results

Patient Characteristics

Table 1 displays the socio-demographic, environmental D, and tumor characteristics of the White and Black non-Hispanic patients in our cohorts. In the prostate cohort, most patients had local cancer diagnosed during the PSA era (1988 to date.) Blacks tended to have a higher or unknown grade of disease and were less likely to undergo surgery. In the colon and rectal cohorts, the majority of all patients tended to have local cancer though a substantial number also had regional disease. Blacks were more likely to have nodal involvement and less likely to receive surgery for both colon and rectal cancers. In all cohorts, Blacks tended to have slightly lower five and 10-year survival from disease. They were also more likely to reside at their time of diagnosis in counties that were more urban, with a higher level of socio-economic deprivation, and with a higher race-specific rate of lung cancer. Blacks also tended to reside in counties with slightly higher vitamin D radiation levels, but despite this required a substantially longer average number of minimum minutes of daily exposure.

Multivariate Cox Regression

Table 2 displays the results of our stratified Cox regressions modeling the hazard of death from disease for our prostate, colon or rectal cancer patients during a 10-year follow up period, adjusted for additional factors. Two separate models using both environmental D exposure characterizations are presented in conjunction with a no-exposure "null" Model (Model 0). In Model 1, environmental D was modeled using vitamin D radiation level (VDR) as a continuous variable with a separate variable for race; in Model 2, minimum minutes of exposure modeled as a continuous variable is presented. When comparing Model 1 against our null model, it is notable that the addition of VDR as an explanatory variable modestly decreases the point estimate for Black race, which was 6.5% (colon), 14% (prostate), or 16% (rectal) lower depending on the cancer. It is also worth noting that in the null model, all-urban level (adj HR 0.85, 95% CI: 0.82, 0.89) is associated with a modest protective association for prostate patients as is mostly-urban level (adj HR 0.98, 95% CI: 0.95, 1.00), although to a far lesser extent. No significant effect by urban level was observed for either colon or rectal cancers in their respective null models.

An interaction between environmental D and categories of urban level were identified in both Models 1 and 2. In general, VDR (Model 1) and MM (Model 2) yield inversely related results that differ slightly in comparability depending on the cancer. As indicated in Model 1, increasing VDR appears to have a protective association on survival at the all-urban level, with the greatest decrease in the hazard of death observed among prostate (adj HR 0.74, 95% CI: 0.69, 0.80) and colon (adj HR 0.83, 95% CI: 0.75, 0.91) cancer patients. Contrary to this, a 10% to 14% increase in the hazard of death

with increasing VDR was observed among all patients residing at the least-urban areas, depending on the cancer. Similarly in Model 2, increasing MM increases the hazard of death at the all-urban level while appearing to be protective at the least-urban level for all cancers. Of note in this Model, the increased risk associated with colon cancer patients (adj HR 1.20, 95% CI: 1.12, 1.29) residing in the all-urban level is slightly higher than that observed for prostate patients (adj HR 1.15, 95% CI: 1.09, 1.22). In addition, a 15% increase in the hazard of death (95% CI: 1.04, 1.27) with increasing MM at the all-urban level appears to be present for rectal cancer, which was not evident when VDR was used (Model 1). These discrepancies are most likely due to the smaller number of Black patients with colon or rectal cancer and the loss of statistical power in the VDR models, which use race as a separate variable. This issue is avoided in our MM models as this exposure characterization combines both race and radiation level into one variable. Higher rates of our proxy for smoking also appear to be associated with an increase in the hazard of death among patients with prostate cancer, while increasing socio-economic deprivation appears to be associated with an increase in the hazard of death primarily among colon cancer patients.

Table 3, which presents separate estimates by race, indicates that the protective association of increasing VDR in all-urban areas may be slightly stronger for Blacks (adj HR 0.64, 95% CI: 0.52, 0.80) than for Whites (adj HR 0.74, 95% CI: 0.69, 0.80). This seems consistent with the modest protective association observed for Blacks that was associated with increasing VDR that we described above (i.e., Model 0 vs. Model 1). Interestingly, an increase in the hazard of death was observed for Blacks with prostate cancer residing in mostly-urban areas (adj HR 1.08, 95% CI: 1.02, 1.14), whereas this

urban level was generally not associated with an increase in risk for Whites. Although likely related to sample size, all effect estimates for colon and rectal cancer fail to reach statistical significance among Blacks. The results of the VDR-urban level interaction for Whites-only are similar to the estimates reported in Table 2, with a moderate protective association was observed for prostate and colon patients residing in all-urban areas and a modest increase in the hazard of death for all cancer patients residing in the least-urban areas.

Finally, Table 4 presents the results of our competing risk analysis for all models appearing in Table 2. This analysis suggests that the protective association observed in the all-urban areas as well as the risk associated with Black race may be slightly overestimated for prostate patients, but is not likely to be for colon or rectal cancer patients. In addition, our socio-economic deprivation index and the proxy for smoking appear to be consistently associated with competing risks of death for patients in all three cancer cohorts.

Sub analyses

We performed several sub-analyses on the results presented in Models 1 and 2 in order to evaluate our choice of environmental D exposure characterizations and length of follow up period. We also evaluated our results to see if they were improved once county-level residential stability or presumed long-term exposures were considered. For all analyses, we focused on the interaction between environmental D and urban level as well as the effect on race, if it was included in the model.

High/Low vs. Average Month Exposure

As mentioned earlier, we conducted our main analyses using a 12 month average for vitamin D radiation level as well as for the minimum minutes of daily exposure. Given that annual high or low radiation levels have sometimes been used in previous studies,[i.e.,13,38,39] we evaluated Models 1 and 2 using June and December values as these best captured the highs and lows in our SEER areas, respectively. Table 5 presents a selection of these results.

Overall, a noticeable change in effect was noted among colon and prostate cancer patients, but not among those with rectal cancer. In general, using June values increased the protective association of environmental D at the all-urban level, while using December values decreased it for those patients. Interestingly, our two exposure characterizations responded differently, with VDR being more sensitive to June values and MM being more sensitive to December values. In either case, there was little change in the effect of environmental D using either measurement for patients residing in the least-urban areas. As presented in Model 1, we found the protective association of increasing June VDR was greater among prostate patients (adj HR 0.49, 95% CI: 0.40, 0.58) than colon patients (adj HR 0.63, 95% CI: 0.49, 0.82) at the all-urban level. Consistent with the results observed using average monthly minimum minutes, Model 2 indicates that the hazard of death associated with increasing December MM was slightly greater among colon patients (adj HR 1.29, 95% CI: 1.18, 1.42) than among prostate patients (adj HR 1.25, 95% CI: 1.17, 1.34) at the all-urban level. Only a very minor change in effect was observed among rectal patients using either June or December

values with either environmental D characterization. The change in effect on race was also minimal in these models compared with those presented in Table 2.

Minimum Minutes Exposure Characterization

We checked our assumptions about our race/ethnicity assigned minimum minutes of exposure categorization (i.e., Model 2) by enlarging our cohorts to include patients with Hispanic ethnicity and estimating the effect separately for Whites and Blacks (data not shown). As the exposure literature on sun-reactive Skin Types suggests, Hispanic Whites typically require more exposure time than non-Hispanic Whites, while Hispanic Blacks typically require less exposure time than non-Hispanic Blacks.

Our findings were consistent with this assumption for White patients across all three cancers. Among White prostate patients, Hispanics had a 7% (95% CI: 1.01-1.14) increase in the hazard of death from disease, while increases of 8% (95% CI: 1.00, 1.17) and 12% (95% CI 1.01, 1.23) were observed among Hispanics with colon or rectal cancers, respectively. Although the number of Blacks identified as Hispanic were few in number and associated estimates for ethnicity failed to reach significance in any model, patterns were consistent with our expectations for prostate and colon cancers. Among Black patients, Hispanics had a 4% (95% CI 0.63, 1.47) decrease in the hazard of death from prostate cancer and a 9% (adj HR 0.91, 95% CI 0.37, 2.20) decrease from colon cancer. Interestingly, Hispanic ethnicity was associated with a 71% (95% CI 0.63, 4.66) increase in the hazard of death from rectal cancer, which seems to suggest the influence of other causal factors.

Length of Follow up Period

Follow up periods of 3, 5 and all years were examined and compared to the 10-year results presented in Table 2. Point estimates for the interaction between VDR and all-urban area became stronger when the follow up period was limited to 3 or 5 years, typically conferring an increase of up to 6 % in the benefit on survival among patients residing in all-urban areas and an increase of up to 2% in the hazard of death among patients in the least-urban areas, depending on the cancer. The results for 5 year survival are presented in Table 6. In this model, Black rectal patients had a 31% (95% CI: 1.17, 1.45) increase in risk during the 5 year follow up period. There was little difference between the results presented in Table 2 for 10 year follow up and those obtained when all follow up time was used.

County-level Residential Stability

Since our analysis depends in part on the assumption that the patient's residence at the time of diagnosis remained constant throughout the follow up period, we tried to estimate the potential impact of residential stability. In order to do this, we used the combined 1990 Census variable described earlier to capture the percent of individuals who resided in the same house or county during the previous 5 years to restrict our study areas to populations with a minimum of 70%, 80% or 90% stability. We then re-ran Models 1 and 2 using these three different thresholds to evaluate the change in our effects (data not shown).

The protective association of increasing VDR were approximately 5% higher at the all-urban level when a threshold of 80% or more was used (*n*: prostate=137,176, colon=32,407; rectal=15,485), while a roughly comparable increase in the hazard of

death was observed when MM were used instead. The effect of this restriction on the estimate associated with increasing VDR among patients residing in our least-urban areas were not as dramatic, increasing the hazard by only 1 or 2% depending on the cancer, with a similar increase in the observed protective association when MM was used. When our threshold was dropped to 70% stability or more (*n*: prostate=256,764; colon=57,545; rectal=27,136), we obtained results that were nearly identical to those presented in Table 2. We could not examine a threshold of 90% or greater in any of cohorts as this greatly reduced our sample size (*n*: prostate=27,384; colon=5,522; rectal=922) yielding highly unstable estimates.

Presumed Long-term Exposure

For our last test we restricted our analysis to cases where their state of birth matched that of their cancer registry, which has been used in a few key studies as a measure of presumed long-term exposure.[29,54] Consistent with those findings, we also found that restricting our analysis thus strengthened the observed effect of environmental D across each cohort in all models. Note that since place of birth in SEER is derived from death certificate data and requires a lag of 15 to 20 years to be complete,[12,37] we restricted this sub analysis to patients diagnosed through 1997. These results are presented in Table 7.

With respect to the restricted prostate cohort (n=62,806) this substantially strengthened the effects of increasing VDR among patients residing in the all-urban areas observed in Model 1, with a 53% (95% CI: 0.41, 0.53) reduction in risk. In this model, only a minor increase in risk was observed with increasing VDR among patients residing at the least-urban areas (adj HR 1.16, 95% 1.12, 1.21) compared to the estimates we

presented in Table 2. Similarly, in our presumed long-term exposure Model 2, there was a 35% (95% CI: 1.25, 1.47) increase the hazard of death with increasing MM among patients residing in the all-urban areas, while little change was noted in risk among those residing in the least-urban areas. Similarly, the observed protective association of increasing VDR among patients residing in all-urban areas was strengthened in our restricted colon (n=16,410) and rectal (n=7,685) cohorts, both with adjusted Hazard ratios of 0.62 (95% CI, respectively: 0.51, 0.75; 0.48, 0.80). When minimum exposure minutes were used in the interaction (Model 2), the hazard of death also increased for colon (adj HR 1.26, 95% CI: 1.13, 1.40) and rectal (adj HR 1.22, 95% CI: 1.05, 1.42) cancer patients residing in all-urban areas. As with prostate cancer patients, the estimates obtained for colon and rectal cancer patients residing in the least-urban areas were little changed from those presented in Table 2 using either environmental D characterization.

Discussion

In this study we observed that increased levels of vitamin D radiation had a moderate protective association on survival for prostate and colon patients residing in all-urban areas. This effect was sometimes observed for rectal patients as well, but only when our analysis was restricted to presumed long-term exposure or when our alternative MM model was used. Furthermore, and of particular concern, we observed a lesser but consistent increase in the hazard of death associated with increasing VDR among patients residing in the least-urban areas in all three cancer cohorts. Our findings, then, differ from those reported in previous studies in several ways.

First, most U.S. based mortality studies have reported a protective association of high versus low environmental D exposure, [i.e.,4,29,31,38] typically with stronger reductions in mortality for colon or rectal cancers (i.e., 27%), than for prostate (10-17%).[4,29] None of these studies reported than an increase in risk that was associated with higher levels of environmental D. In this study, however, we observed a stronger protective association with increasing VDR among prostate cancer patients than those with colon or rectal cancers, which was limited to patients residing in all-urban areas. Notably, our study also found a consistent interaction between environmental D and urban level that was not identified in previous studies, though most did adjust for urban/rural status. In addition, one mortality study reported greater benefits for rectal cancer (53%) than for colon cancer (27%),[4] whereas in our study the benefit observed among colon cancer patients was the greater of the two.

There are a number of possible reasons for these differences between our results and those reported in previous studies. First, we are modeling survival and excluded patients with metastatic disease, which may have increased the estimated benefits on survival for increasing VDR that we reported among patients residing in all-urban areas. Our study design also allowed us to adjust for a number of individual patient characteristics including race and stage of cancer, whereas most other studies on this topic have not had this data. We also used estimates for vitamin D radiation[23] instead of the broader UV-B spectrum used in most earlier studies,[i.e.,4,29,31,38] which may have strengthened our results. Finally, we used 'county' instead of the broader geographic unit of 'state' to estimate vitamin D radiation levels, which likely reduced non-differential misclassification and strengthened our results.[96]

No other studies that the authors are aware of have reported an increase in risk associated with increasing vitamin D radiation exposure among patients in the least-urban areas. One much-discussed serum-based incidence study on prostate cancer by Tuohimaa et al. (2004), however, reported a u-shaped increase in risk that was associated with both high and low levels of blood vitamin D. The authors of that study concluded that "low vitamin D serum concentrations apparently leads to low tissue concentration and to weakened mitotic control of cells", while a higher serum and tissue concentration of vitamin D, on the other hand "may lead to vitamin D resistance", which ultimately might "enhance cancer development".[90] Our findings appear to more in keeping with this paper, though the consistent interaction we observed by urban level makes it difficult to distinguish the independent effects of environmental D on our study population. It has been well documented in other sources that urban areas are known for having much higher levels of pollution than rural areas, which can reduce the amount of available environmental D by as much a 50%.[23,57] Living in urban environments have also been associated with shifts in dietary practices, a greater amount of time spent indoors and/or less time doing physical activity, which have also been associated with an increased risk for both prostate and colorectal cancers. [69,79,80]

One interesting finding of our study was that Black-White differences in survival from prostate and colorectal cancer may be modestly associated with environmental D, particularly for patients residing in all-urban environments. Most previous studies that examined the association between solar radiation and prostate or colorectal cancer mortality were not successful in capturing Black/White differences in their relationship to environmental D.[25,41,42] In addition, we demonstrated that an environmental D

characterization using minimum minutes of exposure could be a useful compliment or alternative for investigating this relationship when the sample size of Blacks was small, making exposure estimates unstable in models using a separate variable for race.

It should be kept in mind that the values we assigned for the minimum minutes of exposure are likely to underestimate the exposure needs of the least sun-reactive individuals (i.e., non-Hispanic Blacks) by as much as 38%. To a lesser extent, the estimates for the most sun-reactive Skin Type (i.e., non-Hispanic Whites) may be overestimated by approximately 20%. Ideally, sun-reactive Skin Type should be measured at the individual level for patients included in a study. In the absence of this data from disease registries and given the importance of the issue, the approach taken in this paper seemed reasonable to use. We acknowledge, however, that race/ethnicity-based estimates may not be possible for groups other than non-Hispanic Whites and non-Hispanic Blacks, who tend to cluster at either end of the Fitzpatrick scale. It would be most advantageous if future studies obtained sun-reactivity data at the individual level as well as additional data on sun behavior activities, vitamin supplementation use, and urban residence.

Limitations

There were a number of obvious limitations to our study. First, we did not have individual data on sun behavior, diet, adiposity/BMI, or physical exercise which are known modifiers of vitamin D status.[48,91,95] However, in studies measuring a variety of individual modifiers, solar radiation levels in the area of residency played a much larger role in predicting vitamin D status than the factors listed above [i.e.,9,18,29,82,93] and this formed the basis of the exposure data used in our study. Furthermore, our study had

individual data on age, race and Hispanic ethnicity status as a proxy for sun-reactive Skin Type, which are among the most important individual variables that modify vitamin D exposure.[9,18,47,68]

We did not have information on vitamin D supplementation use and so ended our study in 2003, before its more widespread use that emerged later in that decade. [21,53,67] We also did not have information on individual sunscreen use, which has the potential to completely block cutaneous synthesis.[48] Most studies have found, however, that individuals do not apply sunscreen to all exposed areas or reapply it as recommended in order to block this route completely.[48,61] We also did not have individual data on smoking which could play a role in the development of fatal prostate[52] or rectal[5] cancers and is also known to reduce vitamin D levels,[6] although we did include an area-based lung cancer rate that has been used as a proxy for smoking in other studies.[i.e.,38] Finally, we did not have individual data on length at residency, which could lead to misclassification bias. First, if misclassification occurred, it seems most likely that it would be non-differential (random) and therefore underestimate any actual effect of exposure. Second, we conducted sensitivity analyses using both an individual measure that has been successfully used in other studies by restricting our analyses to individuals whose state of birth matched their state of death or state of current residence [29] as well as a census-based measure to evaluate county stability. The results of both of these sub analyses indicated that the estimates presented in Table 2 are likely to slightly underestimate any risks or benefits on survival associated with increasing VDR.

Conclusion

In conclusion, while the general importance of increasing our understanding of the association between vitamin D on prostate, colon and rectal cancer has been amply discussed elsewhere,[42,49] special attention needs to be given to addressing the role environmental sources may play in Black-White differences in survival. Furthermore, it may be of particular value to incorporate sun-reactive Skin Type data in future studies investigating vitamin D and cancer, since it is an important factor that mediates an individual's relationship to their environment. If the association with environmental D we reported among the least photo-sensitive (i.e., Blacks) is confirmed by subsequent studies, it may help researchers to clarify and isolate associations that have been more obliquely attributed to 'race/ethnicity' while giving medical practitioners a more usable basis for evaluating and communicating the attendant risks to their patients. Furthermore, additional studies are needed to clarify if there are risks associated with overexposure to the vitamin D spectrum, which we reported in our study for patients residing in the least-urban areas with apparently greater risks for non-Hispanic Whites than for non-Hispanic Blacks.

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Table 1: Patient tumor, socio-demographic and environmental D exposure characteristics of White and Black non-Hispanic males diagnosed with non-metastatic cancer from 1978 to 2003.

	Prostate Cohort (n=281,750)		**Colon Cohort (n=62,312)**		**Rectal Cohort (n=29,331)**	
	White	Black	White	Black	White	Black
Patient and tumor characteristics						
Number of cancer cases	*246,403*	*35,347*	*56,903*	*5,409*	*27,401*	*1,930*
5-year survival rate (KM)	0.94	0.93	0.77	0.71	0.72	0.64
10-year survival rate (KM)	0.86	0.84	0.69	0.64	0.62	0.55
Patient age at diagnosis (%)						
50 to <65	28.3	39.1	27.7	39.5	36.5	49.1
65 to < 74	42.8	40.7	35.7	35.2	36.4	31.5
75+	28.9	20.3	36.6	25.4	27.1	19.4
Married (%)	76.1	59.1	75.1	58.4	75.7	57.9
Year of diagnosis (%)						
1978-1987	16.9	13.3	33.3	26.3	35.7	26.4
1988-1997	46.3	43.7	40.4	41.2	38.7	41.7
1998-2003	36.8	43	26.2	32.5	25.6	31.9
Grade (%)						
1 (well differentiated)	15.6	12.8	13.6	14.1	12.1	9.9
2 (moderately differentiated)	60	60.7	57.1	60.7	58.8	56.6
3 (poorly differentiated)	18.8	20	13.5	9.5	12.6	11.2
4 (undifferentiated)	0.6	0.5	0.6	0.3	0.4	0.2
9 (not determined or stated)	5	6	15.2	15.4	16.1	22.1
Regional extension (%)	9.0	7.8	48.1	46.0	39.0	39.2
Positive nodes (%)	2.6	2.3	28.6	30.9	27.6	28.1
Surgery (%)	56.6	50.4	99.1	98.1	96.8	93.1
Radiotherapy (%)	35.1	35.8	2.6	2.4	31.9	34.9
Socio-demographic characteristics based on county of residence at diagnosis						
Percent urban in 1990 (%)						
Least-urban (<85%)	27.2	2.6	27.7	2.9	28.9	3.4
Mostly-urban (85% - <99%)	53.4	67.4	55.0	68.0	55.1	66.3
All-urban (99% or higher)	19.4	30.0	17.3	29.1	16.0	30.3
1990 Deprivation index (mean and 1 SD)	-0.1 (0.7)	0.7 (0.8)	-0.1 (0.7)	0.7 (0.8)	-0.1 (0.7)	0.7 (0.8)
Percent residing in same house or county in 1985 (mean and 1 SD)	78.7 (7.1)	81.8 (8.6)	79.4 (7.0)	81.9 (8.5)	79.6 (7.0)	81.8 (8.4)
Age-adjusted lung mortality rate 1975-2004 (mean and 1 SD)	247.3 (48.2)	354.0 (47.1)	253.6 (43.7)	356.0 (40.35)	254.3 (44.4)	354.7 (38.4)
Environmental D characteristics based on county of residence at diagnosis						
Vitamin D radiation level in Joules /m^2 (mean and 1 SD)	764.8 (199.0)	798.4 (194.5)	745.6 (187.0)	790.7 (191.2)	737.1 (184.4)	796.9 (192.4)
Minimum minutes of exposure (mean and 1 SD)	17.2 (8.5)	40.1 (17.1)	17.3 (7.7)	40.6 (16.7)	17.6 (7.7)	40.3 (17.0)

Notes: Abbreviations: KM = Kaplan Meier, SD= Standard Deviation.

Table 2. Hazard of death from disease with 10-year follow up among White and Black non-Hispanic males diagnosed with non-metastatic cancer from 1978 to 2003.

Model 0: NULL	**Prostate Cohort**	**Colon Cohort**	**Rectal Cohort**
Hazard of death from	prostate cancer	colon cancer	rectal cancer
Subjects(n)	*281,750*	*62,312*	*29,331*
Failures(n)	*29,697*	*16,261*	*9,644*
Time at risk (person-months)	*24,657,405*	*4,516,195*	*2,088,770*
Urban level			
Least-urban (referent)	1	1	1
Mostly-urban	0.98 (0.95, 1.00)	1.00 (0.96, 1.04)	0.98 (0.93, 1.03)
All-urban	0.85 (0.82, 0.89)	0.98 (0.93, 1.03)	0.96 (0.90, 1.03)
Black race (White=1)	1.29 (1.23, 1.35)	1.31 (1.23, 1.40)	1.31 (1.19, 1.44)
Deprivation index	1.01 (1.00, 1.02)	1.04 (1.02, 1.05)	1.02 (1.00, 1.05)
Proxy for smoking	1.02 (1.00, 1.03)	0.97 (0.95, 0.99)	0.99 (0.97, 1.02)

Model 1: VDR	**Prostate Cohort**	**Colon Cohort**	**Rectal Cohort**
Hazard of death from	prostate cancer	colon cancer	rectal cancer
Subjects(n)	*281,750*	*62,312*	*29,331*
Failures(n)	*29,697*	*16,261*	*9,644*
Time at risk (person-months)	*24,657,405*	*4,516,195*	*2,088,770*
VDR urban level*			
VDR * Least-urban	1.14 (1.11, 1.17)	1.10 (1.06, 1.15)	1.11 (1.06, 1.17)
VDR * Mostly-urban	1.00 (0.98, 1.02)	1.01 (0.98, 1.04)	1.02 (0.98, 1.06)
VDR * All-urban	0.74 (0.69, 0.80)	0.83 (0.75, 0.91)	0.97 (0.85, 1.11)
Black race (White=1)	1.23 (1.18, 1.29)	1.27 (1.18, 1.35)	1.26 (1.15, 1.39)
Deprivation index	0.99 (0.98, 1.10)	1.02 (1.00, 1.04)	1.00 (0.98, 1.03)
Proxy for smoking	1.06 (1.04, 1.07)	0.99 (0.98, 1.05)	1.02 (0.99, 1.05)

Model 2: MM	**Prostate Cohort**	**Colon Cohort**	**Rectal Cohort**
Hazard of death from	prostate cancer	colon cancer	rectal cancer
Subjects(n)	*281,750*	*62,312*	*29,331*
Failures(n)	*29,697*	*16,261*	*9,644*
Time at risk (person-months)	*24,657,405*	*4,516,195*	*2,088,770*
*MM * urban level*			
MM * Least-urban	0.84 (0.81, 0.86)	0.92 (0.89, 0.96)	0.91 (0.87, 0.96)
MM * Mostly-urban	1.01 (0.99, 1.03)	1.02 (1.00, 1.04)	1.01 (0.98, 1.04)
MM * All-urban	1.15 (1.09, 1.22)	1.20 (1.12, 1.29)	1.15 (1.04, 1.27)
Deprivation index	1.01 (0.99, 1.02)	1.04 (1.02, 1.06)	1.02 (1.00, 1.05)
Proxy for smoking	1.07 (1.05, 1.08)	0.99 (0.97, 1.01)	1.02 (0.99, 1.05)

Notes: Stratified by treatment (radiotherapy, surgery), extent of disease (positive nodes, regional extension), grade, and marital status and adjusted for age and period of diagnosis, smoking, deprivation, proximal/distal location (colon only) and other variables in tables. All continuous variables are mean centered and divided by 1 standard deviation. Average month VDR: Mean = ~ 750 J/m^2 ; Per unit VDR = ~ 190 J/m^2 ; Average month MM: Mean =~ 19.5; Per unit MM = ~ 11.0 MM; Urban level: Least-urban: <85%; mostly-urban 85-99%; All-urban = 99% or more. For detailed values by cohort, see the Appendix.

Table 3. Hazard of death from disease with 10-year follow up by race, for White and Black non-Hispanic males diagnosed with non-metastatic cancer from 1978 to 2003.

Model 1: VDR – Whites only	**Prostate Cohort**	**Colon Cohort**	**Rectal Cohort**
Hazard of death from	prostate cancer	colon cancer	rectal cancer
Subjects(n)	*246,403*	*56.903*	*27,401*
Failures(n)	*25,503*	*14,631*	*8,909*
Time at risk (person-months)	*21,681,384*	*4,145,820*	*1,962,991*
VDR urban level*			
VDR * Least-urban	1.15 (1.12, 1.19)	1.10 (1.06, 1.15)	1.11 (1.06, 1.17)
VDR * Mostly-urban	0.99 (0.97, 1.02)	1.01 (0.98, 1.04)	1.01 (0.98, 1.05)
VDR * All-urban	0.74 (0.69, 0.80)	0.83 (0.75, 0.92)	0.94 (0.82, 1.09)
Deprivation index	0.99 (0.97, 1.00)	1.02 (1.00, 1.04)	1.00 (0.97, 1.03)
Proxy for smoking	1.07 (1.05, 1.09)	0.99 (0.97, 1.02)	1.02 (0.99, 1.05)

Model 1: VDR – Blacks only	**Prostate Cohort**	**Colon Cohort**	**Rectal Cohort**
Hazard of death from	prostate cancer	colon cancer	rectal cancer
Subjects(n)	*35,347*	*5,409*	*1,930*
Failures(n)	*4,194*	*1,630*	*736*
Time at risk (person-months)	*2,976,021*	*370.375*	*125,779*
VDR urban level*			
VDR * Least-urban	0.97 (0.81, 1.16)	1.12 (0.84, 1.48)	1.16 (0.69, 1.96)
VDR * Mostly-urban	1.08 (1.02, 1.14)	1.03 (0.94, 1.12)	1.06 (0.93, 1.22)
VDR * All-urban	0.64 (0.52, 0.80)	0.74 (0.54, 1.03)	1.04 (0.61, 1.78)
Deprivation index	1.01 (0.97. 1.05)	1.06 (1.00, 1.12)	1.05 (0.95, 1.16)
Proxy for smoking	0.99 (0.94, 1.05)	0.97 (0.90, 1.04)	0.92 (0.80, 1.07)

Notes: Stratified by treatment (radiotherapy, surgery), extent of disease (positive nodes, regional extension), grade, and marital status and adjusted for age and period of diagnosis, smoking, deprivation, proximal/distal location (colon only) and other variables in tables. All continuous variables are mean centered and divided by 1 standard deviation. Average month VDR: Mean = ~ 750 J/m^2 ; Per unit VDR = ~ 190 J/m^2 ; Average month MM: Mean =~ 19.5; Per unit MM = ~ 11.0 MM; Urban level: Least-urban: <85%; mostly-urban 85-99%; All-urban = 99% or more. For detailed values by cohort, see the Appendix.

Table 4. Hazard of death from competing risks with 10-year follow up among White and Black non-Hispanic males diagnosed with non-metastatic cancer from 1978 to 2003.

Model 1: NULL, Competing Risks	**Prostate Cohort**	**Colon Cohort**	**Rectal Cohort**
Hazard of death from	cause other than prostate cancer	cause other than colon cancer	cause other than rectal cancer
Subjects(n)	*281,750*	*62,312*	*29,331*
Failures(n)	*16,317*	*13,413*	*7,703*
Time at risk (person-months)	*15,204,956*	*2,889,064*	*1,353,560*
Urban level			
Least-urban (referent)	1	1	1
Mostly-urban	0.96 (0.95, 0.98)	0.97 (0.94, 1.01)	0.97 (0.92, 1.02)
All-urban	0.91 (0.89, 0.93)	1.00 (0.95, 1.04)	0.98 (0.90, 1.06)
Black race (White=1)	1.08 (1.05, 1.11)	1.00 (0.94, 1.07)	1.02 (0.91, 1.14)
Deprivation index	1.03 (1.02, 1.04)	1.02 (1.01, 1.04)	1.03 (1.01, 1.06)
Proxy for smoking	1.06 (1.05, 1.07)	1.06 (1.04, 1.08)	1.06 (1.03, 1.10)

Model 1: VDR, Competing Risks	**Prostate Cohort**	**Colon Cohort**	**Rectal Cohort**
Hazard of death from	cause other than prostate cancer	cause other than colon cancer	cause other than rectal cancer
Subjects(n)	*281,750*	*62,312*	*29,331*
Failures(n)	*16,317*	*13,413*	*7,703*
Time at risk (person-months)	*15,204,956*	*2,889,064*	*1,353,560*
*VDR * urban level*			
VDR * Least-urban	1.01 (0.99, 1.03)	0.97 (0.93, 1.00)	0.99 (0.94, 1.05)
VDR * Mostly-urban	0.97 (0.96, 0.99)	0.96 (0.94, 0.99)	0.96 (0.93, 1.00)
VDR * All-urban	0.88 (0.84, 0.92)	1.00 (0.92, 1.10)	0.92 (0.80, 1.07)
Black race (White =1)	1.08 (1.05, 1.11)	1.03 (0.96, 1.10)	1.04 (0.92, 1.16)
Deprivation index	1.03 (1.02, 1.04)	1.03 (0.96, 1.10)	1.04 (1.01, 1.07)
Proxy for smoking	1.06 (1.05, 1.08)	1.04 (1.02, 1.06)	1.05 (1.02, 1.09)

Model 2: MM, Competing Risks	**Prostate Cohort**	**Colon Cohort**	**Rectal Cohort**
Hazard of death from	cause other than prostate cancer	cause other than colon cancer	cause other than rectal cancer
Subjects(n)	*281,750*	*62,312*	*29,331*
Failures(n)	*16,317*	*13,413*	*7,703*
Time at risk (person-months)	*15,204,956*	*2,889,064*	*1,353,560*
*MM * urban level*			
MM * Least-urban	0.98 (0.96, 0.99)	1.01 (0.98, 1.05)	0.98 (0.93, 1.04)
MM * Mostly-urban	1.02 (1.01, 1.03)	1.01 (0.99, 1.03)	1.02 (0.99, 1.05)
MM * All-urban	1.06 (1.03, 1.10)	0.95 (0.89, 1.02)	1.02 (0.91,1.15)
Deprivation index	1.03 (1.02, 1.04)	1.02 (1.00, 1.04)	1.03 (1.01, 1.06)
Proxy for smoking	1.07 (1.06, 1.08)	1.06 (1.04, 1.08)	1.06 (1.03, 1.09)

Notes: Stratified by treatment (radiotherapy, surgery), extent of disease (positive nodes, regional extension), grade, and marital status and adjusted for age and period of diagnosis, smoking, deprivation, proximal/distal location (colon only) and other variables in tables. All continuous variables are mean centered and divided by 1 standard deviation. Average month VDR: Mean = ~ 750 J/m^2 ; Per unit VDR = ~ 190 J/m^2 ; Average month MM: Mean =~ 19.5; Per unit MM = ~ 11.0 MM; Urban level: Least-urban: <85%; mostly-urban 85-99%; All-urban = 99% or more. For detailed values by cohort, see the Appendix.

Table 5. Hazard of death from disease with 10-year follow up in White and Black non-Hispanic males diagnosed with non-metastatic cancer from 1978 to 2003, using June or December exposure values.

Model 1: June VDR	**Prostate Cohort**	**Colon Cohort**	**Rectal Cohort**
Hazard of death from	prostate cancer	colon cancer	rectal cancer
Subjects(n)	*281,750*	*62,312*	*29,331*
Failures(n)	*29,697*	*16,261*	*9,644*
Time at risk (person-months)	*24,657,405*	*4,516,195*	*2,088,770*
*June VDR * urban level*			
June VDR * Least-urban	1.13 (1.10, 1.16)	1.10 (1.06, 1.15)	1.11 (1.05, 1.17)
June VDR * Mostly-urban	0.99 (0.97, 1.01)	1.01 (0.98, 1.03)	1.01 (0.98, 1.05)
June VDR * All-urban	0.49 (0.40, 0.58)	0.63 (0.49, 0.82)	0.91 (0.63, 1.30)
Black race (White =1)	1.23 (1.18, 1.29)	1.26 (1.18, 1.35)	1.26 (1.15, 1.39)
Deprivation index	0.99 (0.98, 1.01)	1.02 (1.00, 1.04)	1.00 (0.98, 1.03)
Proxy for smoking	1.06 (1.04, 1.08)	1.00 (0.97, 1.02)	1.02 (0.99, 1.05)

Model 2: December MM	**Prostate Cohort**	**Colon Cohort**	**Rectal Cohort**
Hazard of death from	prostate cancer	colon cancer	rectal cancer
Subjects(n)	*281,750*	*62,312*	*29,331*
Failures(n)	*29,697*	*16,261*	*9,644*
Time at risk (person-months)	*24,657,405*	*4,516,195*	*2,088,770*
*Dec MM * urban level*			
Dec MM * Least-urban	0.85 (0.83, 0.87)	0.93 (0.90, 1.04)	0.92 (0.88, 0.96)
Dec MM * Mostly-urban	0.99 (0.97, 1.01)	1.01 (0.99, 1.03)	1.00 (0.97, 1.03)
Dec MM * All-urban	1.25 (1.17, 1.34)	1.29 (1.18, 1.42)	1.18 (1.03, 1.35)
Deprivation index	1.01 (1.00, 1.03)	1.05 (1.03, 1.07)	1.03 (1.00, 1.05)
Proxy for smoking	1.07 (1.06, 1.09)	1.00 (0.98, 1.02)	1.03 (1.00, 1.05)

Notes: Stratified by treatment (radiotherapy, surgery), extent of disease (positive nodes, regional extension), grade, and marital status and adjusted for age and period of diagnosis, smoking, deprivation, proximal/distal location (colon only) and other variables in tables. All continuous variables are mean centered and divided by 1 standard deviation. June VDR: Mean = ~ 1295 J/m^2 ; Per unit VDR = ~ 235 J/m^2 ; December MM: Mean = ~ 55.3 MM; Per unit MM = ~ 38. Urban level: Least-urban: <85%; mostly-urban 85-99%; All-urban = 99% or more. For detailed values by cohort, see the Appendix.

Table 6: Hazard of death from disease with 5-year of follow up among White and Black non-Hispanic males diagnosed with non-metastatic cancer from 1978 to 2003.

Model 1: VDR	**Prostate Cohort**	**Colon Cohort**	**Rectal Cohort**
Hazard of death from	prostate cancer	colon cancer	rectal cancer
Subjects(n)	*281,750*	*62,312*	*29,331*
Failures(n)	*16,317*	*13,413*	*7,703*
Time at risk (person-months)	*15,204,956*	*2,889,064*	*1,353,560*
*VDR * urban level*			
VDR * Least-urban	1.16 (1.12, 1.20)	1.11 (1.06, 1.15)	1.13 (1.07, 1.20)
VDR * Mostly-urban	1.00 (0.98, 1.03)	1.02 (0.99, 1.05)	1.02 (0.98, 1.06)
VDR * All-urban	0.68 (0.62, 0.75)	0.78 (0.70, 0.87)	0.93 (0.80, 1.07)
Black race (White =1)	1.23 (1.16, 1.30)	1.27 (1.18, 1.37)	1.31 (1.17, 1.45)
Deprivation index	1.00 (0.98, 1.02)	1.03 (1.00, 1.05)	1.00 (0.97, 1.03)
Proxy for smoking	1.06 (1.04, 1.08)	1.00 (0.98, 1.02)	1.02 (0.99, 1.05)

Model 2: MM	**Prostate Cohort**	**Colon Cohort**	**Rectal Cohort**
Hazard of death from	prostate cancer	colon cancer	rectal cancer
Subjects(n)	*281,750*	*62,312*	*29,331*
Failures(n)	*16,317*	*13,413*	*7,703*
Time at risk (person-months)	*15,204,956*	*2,889,064*	*1,353,560*
*MM * urban level*			
MM * Least-urban	0.81 (0.78, 0.85)	0.92 (0.88, 0.96)	0.90 (0.85, 0.95)
MM * Mostly-urban	1.01 (0.99, 1.03)	1.02 (1.00, 1.04)	1.02 (0.98, 1.05)
MM * All-urban	1.15 (1.07, 1.23)	1.23 (1.14, 1.32)	1.19 (1.07, 1.33)
Deprivation index	1.01 (0.99, 1.03)	1.04 (1.02, 1.07)	1.03 (1.00, 1.06)
Proxy for smoking	1.07 (1.05, 1.09)	1.00 (0.97, 1.02)	1.02 (0.99, 1.05)

Notes: Stratified by treatment (radiotherapy, surgery), extent of disease (positive nodes, regional extension), grade, and marital status and adjusted for age and period of diagnosis, smoking, deprivation, proximal/distal location (colon only) and other variables in tables. All continuous variables are mean centered and divided by 1 standard deviation. Average month VDR: Mean = ~ 750 J/m^2 ; Per unit VDR = ~ 190 J/m^2 ; Average month MM: Mean =~ 19.5; Per unit MM = ~ 11.0 MM; Urban level: Least-urban: <85%; mostly-urban 85-99%; All-urban = 99% or more. For detailed values by cohort, see the Appendix.

Table 7: Hazard of death from disease with 10-year follow up in White and Black non-Hispanic males diagnosed with non-metastatic cancer from 1978 to 1997 with presumed long-term exposure.

Model 1: VDR	**Prostate Cohort**	**Colon Cohort**	**Rectal Cohort**
Hazard of death from	prostate cancer	colon cancer	rectal cancer
Subjects(n)	*62,806*	*16,410*	*7,685*
Failures(n)	*10,415*	*5,220*	*3,064*
Time at risk (person-months)	*5,320,098*	*1,127,563*	*514,918*
*VDR * urban level*			
VDR * Least-urban	1.16 (1.12, 1.21)	1.15 (1.09, 1.22)	1.13 (1.05, 1.22)
VDR * Mostly-urban	1.04 (1.01, 1.08)	1.01 (1.06, 1.15)	1.07 (1.01, 1.13)
VDR * All-urban	0.47 (0.41, 0.53)	0.62 (0.51, 0.75)	0.62 (0.48, 0.80)
Black race (White =1)	1.25 (1.16, 1.34)	1.20 (1.07, 1.33)	1.20 (1.03, 1.40)
Deprivation index	1.00 (0.98, 1.03)	1.00 (0.96, 1.03)	1.01 (0.96, 1.06)
Proxy for smoking	1.05 (1.02, 1.08)	1.03 (0.99, 1.07)	1.05 (0.99, 1.11)

Model 2: MM	**Prostate Cohort**	**Colon Cohort**	**Rectal Cohort**
Hazard of death from	prostate cancer	colon cancer	rectal cancer
Subjects(n)	*62,806*	*16,410*	*7,685*
Failures(n)	*10,415*	*5,220*	*3,064*
Time at risk (person-months)	*5,320,098*	*1,127,563*	*514,918*
*MM * urban level*			
MM * Least-urban	0.82 (0.79, 0.86)	0.88 (0.82, 0.93)	0.92 (0.85, 0.99)
MM * Mostly-urban	1.02 (0.99, 1.04)	1.00 (0.97, 1.03)	1.00 (0.96, 1.04)
MM * All-urban	1.35 (1.25, 1.47)	1.26 (1.13, 1.40)	1.22 (1.05, 1.42)
Deprivation index	1.02 (1.00, 1.05)	1.02 (0.99, 1.05)	1.03 (0.99, 1.08)
Proxy for smoking	1.04 (1.01, 1.07)	1.01 (0.97, 1.05)	1.03 (0.98, 1.08)

Notes: Stratified by treatment (radiotherapy, surgery), extent of disease (positive nodes, regional extension), grade, and marital status and adjusted for age and period of diagnosis, smoking, deprivation, proximal/distal location (colon only) and other variables in tables. All continuous variables are mean centered and divided by 1 standard deviation. Average month VDR: Mean = ~ 750 J/m^2 ; Per unit VDR = ~ 190 J/m^2 ; Average month MM: Mean =~ 19.5; Per unit MM = ~ 11.0 MM; Urban level: Least-urban: <85%; mostly-urban 85-99%; All-urban = 99% or more. For detailed values by cohort, see the Appendix.

VITAMIN D ULTRAVIOLET RADIATION, DISPARITIES AND MULTIPLE PRIMARY CANCERS IN COLORECTAL AND PROSTATE PATIENTS

By AMY E. ABRUZZI

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VITAMIN D ULTRAVIOLET RADIATION, DISPARITIES AND MULTIPLE PRIMARY CANCERS IN COLORECTAL AND PROSTATE PATIENTS

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ABSTRACT

Researchers have studied vitamin D as a protective factor for colorectal and prostate cancer incidence and mortality for over 20 years; in this study, we apply the vitamin D hypothesis to the occurrence of these cancers together in the same individual as multiple primary cancers (MPCs). White and Black male patients aged 50 years and over who were diagnosed with a non-metastatic first primary colon, rectal or prostate cancer from 1978 to 2003 were drawn from the National Cancer Institute's Surveillance, Epidemiology and End results database and followed for development of a subsequent primary cancer. Using data from Environment Canada, vitamin D effective radiation exposure levels were estimated based on county of residence at diagnosis for the first primary cancer. A proxy for smoking based on county Lung mortality rates and a socio-economic deprivation index was also used. The analysis involved the use of multivariate logistic regression as well as a competing risk Cox Proportional Hazards model adjusted for age, extent of disease, radiotherapy treatment and other factors.

Based on the competing risk analysis, we found that Blacks have a much greater risk of rectal-prostate and colon-prostate MPCs overall, with the highest adjusted sub hazard ratios (respectively: SHR 3.17, 95% CI 1.97, 5.11; SHR 2.10, 95% CI 1.62, 2.71) observed after 10 years of follow up. Higher levels of vitamin D radiation also appear to

decrease the risk for rectal-prostate and colon-prostate during this period. Increasing levels of socio-economic deprivation and/or our proxy for smoking were associated with increased risk of all MPC pairings during one or more follow up periods beginning with the first year, sometimes with interaction. Finally, as reported in other studies, patients who received radiotherapy were at increased risk of prostate-rectal or prostate-colon MPCs after 5 years of follow up, with the highest adjusted sub-hazard ratios (respectively: SHR 2.40, 95% CI: 1.89, 3.05; SHR 1.29, 95% CI: 1.10, 1.51) observed after year 10. Conversely, radiotherapy was associated with a decreased risk for rectal-prostate MPCs for most follow up periods, ranging from years >1 to 5 (SHR 0.33, 95% CI: 0.25, 0.44) to >5 to 10 years (SHR 0.70, 95% CI: 0.54, 0.91).

ABBREVIATIONS USED

adj - adjusted

CI – Confidence Interval

HR – Hazard Ratio

I.U. – International Units

J/m^2 – Joules per square meter

KM – Kaplan Meier

MM – minimum minutes of exposure time

MPC – Multiple Primary Cancer

OR – Odds Ratio

SD – Standard Deviation

SEER – Surveillance, Epidemiology, and End Results

SHR – Sub Hazard Ratio

VDR – vitamin D effective radiation

VITAMIN D ULTRAVIOLET RADIATION, DISPARITIES AND MULTIPLE PRIMARY CANCERS IN COLORECTAL AND PROSTATE PATIENTS

Introduction

Research on multiple primary cancers ("MPCS") has generated considerable interest in recent years, due in part to the increasing number and longevity of cancer survivors and their disproportionate risks for distinctive types of additional primary tumors. [12,31,57,58,63,69] Some MPCs occur as the result of prior treatment from the first cancer, but most are thought to arise from shared biological pathways of tumor development in conjunction with lifestyle, environment, and genetic factors.[57,58,63,69] Defects or reductions in DNA repair capacity and/or cell apotopsis are likely to play an important role.[41,69] Identifying factors that are valuable for chemoprevention, screening, and patient follow up is of high priority; currently, there is a special interest in identifying the relative contributions of environmental exposures and patient demographics to the increased risk of common MPC pairs.[41,69] This is particularly challenging for MPCs given that they are best studied as pairs; yet, any particular pair is a relatively rare occurrence.

In the U.S., analyses of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) cancer registry have found a greater than expected frequency of colorectal-prostate* and prostate-colorectal* MPCs among certain age groups[1,3,38,47,53] and among African Americans.[3] A higher frequency of this cancer pair has also been observed in several other countries, including Sweden,[16] Switzerland[61] and Australia.[51] Geographic differences in the frequencies of MPCs occurring within countries have not been analyzed in these studies; nor have most examined the data for

racial disparities, which are likely to be present.[2,19] Treatment effects have been fairly well studied for this MPC pair, with modest but inconsistent risks for colorectal tumors following radiotherapy for primary prostate cancer. [i.e.,1,50,59]

Most prostate-colorectal and colorectal-prostate MPCs are diagnosed within a few years of one another, [3,38,47,53] which is indicative of a shared etiology or biological pathway other than a treatment effect. [1,59,63,69] Genetic links have been explored for both prostate and colorectal cancers, such as a possible BRCA1 associated syndrome, but so far the findings have been inconsistent.[63] One hospital-based study following primary prostate cancer patients treated by radical prostatectomy found that colorectal cancer was the leading cause of death among all other subsequent primary cancers.[25] A shared nutritional or hormonal link for prostate-colorectal MPCs was proposed in the late 1980s but has been little investigated since.[62]

For more than 20 years vitamin D has been studied separately as a protective factor for both colorectal cancer and prostate cancer,[i.e.,26,30,64] though this hypothesis has yet to be explored for MPC development.† More accurately described as a steroid hormone, vitamin D plays an active role in regulating cell growth and the cell cycle, with anti-proliferation, pro-differentiation, and pro-apoptosis effects that are central to cancer prevention.[33-35,39,45] Additional roles in cell signaling pathways, DNA repair and immune modulation have also been identified.[33-35,39,45] Solar exposure to the vitamin D action spectrum contained in ultraviolet-B radiation ("environmental D") is the primary source of human vitamin D, which is synthesized by the skin and subsequently converted through a complex multi-organ pathway into its bioactive form.[18,33] Bioactive D (also known as calcitriol) works by binding with the Vitamin D Receptors found in cells,

which are present in a wide range of organs.[33,35,39] It is well established that the conversion to bioactive D occurs in kidneys; it also appears that this conversion occurs in extra-renal organs and that this activity is central to its site-specific, anti-cancer actions.[39,45]

In this paper, a cohort of non-Hispanic White and Black male patients who were diagnosed from 1978 to 2003 with a non-metastatic first primary colorectal or first primary prostate tumor were drawn from a population based cancer registry and followed through 2008 for the development of the MPC pair of interest; these patients were then compared by clinical characteristics, county level environmental D and other factors including a proxy for smoking using a multivariate Cox model adjusted for the competing risk of death in our patients.[20]

* Prostate-colorectal indicates primary prostate cancer followed by primary colorectal cancer, while colorectal-prostate indicates primary colorectal cancer followed by primary prostate cancer. Both are meant to include both synchronically (concurrently) as well as metachronically (subsequently) diagnosed primary tumors. Within this paper, synchronic will be defined as tumors diagnosed within 2 months of each other.[11,12] Tumors diagnosed more than 2 months after the first primary cancer will be considered metachronic. This is not meant to indicate origin, as metachronic tumors may have a synchronous (shared) origin.[11]

†Some studies have examined patterns of individual primary tumor development following non-melanoma skin cancer in which skin cancer is assumed to be a marker of high cutaneous vitamin D exposure.[70] The co-occurrence of colorectal-prostate MPCs is not examined in these studies, nor is any other indicator of vitamin D status or exposure included. These studies may be problematic in a number of their assumptions about exposure; they also overlook the likelihood of a change in sun exposure behavior after the diagnosis of skin cancer which may actually increase the risk for either prostate or colorectal cancer.

Data Sources

The data sources used in this analysis have been described in more detail elsewhere.[2]

Study Population

The National Cancer Institute's SEER database was the source of our patient data,[55] which has been used extensively in the study of MPCs.[i.e.,1,7,12,38] White and Black

male patients aged 50 years and over were included if they were diagnosed with a histologically confirmed, first primary colorectal or prostate cancer between 1978 and 2003. Patients were excluded if they had missing or unknown data on age at diagnosis, race/ethnicity, county of residence at diagnosis, treatment or extent of disease status, were diagnosed at autopsy or by death certificate only, or had survival time greater than zero. Site-specific SEER Extent of Disease fields were used to identify and exclude any patients with distant lymph nodes or metastatic cancer from the cohorts as well as to identifying patients with positive regional lymph node involvement or regional extension. For colorectal patients, this was defined as extension into the serosa; for prostate patients, where disease had spread beyond the prostate capsule. In addition, we also categorized our colon patients by proximal (the cecum, appendix, ascending colon, hepatic flexure, transverse colon and splenic flexure) and distal (descending colon, sigmoid colon, and large intestine).

For this analysis, members of each cohort were searched using the unique numeric identifier assigned to each patient in the SEER database to locate additional malignancies. Individuals diagnosed with both primary prostate and either primary colon or primary rectal cancer will be referred to as having an MPC pair of interest and form the basis for this analysis. Males with first primary prostate cancer were identified as having an MPC pair of interest if they were diagnosed with synchronic or metachronic primary colon or primary rectal cancer before November 1, 2008; individuals without another recorded primary cancer in the SEER database as of this date were assumed not to have had one. Similarly, patients with first primary colon or first primary rectal cancer

were identified as having an MPC pair of interest if they were diagnosed with synchronic or metachronic primary prostate cancer during the follow up period.

Relevant information was extracted from SEER including date of diagnosis, histological confirmation, stage, and grade of the subsequent primary tumor. Follow up time was defined as time from date of the first primary cancer diagnosis to either the date of diagnosis of the subsequent primary cancer, the date of last follow up, or the date of death, whichever occurred first as measured in months. Patients were excluded if the date of their subsequent primary tumor preceded the date of the first in the SEER registry, which resulted in the exclusion of 352 prostate-colon, 188 prostate-rectal, 10 colon-prostate, and 5 rectal-prostate cases from the Cox analysis.

Environmental D exposure and other county-level covariates

Two types of environmental D exposure characterizations were estimated for each SEER county included in the study using the *Vitamin D Action Spectrum-Weighted UV Climatology for North America* from Environment Canada.[21] The first type was the mean monthly vitamin D radiation (VDR) in Joules per square meter (J/m^2) at the noon hour, noon representing the hour of the day when the time needed for exposure is shortest.[21] This measure was applied to each patient based on their county of residence at the diagnosis of their first primary cancer. For the second type, the minimum minutes of exposure time (MM) required to acquire sufficient Vitamin D radiation to synthesize a standard dermal dose of vitamin D using the face, hands and arms without erythemal damage were estimated for each patient based on their race/ethnicity and county of residence. Our estimates were constructed using the data on Fitzpatrick sun-reactive Skin Types[23] present in the Environment Canada dataset[21] which we then averaged over the

Types most often associated with non-Hispanic Whites (i.e., Types I-III) and non-Hispanic Blacks (Types IV-VI) in other U.S. based studies.[9,42] This measure offers an alternative way to examine this effect that researchers and clinicians may find practical.

Since the geographic and racial distribution of prostate and colorectal cancer in the U.S. may be associated with poverty or other indicators of economic deprivation;[14,15,46,48] we constructed and included a county-level socio-economic deprivation index for use in our study following the recommended methods.[40,49,66] In addition, race-specific county lung cancer mortality rates[54] were obtained from the National Cancer Institute and used as a proxy for individual smoking, which has been associated with rectal cancer and fatal prostate cancer in some studies and is also known to reduce vitamin D.[6,8,37] This study was approved by the UMDNJ IRB (July 2012).

Statistical Analysis

The primary outcome of our study was the development of a primary colon or rectal cancers following a diagnosis of primary prostate cancer (i.e., prostate-colorectal MPCs) or the development of primary prostate cancer following a diagnosis of primary colon or rectal cancer (i.e., colorectal-prostate MPCs). The primary exposure of interest was environmental D and race, adjusted for other tumor and socio-demographic factors. Our primary hypothesis is that patients residing in areas with higher vitamin D radiation levels will have a lowest risk of MPCs. In addition, Blacks will have a higher risk of MPCs than Whites, which is associated with their greater environmental D exposure needs.

Two characterizations were used and compared in separate models for environmental D: vitamin D radiation levels with a separate variable for race vs. our

race-based minimum minutes of exposure. Our main analysis focused on the development of multivariate Cox Proportional Hazards models for each cohort using the method of Fine and Gray[20] that estimated the sub-hazard ratio (risk) of MPC development, and treated the risk of death as a competing risk.[4,10,68] In addition, multivariate logistic regression was used to examine predictors of radiotherapy status and also to estimate the odds of being diagnosed with an MPC over the entire follow up period adjusted for other covariates.[36] Although multivariate logistic regression has not been heavily used in MPC analyses to date, it seemed appropriate for use in this analysis since we were analyzing a rare outcome of patients within a population based study and wished to adjust for a number of variables in our estimates before proceeding with our main analysis.

The preliminary competing risk Cox model for each cohort included all relevant covariates, with continuous variables centered around their mean and divided by 1 standard deviation. The distribution of our data and assumptions of log-linearity were conducted. The differences in risk estimated between colon and rectal cancers for several variables made them desirable to treat separately with our analyses. In general, we retained all variables of clinical significance or any coefficient with a P value less than 0.05. Interactions were then examined, and highly significant ($p<0.0001$) interactions between disparities and our proxy for smoking were identified in several models. The assumption of proportional hazards was assessed for all the covariates for our models by running an extended competing risk Cox model that checked each variable for its possible interaction with time. The interaction of radiotherapy status with time in both cohorts necessitated stratifying our results by period into early (0 -1 year, >1-5 year) and

late (>5-10 year, >10 year) MPCs. These stratifications also offer a reasonable comparison of our results with previous MPC studies examining treatment effects.[i.e.,1,3,13,38] No other variables violating the proportional hazard assumption were identified within these strata. All analyses were conducted using Stata/MP 12. [10,67]

Results

Table 1 presents the baseline characteristics of our first primary cohorts, including the proportion of those patients who were diagnosed with the MPC pairs of interest for our analysis. A greater proportion of first primary colon and rectal cancer patients were diagnosed with 2 or more MPCs in any organ compared with first primary prostate cancer patients, where approximately 25%, 21% and 16% (respectively) experienced a subsequent primary tumor with variations noted by race. For our MPC pairs of interest, Blacks had a greater percentage of prostate-colorectal and colorectal-prostate tumors than Whites, while having a lower rate of 5-year and 10-year survival depending on the first primary cancer.

Tables 2 through 8 present the main findings of our analysis, and are discussed in conjunction with each other topically below. Table 2 presents the adjusted odds of being diagnosed with the MPC pair of interest over the entire follow up period of our study, adjusted for baseline first primary cancer factors and county level covariates including VDR as our environmental D characterization. Tables 3 through 8 display the results of our competing risk multivariate Cox regression analyses, which are arranged by MPC pair and stratified into early (within 1 year, >1-5 years) and late (>5-10 years, >10 years) subsequent primary tumors based on the lag time in diagnosis from the first primary tumor. The models presented in Tables 3 and 4 present a non-exposure ("null

model") adjusted for the same covariates as the models including VDR presented in Tables 5 and 6. Unless otherwise specified, all of the estimates discussed in the follow section are drawn from Tables 2, 5 and 6. In addition, an alternative characterization using the minimum minutes of exposure to capture the joint effects of race/ethnicity and vitamin D radiation levels are presented in Tables 7 and 8.

Key Findings:

1. *Blacks were at much higher risk of developing rectal-prostate or colon-prostate MPCs than Whites; Blacks were also at increased risk of developing prostate-colon MPCs during some follow up periods.*

Our analyses indicated that with one exception, Blacks had a much higher risk of being diagnosed with an MPC pair of interest. Of note, Blacks with a first primary rectal cancer were at considerably higher risk (adjusted OR 2.40, 95% CI 1.93, 2.98) of being diagnosed with a subsequent primary prostate tumor across the entire follow up period. The risk was highest during the first year of follow up (SHR: 2.97, 95% CI: 1.92, 4.59) and again after year 10 (SHR: 3.17, 95% CI: 1.97, 5.11). Blacks with first primary colon cancer also had a higher risk of being diagnosed with a subsequent primary prostate cancer over the entire follow up period, with an adjusted OR 1.80 (95% CI: 1.59, 2.04). Unlike the pattern observed following primary rectal cancer, the risk of colon-prostate MPCs increased steadily over time between the first year of follow up (SHR 1.61, 95% CI: 1.21, 2.15) and after year 10 (SHR 2.10, 95% CI: 1.62, 2.71).

A somewhat different pattern was observed for prostate-colon and prostate-rectal MPCs. Among patients in our first primary prostate cohort, Blacks had a modest (adj OR 1.18, 95% CI: 1.07, 1.30) increase in the risk of developing a subsequent primary colon tumor, with the highest risk occurring during years >1 to 5 (SHR: 1.32, 95% CI:

1.15, 1.52) and year >5 to 10 (SHR: 1.28, 95% CI: 1.08, 1.51). Interestingly, a lower risk for Blacks for prostate-rectal MPCs was observed during follow up years >5 to 10 (SHR 0.72, 95% CI: 0.52, 0.99); no significant differences between Blacks and Whites for prostate-rectal MPCs were observed during the other follow up periods in this study.

2. *Increasing levels of vitamin D radiation were mildly protective for late colon-prostate or rectal-prostate MPCs; this benefit does not appear to be shared equally among Black and White patients.*

As presented in Table 2, increasing levels of VDR (1 unit = ~ 190 J m^{-2}) among first primary colon and first primary rectal patients were associated with a 9% (adj OR 0.91, 95% CI: 0.88, 0.95) and 10% (adj OR 0.90, 95% CI: 0.84, 0.96) reduction in the risk of being diagnosed with a subsequent primary prostate cancer across the entire follow up period. As presented in Tables 5 and 6, the greatest benefit was observed after year 5 for first primary rectal patients and after year 10 for first primary colon patients. The results for these models using our combined race/ethnicity-exposure metric of minimum exposure minutes (see Tables 7 and 8), offer an alternative way to examine this effect. These models estimated an 11-24% increase with increasing minimum minutes of exposure (1 unit = approximately 10 minutes), depending on the first primary cancer and follow up period. Unlike the results presented in our survival analysis on this topic,[2] no interaction between environmental D and percent urban was found in any of our analyses.

A further analysis of this data by race (data not shown) suggests that the benefit of increasing VDR is not shared equally by Whites and Blacks, particularly for rectal-prostate MPCs. Increasing VDR appears to be protective among both Whites (adj OR 0.92, 95% CI: 0.88, 0.97) and Blacks (adj OR 0.89, 95% CI: 0.81, 0.98) in reducing the risk of being diagnosed with a colon-prostate MPC over the entire follow up period. With

respect to rectal-prostate MPCs, however, increasing VDR is only protective among Whites (adj OR 0.89, 95% CI: 0.83, 0.97) when compared with Blacks (adj OR 0.95, 95% CI: 0.79, 1.13). Furthermore, an increase in risk was observed for Blacks during some follow up periods for both rectal-prostate and colon-prostate MPCs when VDR was added to our models (i.e., Tables 3 and 4 vs. Tables 5 and 6). The greatest increase in the estimate for Black race was observed for late rectal-prostate MPCs, particularly those diagnosed after 10 follow up years. Interestingly, any increase observed for Black race in any of our VDR models was accompanied by a decrease in the risk associated with our race-based proxy for smoking. While it seems reasonable not to over interpret these findings given the small number of Black patients included in some of these analyses, it does seem reasonable to conclude that any overall benefit observed in those models with increasing VDR may not be shared equally between White and Black patients.

A weaker protective association of increasing VDR was noted among patients with first primary prostate cancer who were diagnosed with a subsequent primary colon tumor (adj OR 0.96, 95% CI: 0.93, 1.00). Among these patients, the strongest protective association of increasing VDR was observed after 10 follow up years (SHR 0.85, 95% CI: 0.78, 0.93). A separate analysis by race (data not shown), suggests a similarly weak effect for both Whites (adj OR 0.98, 95% CI: 0.94, 1.02) and Blacks (0.98, 0.91, 1.06) for prostate-colon MPCs. Finally, no significant difference in risk was observed for prostate-rectal MPCS using either of our exposure characterizations when stratified by follow up period (Tables 5 to 8), though a slight protective association was observed for Whites (adj OR 0.94, 95% CI: 0.88, 1.00) but not for Blacks (adj OR 0.83, 95% CI: 0.80, 1.08) across all follow-up periods (data not shown). These differences by race may largely be

due to the increase in risk associated with Black race that was observed during follow-up years 0 to 1 and again during years >5 to 10 when VDR was added to models (i.e., Table 3 and 4 vs. Tables 5 and 6).

3. *Increasing levels of our proxy for smoking and/or socio-economic deprivation were associated with an increased risk of MPCs; the highest risks were observed for prostate-colon and prostate-rectal MPCs.*

First primary prostate patients with higher levels of our proxy for smoking were at increased risk for a subsequent primary colon tumor across the entire follow up period (adj OR 1.06, 95% CI: 1.02, 1.09), with the greatest risk observed after 10 years (SHR 1.12, 95% CI: 1.03, 1.23). First primary prostate patients were also at increased risk for subsequent primary rectal cancer (SHR 1.09, 95% CI: 1.06, 1.13) during follow up years >1 to 5. An increased effect was also observed during follow up years >5 to 10 modified by level of disparities, which is discussed below.

An interaction between smoking and socio-economic deprivation was observed during one or more of the follow up periods for most of our MPC pairs. The greatest increase in risk was observed during years >5 to 10 for prostate-rectal MPCs (SHR 1.13, 95% CI: 1.04, 1.24). A significant interaction between smoking and socio-economic deprivation was also associated with 7-10% higher risk of colon-prostate and rectal-prostate MPCs during one or more periods. Finally, increased risks were also associated with increasing socio-economic deprivation alone during one or more periods for most of our MPC pairings, with the highest risk observed for colon-prostate MPCs diagnosed during the first year of follow up (SHR 1.13, 95% CI: 1.04, 1.22).

4. *Patients who received radiotherapy for their first primary prostate cancer were at increased risk of a late subsequent primary colon or primary rectal cancer; conversely, radiotherapy for first primary rectal cancer appears to be*

protective for subsequent primary cancer, with the greatest benefit observed during >1 to 5 follow up years.

Primary prostate patients who received radiotherapy for their cancer were at greater risk of developing a late primary colon or rectal cancers, with a 20% higher risk observed during years >5 to 10. The risks were highest after year 10, with higher risks observed for prostate-rectal MPCs (SHR 2.40, 1.89, 3.05) than for prostate-colon (SHR 1.29, 95% CI 1.10, 1.51). Conversely, primary rectal patients who received radiotherapy were at significantly lower risk of developing a subsequent prostate cancer than non-radiotherapy patients, with a 39% (adj OR 0.61, 95% CI: 0.53, 0.69) decrease in risk over the entire follow up period. This effect was noted starting after the first year of follow up (SHR 0.33, 95% CI: 0.25, 0.44) and appeared to diminish over time (SHR 0.64, 95% CI: 0.46, 0.90) after year 10. Radiotherapy was not associated with the development of colon-prostate MPCs during any part of the late follow up period.

Significant increases or decreases in risk were also observed during the first year of follow up for prostate-colon, prostate-rectal and colon-prostate patients. As noted elsewhere in the literature, these are not likely to be treatment effects, but are more likely to reflect other patient and disease factors influencing the choice of first course radiotherapy treatment. For a summary of factors associated with the odds of radiotherapy treatment as first course treatment for our patients, see Table 9.

Discussion

To date, no studies have examined if higher levels of environmental D decreases the risk of MPCs and few studies have examined if Blacks were are higher risk than Whites for MPC development. Our study found that for first primary colon or rectal patients, increasing levels of vitamin D radiation may modestly decrease the risk of a

being diagnosed with a subsequent prostate cancer, but this benefit may not be shared equally among Whites and Blacks. In general, non-Hispanic Blacks have an increased risk for colorectal-prostate and prostate-colon MPCs, with the highest risks observed for rectal-prostate MPCs. Our general findings for an increased risk of colon-prostate MPCs among Black males are consistent with the one other SEER based study that examined race differences, which reported a high absolute excess risk (AER 26.5 per 10,000 person years) among Blacks aged 50 years and over with primary colon cancer for subsequent primary prostate cancer. [3]

Hou *et al.*'s analysis of the 1973-2005 SEER data for the primary cancer pairings examined in our analysis found elevated SIRs among males, adjusted for age, race/ethnicity and calendar year, for both colon-prostate (SIR 1.03, 95% CI: 1.01-1.06) and prostate-colon (SIR: 1.05, 95% CO: 1.03-1.08) MPCS.[38] A protective association was observed for rectal-prostate (SIR 0.88, 95% CI: 0.85-0.92) MPCs, while no significant increase in risk was observed for the prostate-rectal (SIR 0.98, 95% CI: 0.95-1.02) pairing. While our results follows a somewhat similar pattern, Hou *et al.*'s analysis included cancer patients of any stage and a wider range of registries where as our study was restricted to White and Black non-Hispanic non-metastatic cancer patients residing and diagnosed in the coterminous U.S. between 1978 and 2003, and adjusted for number of other factors as well as the competing risk of death.

An interesting finding of this study was that increasing levels of our proxy for smoking, often in conjunction with increasing levels of socio-economic deprivation, was associated with an increased risk during one or more follow up period for all of our MPC pairings. To date, few studies have examined smoking as a common risk factor but it is

generally thought to contribute to a large number of MPCs.[17] Interestingly, smoking has also been reported to reduce the amount of bioavailable vitamin D in individuals,[8] though no interaction between this variable and environmental D was observed in this study.

In this study, we also found that radiotherapy status was associated with increased risks of both prostate-colon and prostate-rectal MPCs. This finding has been reported in other SEER based analyses of this pair, with some analyses finding increased risks for subsequent tumors in certain areas of the colon[1,50] (e.g., cecum= OR 1.63, 95% CI: 1.10, 1.70), transverse colon= OR 1.85, 95% CI: 1.30, 2.63),[50] and occasionally in the rectum (e.g., HR 1.79, 95% CI: 1.05, 3.07)[59] following radiotherapy for prostate cancer. Consistent with effects reported elsewhere,[i.e.,5,13,29] the increased risk associated with radiotherapy in our study largely occurred at least 5 years after radiotherapy with most occurring after a lag of 10 or more years.[i.e.,1,7,43] At least one other SEER-based study suggested that radiotherapy treatment for rectal cancer reduces the risk of subsequent prostate cancer (e.g., O/E 0.28, 95% CI: 0.17, 0.43)[32] to a degree that was also observed in our study. Although the reasons for this are not clear, it is hypothesized that the unintended radiation reaching the prostate may effectively pre-treat any developing cancer.[32,38,43] Our study found that this protective association was greatest in years >1 to 5 following radiotherapy treatment for the first primary cancer, and diminished afterwards. No interaction was observed between radiotherapy and any of the other variables in our study, including environmental D.

Limitations

In addition to the exposure limitations discussed elsewhere for our dataset,[2] the limitations specific to this study are those shared by other registry based MPC analyses

including all others using SEER data.[i.e.,12,56] First, there may have been loss to follow up of patients for subsequent cancer development due to their moving out of the SEER area where their first primary cancer was diagnosed. While SEER estimates that loss to follow up is minimal, we also suggest that it would most likely be random and result in an underestimation of the true effect. Second, the radiotherapy/surgery data used in this study is limited to the first course of treatment only. Since we have followed other studies and stratified by the timing of the second primary tumor, we are fairly confident that we have properly identified the risks associated with treatment induced tumors.

Concluding Remarks

This study is the first the authors are aware of to examine the role of race and environmental D in prostate-colorectal and colorectal-prostate MPCs. It is also the first to examine smoking and socio-economic deprivation as risk factors for any MPC pairing using a U.S. cancer registry. It is hoped that the design of our study, which applied a competing risk survival model to a population-based cohort, provides a reasonable model for further investigations of other MPC pairs and will lead to additional research in this area. It is also our hope that our findings may be of particular use to the clinician who has little other information available on which male patients may be at higher risk for MPCs other than the much-analyzed effect of radiotherapy status.

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Table 1: Patient tumor, socio-demographic and environmental D exposure characteristics of White and Black non-Hispanic males diagnosed with non-metastatic cancer from 1978 to 2003.

	Prostate Cohort (n=281,750)		**Colon Cohort (n=62,312)**		**Rectal Cohort (n=29,331)**	
	White	Black	White	Black	White	Black
Patient and tumor characteristics						
Number of cancer cases	*246,403*	*35,347*	*56,903*	*5,409*	*27,401*	*1,930*
5-year survival rate (KM)	0.94	0.93	0.77	0.71	0.72	0.64
10-year survival rate (KM)	0.86	0.84	0.69	0.64	0.62	0.55
Patient age at diagnosis (%)						
50 to <65	28.3	39.1	27.7	39.5	36.5	49.1
65 to < 74	42.8	40.7	35.7	35.2	36.4	31.5
75+	28.9	20.3	36.6	25.4	27.1	19.4
Married (%)	76.1	59.1	75.1	58.4	75.7	57.9
Year of diagnosis (%)						
1978-1987	16.9	13.3	33.3	26.3	35.7	26.4
1988-1997	46.3	43.7	40.4	41.2	38.7	41.7
1998-2003	36.8	43	26.2	32.5	25.6	31.9
Grade (%)						
1 (well differentiated)	15.6	12.8	13.6	14.1	12.1	9.9
2 (moderately differentiated)	60	60.7	57.1	60.7	58.8	56.6
3 (poorly differentiated)	18.8	20	13.5	9.5	12.6	11.2
4 (undifferentiated)	0.6	0.5	0.6	0.3	0.4	0.2
9 (not determined or stated)	5	6	15.2	15.4	16.1	22.1
Regional extension (%)	9.0	7.8	48.1	46.0	39.0	39.2
Positive nodes (%)	2.6	2.3	28.6	30.9	27.6	28.1
Surgery (%)	56.6	50.4	99.1	98.1	96.8	93.1
Radiotherapy (%)	35.1	35.8	2.6	2.4	31.9	34.9
Total no. primary cancers (%)						
1	83.70	85.20	75.20	74.00	79.50	79.00
2	14.40	13.40	20.50	21.40	17.50	18.00
≥3	1.90	1.40	4.30	4.80	3.00	3.00
MPCs of interest (%)						
never	97.23	96.99	92.86	89.42	94.65	91.36
<= 1 year	0.37	0.45	1.18	1.76	1.29	2.69
> 1 - 5 years	1.08	1.27	2.51	3.85	1.57	2.59
> 5 to 10 years	0.85	0.91	1.91	2.92	1.38	2.12
> 10 years	0.47	0.38	1.54	2.05	1.11	1.24
Socio-demographic characteristics based on county of residence at diagnosis						
Percent urban in 1990 (%)						
Least-urban (<85%)	27.2	2.6	27.7	2.9	28.9	3.4
Mostly-urban (85% - <99%)	53.4	67.4	55.0	68.0	55.1	66.3
All-urban (99% or higher)	19.4	30.0	17.3	29.1	16.0	30.3
1990 Deprivation index (mean and 1 SD)	-0.1 (0.7)	0.7 (0.8)	-0.1 (0.7)	0.7 (0.8)	-0.1 (0.7)	0.7 (0.8)
Percent residing in same house or county in 1985 (mean and 1 SD)	78.7 (7.1)	81.8 (8.6)	79.4 (7.0)	81.9 (8.5)	79.6 (7.0)	81.8 (8.4)
Age-adjusted lung mortality rate 1975-2004 (mean and 1 SD)	247.3 (48.2)	354.0 (47.1)	253.6 (43.7)	356.0 (40.35)	254.3 (44.4)	354.7 (38.4)
Environmental D characteristics based on county of residence at diagnosis						
Vitamin D radiation level in Joules /m^2 (mean and 1 SD)	764.8 (199.0)	798.4 (194.5)	745.6 (187.0)	790.7 (191.2)	737.1 (184.4)	796.9 (192.4)
Minimum minutes of exposure (mean and 1 SD)	17.2 (8.5)	40.1 (17.1)	17.3 (7.7)	40.6 (16.7)	17.6 (7.7)	40.3 (17.0)

Notes: Abbreviations: KM = Kaplan Meier, SD= Standard Deviation.

Table 2: Adjusted odds of being diagnosed with an MPC by cancer site and first primary cancer factors for patients in the First Primary Prostate and Colorectal Cohorts.

First Primary Cancer Factors	Odds of Colon or Rectal MPC among patients in the Prostate Cohort		Odds of Prostate MPC among patients in the Colorectal Cohort	
	Prostate - Colon n= 281,398	***Prostate - Rectal*** n=281,562	***Colon - Prostate*** n= 62,310	***Rectal - Prostate*** n=29,328
	MPCs= 5,752	MPCs= 2,158	MPCs = 4,636	MPCs= 1,631
	adjusted OR (95% CI)	adjusted OR (95% CI)	adjusted OR (95% CI)	adjusted OR (95% CI)
Constant	0.02 (0.01, 0.02)	0.01 (0.01, 0.01)	0.06 (0.04, 0.09)	0.05 (0.04, 0.08)
Vitamin D radiation	0.96 (0.93, 1.00)	0.94 (0.89, 0.99)	0.91 (0.88, 0.95)	0.90 (0.84, 0.96)
Percent Urban	0.98 (0.96, 1.01)	0.95 (0.91, 1.00)	1.00 (0.97, 1.03)	0.97 (0.92, 1.02)
Proxy for Smoking	1.06 (1.02, 1.09)	1.05 (0.99, 1.11)	0.94 (0.90, 0.98)	0.89 (0.83. 0.95)
Deprivation index	1.03 (1.00, 1.06)	1.04 (0.99, 1.10)	1.03 (0.99, 1.07)	1.06 (1.00, 1.13)
Patient age at diagnosis:				
50 to <65†	1	1	1	1
65 to < 74	1.73 (1.61, 1.86)	1.41 (1.27, 1.58)	1.13 (1.05, 1.22)	1.46 (1.29. 1.64)
75+	1.87 (1.73, 2.02)	1.23 (1.08, 1.39)	0.78 (0.72, 0.85)	1.25 (1.09, 1.43)
Race				
White†	1	1	1	1
Black	1.18 (1.07, 1.30)	0.82 (0.69, 0.97)	1.80 (1.59, 2.04)	2.40 (1.93, 2.98)
Married				
No†	1	1	1	1
Yes	1.15 (1.08, 1.22)	1.05 (0.95, 1.16)	1.25 (1.16, 1.35)	1.22 (1.08, 1.38)
Year of Diagnosis				
1978 – 1988†	1	1	1	1
1988 - 1998	0.97 (0.90, 1.04)	1.02 (0.91, 1.15)	0.94 (0.87, 1.00)	0.90 (0.80, 1.01)
1998 - 2003	0.56 (0.51, 0.61)	0.56 (0.49, 0.65)	0.55 (0.50, 0.60)	0.56 (0.48, 0.65)
Regional extension				
No†	1	1	1	1
Yes	0.95 (0.87, 1.05)	1.23 (1.07, 1.41)	0.78 (0.73, 0.84)	0.71 (0.63, 0.80)
Positive nodes				
No†	1	1	1	1
Yes	0.77 (0.64, 0.94)	1.09 (0.85, 1.40)	0.67 (0.62, 0.72)	0.74 (0.65, 0.85)
Grade				
1†	1	1	1	1
2	0.89(0.83, 0.96)	0.91(0.81, 1.02)	1.04 (0.95, 1.14)	0.92 (0.79, 1.07)
3	0.78 (0.71, 0.86)	0.81 (0.70, 0.94)	0.87 (0.77, 0.99)	0.85 (0.69, 1.06)
4	0.51 (0.33, 0.77)	0.63 (0.35, 1.15)	0.92 (0.59, 1.44)	1.00 (0.40, 2.49)
9	0.94 (0.83, 1.06)	0.99 (0.82, 1.21)	0.95 (0.86, 1.06)	1.11 (0.94, 1.33)
Surgery				
No†	1	1	1	1
Yes	0.94 (0.88, 1.01)	1.04 (0.94, 1.16)	1.67 (1.15, 2.42)	1.84 (1.27, 2.67)
Radiotherapy				
No†	1	1	1	1
Yes	1.09 (1.02, 1.16)	1.22 (1.10, 1.35)	0.91 (0.74, 1.12)	0.61 (0.53, 0.69)
Proximal or Distal				
Proximal†	--	--	1	--
Distal			0.98 (0.92, 1.04)	

Notes: †=referent. All variables have been adjusted for the other variables presented in this table. The continuous variables presented above are mean centered and divided by 1 standard deviation. See the Appendix for details.

Table 3. No-exposure ("null") models for the risk of developing an early (0 to 5 years) subsequent primary cancer among male White and Black first primary cancer patients, adjusted for death as a competing risk and other factors.

Sub-Hazard of MPC during year 0 to 1	**Prostate Cohort**		**Colorectal Cohort**	
	Prostate-Colon MPC	Prostate-Rectal MPC	Colon – Prostate MPC	Rectal-Prostate MPC
subjects (n)	*281,398*	*281,562*	*62,310*	*29,328*
failures (n)	*777*	*304*	*767*	*405*
competing risks (n)	*144,494*	*146,910*	*42,450*	*20,354*
censored (n)	*136,127*	*134,348*	*19,093*	*8,569*
Percent urban	0.94 (0.88, 1.01)	0.98 (0.88, 1.09)	0.94 (0.88, 1.02)	0.94 (0.86, 1.03)
Race				
White†	1	1	1	1
Black	1.22 (0.97, 1.54)	1.19 (0.78, 1.81)	1.54 (1.16, 2.04)	2.66 (1.78, 3.96)
Deprivation index	1.03 (0.95, 1.11)	1.02 (0.89, 1.16)	1.11 (1.03, 1.19)	1.04 (0.94, 1.17)
Proxy for smoking	1.09 (1.04, 1.13)	0.94 (0.83, 1.07)	1.03 (0.94, 1.12)	0.84 (0.75, 0.95)
Deprivation * Smoking	--	--	--	1.13 (1.03, 1.24)
Radiotherapy treatment				
No†	1	1	1	1
Yes	0.63 (0.53, 0.76)	0.69 (0.52, 0.93)	2.25 (1.54, 3.27)	1.07 (0.84, 1.35)

Sub-Hazard of MPC during years >1 to 5	**Prostate Cohort**		**Colorectal Cohort**	
	Prostate-Colon MPC	Prostate-Rectal MPC	Colon – Prostate MPC	Rectal-Prostate MPC
subjects (n)	270,586	271,148	*54,655*	*25,954*
failures (n)	2,292	824	*1,638*	*480*
competing risks (n)	134,657	137,007	*35,598*	*17,405*
censored (n)	133,637	133,317	*17,419*	*8,069*
Percent urban	1.02 (0.98, 1.07)	0.93 (0.87, 0.99)	1.05 (0.99, 1.10)	0.93 (0.85, 1.02)
Race				
White†	1	1	1	1
Black	1.32 (1.15, 1.52)	0.81 (0.63, 1.03)	1.61 (1.32, 1.95)	1.63 (1.11, 2.38)
Deprivation index	1.01 (0.97, 1.06)	1.07 (1.00, 1.16)	0.98 (0.93, 1.04)	1.03 (0.94, 1.13)
Proxy for smoking	1.05 (1.01, 1.09)	1.10 (1.07, 1.13)	1.03 (0.97, 1.09)	1.10 (0.98, 1.23)
Deprivation * Smoking	--	--	--	--
Radiotherapy treatment				
No†	1	1	1	1
Yes	1.07 (0.97, 1.18)	1.10 (0.93, 1.29)	0.52 (0.33, 0.84)	0.33 (0.25, 0.44)

Notes: All analyses have been adjusted for age and period of diagnosis, marital status, surgery, regional extension, regional lymph nodes, and grade of First Primary Cancer, and other variables in table. Colon cancer also adjusted for proximal or distal location of tumor. All continuous variables are mean centered and divided by 1 standard deviation. Urban level: Least-urban: <85%; mostly-urban 85-99%; All-urban = 99% or more. For detailed values, see the Appendix. †=referent.

Table 4. No-exposure ("null") models for the risk of developing a late (>5 years) subsequent primary cancer among male White and Black first primary cancer patients, adjusted for death as a competing risk and other factors.

Sub-Hazard of MPC during years >5 to 10	**Prostate Cohort**		**Colorectal Cohort**	
	Prostate-Colon MPC	Prostate-Rectal MPC	Colon – Prostate MPC	Rectal-Prostate MPC
subjects (n)	*218,004*	*219,318*	*35,429*	*16,313*
failures (n)	*1,738*	*687*	*1,243*	*418*
competing risks (n)	*86,540*	*88,220*	*18,238*	*8,352*
censored (n)	*129,726*	*130,411*	*15,948*	*7,543*
Percent urban	0.94 (0.90, 0.99)	0.97 (0.90, 1.05)	0.96 (0.91, 1.02)	0.99 (0.89, 1.10)
Race				
White†	1	1	1	1
Black	1.24 (1.06, 1.46)	0.68 (0.50, 0.93)	1.89 (1.51, 2.37)	1.95 (1.31, 2.90)
Deprivation index	1.02 (0.97, 1.08)	0.93 (0.85, 1.01)	0.94 (0.87, 1.00)	1.04 (0.94, 1.15)
Proxy for smoking	1.08 (1.04, 1.13)	1.08 (1.04, 1.13)	0.97 (0.90, 1.03)	1.01 (0.91, 1.14)
Deprivation * Smoking	--	1.16 (1.07, 1.26)	1.08 (1.03, 1.13)	--
Radiotherapy treatment				
No†	1	1	1	1
Yes	1.21 (1.08, 1.36)	1.20 (1.00, 1.43)	1.10 (0.75, 1.61)	0.71 (0.54, 0.92)

Sub-Hazard of MPC during years >10	**Prostate Cohort**		**Colorectal Cohort**	
	Prostate-Colon MPC	Prostate-Rectal MPC	Colon – Prostate MPC	Rectal-Prostate MPC
subjects (n)	*98,609*	*99,631*	*17,115*	*7,829*
failures (n)	*945*	*343*	*988*	*328*
competing risks (n)	*37,189*	*38,066*	*8,075*	*3,703*
censored (n)	*60,475*	*61,222*	*8,052*	*3,798*
Percent urban	0.95 (0.89, 1.02)	0.92 (0.83, 1.01)	0.93 (0.87, 0.99)	0.97 (0.88, 1.08)
Race				
White†	1	1	1	1
Black	0.89 (0.69, 1.14)	0.74 (0.47, 1.15)	1.88 (1.46, 2.42)	2.87 (1.78, 4.63)
Deprivation index	1.05 (0.98, 1.12)	1.05 (0.94, 1.17)	1.03 (0.96, 1.10)	0.94 (0.82, 1.07)
Proxy for smoking	1.18 (1.09, 1.27)	1.03 (0.91, 1.18)	0.96 (0.89, 1.04)	0.81 (0.73, 0.91)
Deprivation * Smoking	--	--	--	--
Radiotherapy treatment				
No†	1	1	1	1
Yes	1.30 (1.11, 1.52)	2.40 (1.89, 3.04)	1.09 (0.74, 1.61)	0.65 (0.46, 0.91)

Notes: All analyses have been adjusted for age and period of diagnosis, marital status, surgery, regional extension, regional lymph nodes, and grade of First Primary Cancer, and other variables in table. Colon cancer also adjusted for proximal or distal location of tumor. All continuous variables are mean centered and divided by 1 standard deviation. Urban level: Least-urban: <85%; mostly-urban 85-99%; All-urban = 99% or more. For detailed values, see the Appendix. †=referent.

Table 5: Risk of developing an early (0 to 5 years) subsequent primary cancer among male White and Black male first primary cancer patients, adjusted for death as a competing risk and other factors.

Sub-Hazard of MPC during year 0 to 1	**Prostate Cohort**		**Colorectal Cohort**	
	Prostate-Colon MPC	Prostate-Rectal MPC	Colon – Prostate MPC	Rectal-Prostate MPC
subjects (n)	*281,398*	*281,562*	*62,310*	*29,328*
failures (n)	*777*	*304*	*767*	*405*
competing risks (n)	*144,494*	*146,910*	*42,450*	*20,354*
censored (n)	*136,127*	*134,348*	*19,093*	*8,569*
Vitamin D radiation	1.01 (0.93, 1.09)	0.91 (0.79, 1.05)	0.95 (0.86, 1.04)	0.92 (0.80, 1.07)
Percent urban	0.94 (0.88, 1.01)	1.00 (0.90, 1.11)	0.95 (0.89, 1.03)	0.95 (0.87, 1.04)
Race				
White†	1	1	1	1
Black	1.22 (0.97, 1.55)	1.27 (0.84, 1.92)	1.61 (1.21, 2.15)	2.97 (1.92, 4.59)
Deprivation index	1.03 (0.95, 1.11)	1.05 (0.91, 1.21)	1.13 (1.04, 1.22)	1.08 (0.96, 1.23)
Proxy for smoking	1.09 (1.05, 1.13)	0.89 (0.77, 1.03)	0.99 (0.90, 1.10)	0.81 (0.71, 0.93)
Deprivation * Smoking	--	--	--	1.10 (1.00, 1.21)
Radiotherapy treatment				
No†	1	1	1	1
Yes	0.63 (0.53, 0.76)	0.69 (0.51, 0.92)	2.24 (1.54, 3.26)	1.07 (0.84, 1.35)

Sub-Hazard of MPC during years >1 to 5	**Prostate Cohort**		**Colorectal Cohort**	
	Prostate-Colon MPC	Prostate-Rectal MPC	Colon – Prostate MPC	Rectal-Prostate MPC
subjects (n)	270,586	271,148	*54,655*	*25,954*
failures (n)	2,292	824	*1,638*	*480*
competing risks (n)	134,657	137,007	*35,598*	*17,405*
censored (n)	133,637	133,317	*17,419*	*8,069*
Vitamin D radiation	1.00 (0.95, 1.05)	0.95 (0.88, 1.03)	0.93 (0.87, 1.00)	1.01 (0.90, 1.14)
Percent urban	1.02 (0.98, 1.07)	0.93 (0.87, 1.00)	1.06 (1.00, 1.12)	0.93 (0.85, 1.02)
Race				
White†	1	1	1	1
Black	1.32 (1.15, 1.52)	0.81 (0.64, 1.04)	1.70 (1.39, 2.08)	1.61 (1.08, 2.39)
Deprivation index	1.01 (0.97, 1.06)	1.09 (1.01, 1.18)	1.01 (0.95, 1.07)	1.02 (0.93, 1.14)
Proxy for smoking	1.05 (1.00, 1.09)	1.09 (1.06, 1.13)	0.98 (0.92, 1.06)	1.11 (0.98, 1.26)
Deprivation * Smoking	--	--	--	--
Radiotherapy treatment				
No†	1	1	1	1
Yes	1.07 (0.97, 1.18)	1.09 (0.92, 1.28)	0.52 (0.33, 0.83)	0.33 (0.25, 0.44)

Notes: All analyses have been adjusted for age and period of diagnosis, marital status, surgery, regional extension, regional lymph nodes, and grade of First Primary Cancer, and other variables in table. Colon cancer also adjusted for proximal or distal location of tumor. All continuous variables are mean centered and divided by 1 standard deviation. Average month VDR: Mean = ~ 750 J/m^2 ; Per unit VDR = ~ 190 J/m^2 ; Average month MM: Mean =~ 19.5; Per unit MM = ~ 11.0 MM; Urban level: Least-urban: <85%; mostly-urban 85-99%; All-urban = 99% or more. For detailed values, see the Appendix.†=referent.

Table 6: Risk of developing a late (>5 years) subsequent primary cancer among male White and Black first primary cancer patients, adjusted for death as a competing risk and other factors.

Sub-Hazard of MPC during years >5 to 10	**Prostate Cohort**		**Colorectal Cohort**	
	Prostate-Colon MPC	Prostate-Rectal MPC	Colon – Prostate MPC	Rectal-Prostate MPC
subjects (n)	*218,004*	*219,318*	*35,429*	*16,313*
failures (n)	*1,738*	*687*	*1,243*	*418*
competing risks (n)	*86,540*	*88,220*	*18,238*	*8,352*
censored (n)	*129,726*	*130,411*	*15,948*	*7,543*
Vitamin D radiation	0.95 (0.89, 1.00)	0.94 (0.85, 1.03)	0.97 (0.89, 1.05)	0.88 (0.77, 1.01)
Percent urban	0.95 (0.90, 1.00)	0.98 (0.91, 1.06)	0.97 (0.91, 1.03)	1.01 (0.91, 1.13)
Race				
White†	1	1	1	1
Black	1.28 (1.08, 1.51)	0.72 (0.52, 0.99)	1.96 (1.54, 2.51	2.17 (1.45, 3.25)
Deprivation index	1.04 (0.99, 1.10)	0.95 (0.87, 1.04)	0.95 (0.88, 1.03)	1.08 (0.97, 1.21)
Proxy for smoking	1.06 (1.00, 1.12)	1.07 (1.01, 1.13)	0.95 (0.88, 1.02)	0.95 (0.83, 1.08)
Deprivation * Smoking	--	1.13 (1.04, 1.24)	1.07 (1.01, 1.13)	--
Radiotherapy treatment				
No†	1	1	1	1
Yes	1.20 (1.07, 1.35)	1.19 (0.99, 1.43)	1.10 (0.74, 1.61)	0.70 (0.54, 0.91)

Sub-Hazard of MPC during years >10	**Prostate Cohort**		**Colorectal Cohort**	
	Prostate-Colon MPC	Prostate-Rectal MPC	Colon – Prostate MPC	Rectal-Prostate MPC
subjects (n)	*98,609*	*99,631*	*17,115*	*7,829*
failures (n)	*945*	*343*	*988*	*328*
competing risks (n)	*37,189*	*38,066*	*8,075*	*3,703*
censored (n)	*60,475*	*61,222*	*8,052*	*3,798*
Vitamin D radiation	0.92 (0.84, 1.00)	1.03 (0.89, 1.18)	0.85 (0.78, 0.93)	0.86 (0.74, 1.00)
Percent urban	0.97 (0.91, 1.04)	0.91 (0.82, 1.01)	0.96 (0.89, 1.02)	1.00 (0.90, 1.11)
Race				
White†	1	1	1	1
Black	0.94 (0.73, 1.22)	0.73 (0.46, 1.15)	2.10 (1.62, 2.71)	3.17 (1.97, 5.11)
Deprivation index	1.08 (1.00, 1.16)	1.04 (0.92, 1.17)	1.08 (1.00, 1.16)	0.99 (0.86, 1.13)
Proxy for smoking	1.12 (1.03, 1.23)	1.05 (0.90, 1.22)	0.89 (0.82, 0.97)	0.76 (0.67, 0.87)
Deprivation * Smoking	--	--	--	--
Radiotherapy treatment				
No†	1	1	1	1
Yes	1.29 (1.10, 1.51)	2.40 (1.89, 3.05)	1.09 (0.74, 1.60)	0.64 (0.46, 0.90)

Notes: All analyses have been adjusted for age and period of diagnosis, marital status, surgery, regional extension, regional lymph nodes, and grade of First Primary Cancer, and other variables in table. Colon cancer also adjusted for proximal or distal location of tumor. All continuous variables are mean centered and divided by 1 standard deviation. Average month VDR: Mean = ~ 750 J/m^2 ; Per unit VDR = ~ 190 J/m^2 ; Average month MM: Mean =~ 19.5; Per unit MM = ~ 11.0 MM; Urban level: Least-urban: <85%; mostly-urban 85-99%; All-urban = 99% or more. For detailed values, see the Appendix.†=referent.

Table 7: Risk of developing an early (0 to 5 years) subsequent primary cancer using minimum exposure minutes among male White and Black first primary cancer patients, adjusted for death as a competing risk and other factors.

Sub-Hazard of MPC during year 0 to 1	**Prostate Cohort**		**Colorectal Cohort**	
	Prostate–Colon MPC	Prostate-Rectal MPC	Colon – Prostate MPC	Rectal-Prostate MPC
subjects (n)	*281,398*	*281,562*	*62,310*	*29,328*
failures (n)	*777*	*304*	*767*	*405*
competing risks (n)	*144,494*	*146,910*	*42,450*	*20,354*
censored (n)	*136,127*	*134,348*	*19,093*	*8,569*
Minimum minutes	1.02 (0.94, 1.10)	1.08 (0.95, 1.22)	1.11 (1.03, 1.19)	1.24 (1.12, 1.38)
Percent urban	0.95 (0.88, 1.02)	0.99 (0.89, 1.10)	0.96 (0.89, 1.03)	0.96 (0.88, 1.06)
Deprivation index	1.05 (0.97, 1.12	1.03 (0.91, 1.17)	1.14 (1.06, 1.22)	1.11 (0.99, 1.25)
Proxy for smoking	1.10 (1.06, 1.14)	0.93 (0.81, 1.06)	1.03 (0.94, 1.13)	0.85 (0.75, 0.96)
Deprivation * Smoking	--	--	--	1.14 (1.04, 1.25)
Radiotherapy treatment				
No†	1	1	1	1
Yes	0.63 (0.52, 0.75)	0.69 (0.52, 0.92)	2.22 (1.53, 3.24)	1.05 (0.83, 1.33)

Sub-Hazard of MPC during years >1 to 5	**Prostate Cohort**		**Colorectal Cohort**	
	Prostate–Colon MPC	Prostate-Rectal MPC	Colon – Prostate MPC	Rectal-Prostate MPC
subjects (n)	270,586	271,148	*54,655*	*25,954*
failures (n)	2,292	824	*1,638*	*480*
competing risks (n)	134,657	137,007	*35,598*	*17,405*
censored (n)	133,637	133,317	*17,419*	*8,069*
Minimum minutes	1.02 (0.98, 1.06)	0.99 (0.92, 1.16)	1.13 (1.08, 1.19)	1.05 (0.95, 1.17)
Percent urban	1.03 (0.99, 1.08)	0.92 (0.86, 0.98)	1.07 (1.01, 1.13)	0.94 (0.86, 1.04)
Deprivation index	1.03 (0.99, 1.08)	1.06 (0.99, 1.14)	1.02 (0.96, 1.07)	1.05 (0.95, 1.15)
Proxy for smoking	1.08 (1.05, 1.12)	1.09 (1.05, 1.13)	1.03 (0.97, 1.09)	1.15 (1.02, 1.29)
Deprivation * Smoking	--	--	--	--
Radiotherapy treatment				
No†	1	1	1	1
Yes	1.06 (0.96, 1.17)	1.10 (0.93, 1.30)	0.52 (0.33, 0.83)	0.33 (0.25, 0.44)

Notes: All analyses have been adjusted for age and period of diagnosis, marital status, surgery, regional extension, regional lymph nodes, and grade of First Primary Cancer, and other variables in table. Colon cancer also adjusted for proximal or distal location of tumor. All continuous variables are mean centered and divided by 1 standard deviation. Average month VDR: Mean = ~ 750 J/m^2 ; Per unit VDR = ~ 190 J/m^2 ; Average month MM: Mean =~ 19.5; Per unit MM = ~ 11.0 MM; Urban level: Least-urban: <85%; mostly-urban 85-99%; All-urban = 99% or more. For detailed values, see the Appendix.†=referent.

Table 8: Risk of developing a late (>5 years) subsequent primary cancer using minimum exposure minutes among male White and Black first primary cancer patients, adjusted for death as a competing risk and other factors.

Sub-Hazard of MPC during years >5 to 10	**Prostate Cohort**		**Colorectal Cohort**	
	Prostate–Colon MPC	Prostate-Rectal MPC	Colon – Prostate MPC	Rectal-Prostate MPC
subjects (n) *failures (n)* *competing risks (n)* *censored (n)*	*218,004* *1,738* *86,540* *129,726*	*219,318* *687* *88,220* *130,411*	*35,429* *1,243* *18,238* *15,948*	*16,313* *418* *8,352* *7,543*
Minimum minutes	1.05 (0.99, 1.10)	0.96 (0.87, 1.05)	1.15 (1.09, 1.22)	1.14 (1.04, 1.26)
Percent urban	0.95(0.90, 0.99)	0.96 (0.90, 1.03)	0.98 (0.93, 1.04)	1.01 (0.91, 1.12)
Deprivation index	1.04 (0.99, 1.09)	0.91 (0.83, 0.99)	0.98 (0.91, 1.05)	1.08 (0.97, 1.19)
Proxy for smoking	1.09 (1.05, 1.13)	1.07 (1.01, 1.13)	0.98 (0.91, 1.05)	1.03 (0.91, 1.17)
Deprivation * Smoking	--	1.13 (1.05, 1.23)	1.09 (1.03, 1.14)	--
Radiotherapy treatment No† Yes	 1 1.20 (1.07, 1.35)	 1 1.21 (1.01, 1.45)	 1 1.08 (0.74, 1.59)	 1 0.70 (0.53, 0.91)

Sub-Hazard of MPC during years >10	**Prostate Cohort**		**Colorectal Cohort**	
	Prostate–Colon MPC	Prostate-Rectal MPC	Colon – Prostate MPC	Rectal-Prostate MPC
subjects (n) *failures (n)* *competing risks (n)* *censored (n)*	*98,609* *945* *37,189* *60,475*	*99,631* *343* *38,066* *61,222*	*17,115* *988* *8,075* *8,052*	*7,829* *328* *3,703* *3,798*
Minimum minutes	1.08 (1.01, 1.15)	0.97 (0.84, 1.10)	1.24 (1.17, 1.32)	1.24 (1.11, 1.38)
Percent urban	0.96 (0.90, 1.02)	0.91 (0.82, 1.01)	0.96 (0.89, 1.02)	1.00 (0.90, 1.11)
Deprivation index	1.05 (0.98, 1.13)	1.03 (0.93, 1.15)	1.08 (1.01, 1.16)	1.00 (0.87, 1.14)
Proxy for smoking	1.11 (1.03, 1.20)	1.01 (0.89, 1.15)	0.93 (0.86, 1.00)	0.81 (0.71, 0.92)
Deprivation* Smoking	--	--	--	--
Radiotherapy treatment No† Yes	 1 1.30 (1.11,1.52)	 1 2.40 (1.90, 3.05)	 1 1.06 (0.72, 1.57)	 1 0.63 (0.45, 0.89)

Notes: All analyses have been adjusted for age and period of diagnosis, marital status, surgery, regional extension, regional lymph nodes, and grade of First Primary Cancer, and other variables in table. Colon cancer also adjusted for proximal or distal location of tumor. All continuous variables are mean centered and divided by 1 standard deviation. Average month VDR: Mean = ~ 750 J/m^2 ; Per unit VDR = ~ 190 J/m^2 ; Average month MM: Mean =~ 19.5; Per unit MM = ~ 11.0 MM; Urban level: Least-urban: <85%; mostly-urban 85-99%; All-urban = 99% or more. For detailed values, see the Appendix.†=referent.

Table 9: The Adjusted odds of first course radiotherapy treatment among male White and Black first primary prostate, colon or rectal cancer patients.

First Primary Cancer Factors	Odds of Radiotherapy Treatment for First Primary Prostate Cancer	Odds of Radiotherapy Treatment for First Primary Colon Cancer	Odds of Radiotherapy Treatment for First Primary Rectal Cancer
	n=281,750	n=62,312	n=29,331
	adjusted OR (95% CI)	adjusted OR (95% CI)	adjusted OR (95% CI)
Constant	2.00 (1.92, 2.09)	0.03 (0.02, 0.05)	0.55 (0.47, 0.66)
Patient age at diagnosis:			
50 to <65†	1	1	1
65 to < 74	1.22 (1.20, 1.25)	0.70 (0.63, 0.79)	0.72 (0.68, 0.77)
75+	0.48 (0.47, 0.50)	0.34 (0.30, 0.40)	0.41 (0.38, 0.44)
Race			
White†	1	1	1
Black	0.90 (0.87, 0.92)	0.93 (0.77, 1.12)	0.99 (0.89, 1.10)
Married at diagnosis			
No†	1	1	1
Yes	1.61 (1.57, 1.64)	1.20 (1.06, 1.36)	1.20 (1.13, 1.28)
Year of Diagnosis			
1978 – 1988†	1	1	1
1988 - 1998	0.50 (0.48, 0.51)	0.79 (0.71, 0.89)	2.09 (1.96, 2.23)
1998 - 2003	0.47 (0.46, 0.49)	0.61 (0.53, 0.71)	2.76 (2.57, 2.97)
Grade			
1†	1	1	1
2	1.43 (1.39, 1.47)	1.24 (1.04, 1.49)	1.45 (1.32, 1.60)
3	1.52 (1.47, 1.57)	1.76 (1.43, 2.15)	1.99 (1.78, 2.22)
4	1.52 (1.35, 1.72)	1.63 (0.94, 2.83)	2.03 (1.33, 3.08)
9	0.79 (0.76, 0.83)	1.07 (0.86, 1.32)	0.85 (0.76, 0.95)
Regional extension			
No†	1	1	1
Yes	1.56 (1.51, 1.62)	3.08 (2.71, 3.49)	2.49 (2.35, 2.64)
Positive nodes			
No†	1	1	1
Yes	1.44 (1.36, 1.52)	2.05 (1.84, 2.28)	2.49 (2.35, 2.65)
Surgery			
No†	1	1	1
Yes	0.07 (0.07, 0.07)	0.27 (0.18, 0.41)	0.21 (0.18, 0.24)
Proximal or Distal			
Proximal †	--	1	--
Distal		2.24 (2.01, 2.49)	

Notes: †=referent. All variables have been adjusted for the other variables presented in this table. The continuous variables presented above are mean centered and divided by 1 standard deviation. See the Appendix for details.

CONCLUSION

Our review article suggests that environmental D plays an important role for most adults as a primary source of vitamin D and characterizes current survey data on race/ethnicity deficiency levels in the U.S. population. In any given environment, those with the highest level of deficiencies are non-Hispanic Blacks and those with the lowest levels are non-Hispanic Whites, with most Hispanics (of any race) falling in between.[3,13,17] This is consistent with our understanding of the relationship between sun-reactive Skin Types, their correspondence to White, Blacks and Hispanic populations in the U.S., and the relative differences in exposure time needed to obtain an adequate amount of vitamin D from environmental sources. [4,11,25,37]

There appear to be important differences between colorectal and prostate cancer, as well as other factors, that have bearing on assessing their association with vitamin D. Both prospective studies measuring circulating vitamin D concentrations and ecologic studies based on estimates of UV-B radiation levels have yielded similar protective associations for colorectal cancer, with a stronger effect observed for mortality than incidence.[1,19,29,35] Study findings for prostate cancer have been less consistent depending on the study design and exposure characterization used.[1,5,19,20] The strongest protective association for prostate cancer appears to be on incidence and results from a high early life or long-term environmental exposure, as documented in the few analytic observational studies with this data.[14,23,24] Additional research suggests that colorectal cells are able to convert or utilize vitamin D after the onset of cancer, while prostate cells may not.[12,18] At least one study has also suggested that high annual environmental

exposure to vitamin D effective radiation may also be protective against fatal prostate cancer.[36] A similar beneficial effect on survival has also been reported for males diagnosed with prostate cancer during summer or autumn months when circulating levels of vitamin D are at their highest.[28,30,34]

Interestingly, most studies that reported a strong protective association of high environmental UV-B radiation levels on prostate or colorectal cancer in the U.S. were conducted on White populations; [15,21,23,24,35] contrary to expectations, studies that included Blacks usually reported a much weaker geographic association.[1,5,19] These disparate findings have been attributed to differences between Whites and Blacks in the length of exposure needed to obtain a comparable amount of vitamin D from the same environment, but how this may be associated with the distribution of colorectal or prostate cancer has yet to be determined. Many of these studies were limited by a purely ecologic design and/or used exposure data that failed to address the needs of non-Caucasian populations.[1,15,19] This dissertation specifically attempts to address this issue.

In our first analysis, a cohort of non-Hispanic Black ("Black) and non-Hispanic White ("White) males aged 50 years and older who were diagnosed with a non-metastatic first primary colorectal or first primary prostate cancer during 1978-2003 were selected from the SEER cancer registry and followed for 10 year survival from disease. Our findings in that study suggest that increasing levels of vitamin D radiation are moderately associated with a decreased risk of death from disease within 10 years for both prostate and colorectal cancer patients residing in all-urban areas (99% urban or more). Contrary to this, a moderate increase in risk with levels of vitamin D radiation were observed for all patients residing at the least-urban areas (<85% urban). Previous

studies have identified urban residence as an independent risk factor for both prostate and colorectal cancers, though the reasons for this are somewhat unclear.[31-33] Urban living has also been associated with decreased time spent outdoors and a reduction in physical activity;[31-33] it is also known that urban pollution may reduce the amount of environmental D available in the environment by as much as 50%.[7,10,27]

Given the more than adequate sample size, this manuscript also included a sub-analysis of patients whose state of birth matched their state of residence at time of diagnosis which has been successfully used in the few other observational studies to infer presumed long-term exposure.[14,23] In keeping with these studies, we also observed a stronger protective association of presumed long-term exposure among patients who resided at the all-urban level, while it had little effect on risk estimates we observed among patients residing in least-urban areas. In most of our analyses, a slightly stronger effect was observed among prostate patients than among those with colon or rectal cancers, although our competing risk analysis suggests this effect may be overestimated for the former. In general, our findings also support that Blacks residing in all-urban areas appear to be at greater risk than Whites and that this risk may be associated with their environmental D exposure needs.

The results of our MPC analysis indicate that non-Hispanic Blacks have an increased risk for colon-prostate, rectal-prostate and prostate-colon MPCs compared to non-Hispanic White patients. It is possible that some of this risk may be related to differences between Blacks and Whites in their relationship to environmental D in their residential environment. Among patients with first primary rectal or first primary colon cancer, increasing levels of vitamin D radiation appears to be modestly protective for the

development of subsequent primary prostate cancer. To a lesser extent, increasing levels of vitamin D radiation among primary prostate cancer patients may be protective for subsequent primary colon cancer. This protective association, however, does not appear to be shared equally by Blacks during all follow up periods, particularly for rectal-prostate MPCs.

Unlike the results discussed above from our survival analysis, no interaction between environmental D and urban level was found in our MPC analysis. Our study also found that increasing levels of our proxy for smoking, often in conjunction with increasing levels of socio-economic deprivation, was associated with an increased risk during various follow up periods for all of our MPC pairings. To date, few studies have examined smoking as a common factor but it is thought to contribute to a large number of MPC.[8] Interestingly, smoking has also been reported to reduce the amount of vitamin D in individuals,[2] though no interaction between this variable and either of environmental D exposure characterizations was observed in this study.

In keeping with other papers, we also found that radiotherapy status was associated with increased risks of both prostate-colon and prostate-rectal MPCs and that this risk depended heavily on the period of follow-up. In our study, the increased risk associated with radiotherapy in our study largely occurred at least 5 years after radiotherapy with most occurring after a lag of 10 or more years. Contrary to this but in keeping with another analysis of the SEER data reported elsewhere,[22] our study also suggests that radiotherapy treatment for rectal cancer reduces the risk of subsequent prostate cancer. Although the reasons for this are not clear, it is hypothesized that the unintended radiation reaching the prostate may effectively pre-treat any developing

cancer.[22,26] Our study also suggests that this protective association is greatest within the first 5 years after radiotherapy and diminishes afterwards. No interaction was observed between radiotherapy and any of the other variables in our MPC analysis, including environmental D.

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PUBLIC HEALTH IMPLICATIONS

One of the aims of our analysis was to estimate the differential effects of environmental D on non-Hispanic Whites and Blacks given the suggested role that vitamin D may play in the disparities observed between these groups for prostate and colorectal cancers. As such, this research works towards our national goal of reducing health disparities by identifying possible factors and high-risk groups for intervention.

The findings of the survival analysis conducted on non-metastatic cancer patients suggests that after adjusting for other factors, Blacks have a higher hazard of death than Whites and that this risk may be modestly associated with their greater environmental D exposure needs. Interestingly, a protective association was observed with increasing vitamin D radiation levels among prostate and colon patients residing in all-urban areas, while an increase in risk was observed among patients residing in the least-urban areas. Our study also supports that Blacks are generally at higher risk than Whites for developing most MPCs in this pairing and that multiple factors including environmental D, smoking and socio-economic deprivation may increase the risk of developing subsequent primary cancers. Given these findings reported on survival, further research on the possible interaction between environmental D and urban level seems justified. With respect to MPCs, our results may be of particular use to physicians in identifying patients who may be at higher risk for subsequent primary tumors since the risks associated with several of the factors examined in this study have not been previously reported.

Finally, in our survival analysis we introduced an exposure characterization based on sun-reactive Skin Type that offered a fairly comparable way to examine the differential effects of race/ethnicity and vitamin D radiation level. The well-known UV Index, which is estimated based on maximum UV exposure times for Fitzpatrick sun-reactive Skin Types I –

II, is one such widely used measure. The results of this analysis found that patients of either race/ethnicity residing in all-urban areas had a moderate increase in the hazard of death as their environmental D exposure needs increased, while having greater exposure needs appeared to be protective for patients residing in the least-urban areas. It is possible that this type of exposure characterization, which is easily presented in terms of minutes spent outdoors during the noon hour, offers an easier way to communicate these issues to a wider, less-technical audience than using vitamin D radiation level. For medical practitioners in particular, it may offer a more usable basis for evaluating and communicating the attendant risks to their patients.

APPENDIX

Table 1. The distribution of White and Black non-Hispanic male patients in the Prostate, Colon and Rectal Cohorts by SEER Registry, 1978-2003.

SEER Registry	Prostate Cohort *n=300,281*		Colon Cohort *n= 65,563*		Rectal Cohort *n= 31,205*	
	White, non-Hispanic (%)	**Black, non-Hispanic (%)**	**White, non-Hispanic (%)**	**Black, non-Hispanic (%)**	**White, non-Hispanic (%)**	**Black, non-Hispanic (%)**
	n=246,403	*n=35,347*	*n=56,903*	*n=5,409*	*n=27,401*	*n=1,930*
San Francisco-Oakland	11.1	13.4	12.6	15.5	12.1	16.6
Connecticut	12.5	6.8	18.0	8.8	18.4	8.1
Metropolitan Detroit	14.6	36.4	14.4	35.8	15.4	34.9
Iowa	13.2	1.2	16.9	1.7	17.1	1.4
New Mexico	5.0	0.9	3.6	0.9	3.7	1.1
Seattle-Puget Sound	16.1	3.7	13.3	3.6	13.9	3.9
Utah	7.2	0.3	4.5	0.2	4.8	0.4
Metropolitan Atlanta	5.3	15.8	5.0	14.8	4.3	13.9
San Jose-Montery†	3.6	1.0	2.6	0.7	2.4	0.9
Los Angeles†	11.2	19.7	8.9	17.2	7.8	17.8
Rural Georgia†	0.2	0.7	0.2	0.8	0.1	1.1

Notes: † Joined SEER in 1992; all other registries in this table in SEER by 1978.

Source:
Data retrieved from: National Cancer Institute. Surveillance Research Program. Surveillance, Epidemiology and End Results. (2011). *SEER Program Limited-Use Data* (1973-2008), released April 27, 2011. (Error reported October 28, 2011: Corrected copy, 11/9/11).

Table 2. The range of county level vitamin D radiation and minimum minutes of exposure by SEER Registry.

SEER Registry Name:	No. of counties	Vitamin D Effective Radiation at Noon††			Minimum Minutes at peak hours required to achieve 1 SDD using ¼ MED†††					
		Average month	June	December	Average month		June		December	
		Joules /m^2	Joules /m^2	Joules /m^2	Types I-III	Types IV-VI	Types I-III	Types IV-VI	Types I-III	Types IV-VI
	n=211	Min, Max	Min, Max	Min, Max	Min, Max	Min-Max	Min-Max	Min-Max	Min-Max	Min-Max
San Francisco-Oakland	5	926.2, 951.9	1564.8, 1600.8	230.0, 244.1	10.7, 11.3	29.3, 30.8	4.1, 4.2	11.2, 11.5	27.4, 29.1	74.8, 79.6
Connecticut	8	597.4, 629.6	1084.9, 1123.6	116.5, 133.9	17.9, 19.8	48.9, 54.2	5.8, 6.0	15.9, 16.4	49.1, 56.3	134.2, 154
Metropolitan Detroit	3	587.9, 607.0	1097.4, 1121.5	106.2, 115.1	19.8, 21.0	54.1, 57.5	5.8, 6.0	15.9, 16.3	57.2, 61.8	156.3, 168.9
Iowa	99	624.2, 711.7	1165.3, 1270.7	117.7, 162.8	15.2, 19.4	41.6, 53.1	5.1, 5.6	14.1, 15.4	40.3, 55.8	110.1, 152.4
New Mexico	34	977.4, 1201.5	1560.5, 1829.3	327.3, 489.5	6.7, 9.0	18.4, 24.6	3.6, 4.2	9.9, 11.5	13.4, 20.1	37.0, 54.9
Seattle-Puget Sound	13	491.0, 552.1	960.8, 1061.4	44.7, 62.8	31.0, 41.2	84.7, 112.6	6.2, 6.8	16.9, 18.6	105.1, 149.3	287.4, 408.2
Utah	29	815.9, 1031.4	1451.0, 1681.6	177.7, 327.1	8.8, 13.5	24.1, 36.9	3.9, 4.5	10.7, 12.3	20.1, 37.0	56.0, 101.0
Metropolitan Atlanta	5	906.7, 918.0	1368.2, 1373.9	344.4, 358.7	8.9, 9.1	24.3, 24.9	4.8, 4.8	13.1, 13.1	18.3, 19.0	50.0, 51.9
San Jose-Monterey†	4	968.6, 1003.2	1622.0, 1655.7	253.1, 279.9	9.7,-10.4	26.5,-28.4	4.0, 4.1	10.8, 11.1	23.9, 26.3	65.2, 71.9
Los Angeles†	1	1059.9	1621.3	381.0	8.1	22.1	4.0	11.0	17.3	47.1
Rural Georgia†	10	909.6,-926.9	1344.4, 1363.4	360.2, 382.0	8.6, 8.9	23.5, 24.3	4.8, 4.9	13.1, 13.3	17.2, 18.2	46.9, 49.8
Mean (1 S.D.)		791.6 (185.9)	1352.2 (223.7)	212.4 (115.3)	15.1 (6.7)	41.2 (18.4)	5.0 (0.8)	13.6 (2.2)	41.7 (25.5)	114.0 (69.7)

Notes: Average month = sum of values for (January to December), divided by 12.
† Joined SEER in 1992; all other registries in this table in SEER by 1978.
††The vitamin D action spectrum-weighted UV (VDER) in J/m^2 at the noon hour.
†††1 SDD (Standard vitamin D Dose) equal to approximately 1000 I.U., achieved using ¼ MED (personal Minimal Erythemal Dose) using hands face and arms; calculated for Types I-III using the mean value for Fitzpatrick sun-reactive Skin Types I-III; calculated for Types IV-VI using mean values for Fitzpatrick sun-reactive Skin Types IV-VI.

Source: Environmental D values calculated for SEER areas using data from Fioletov, V.E., McArthur, L. J. B., Mathews, T. W., & Marrett, L. (2010b). Estimated ultraviolet exposure levels for a sufficient vitamin D status in North America. *Journal of Photochemistry and Photobiology B-Biology*, 100(2), 57-66. doi:10.1016/j.jphotobiol.2010.05.002.

Table 3. The range of county level social and economic covariates by SEER Registry.

SEER Registry Name	No. of counties n=211	Percent Urban Population			Percent in Same House or County for 5 years			Deprivation index			Age-Adjusted County Lung Mortality Rate per 100,000 1975-2004	
		1980	1990	2000	1980	1990	2000	1980	1990	2000	Whites	Blacks
		Min, Max	Min, Max	Min, Max	Min, Max	Min, Max	Min, Max	Min, Max	Min, Max	Min, Max	Min, Max	Min, Max
San Francisco-Oakland	5	93.3, 100.0	93.2, 100.0	94.2, 100.0	69.8, 77.2	72.5, 75.4	73.9, 77.2	-1.42, 0.64	-1.04, 0.2	-1.1, 0.3	206.6, 254.6	318.6, 397.1
Connecticut	8	34.9, 87.5	31.9, 88.2	51.1, 95.9	71.7, 86.4	69.6, 85.0	73.9, 85.7	-1.02, -0.24	-1.11, -0.3	-1.0, 0.6	229.6, 297.8	133.8, 374.6
Metropolitan Detroit	3	89.5, 98.4	89.5, 98.8	94.9, 99.3	77.9, 91.6	79.1, 91.5	80.6, 89.9	-0.65, 1.29	-0.73, 1.5	-0.8, 1.3	253.7, 316.0	296.7, 440.4
Iowa	99	0.0, 92.1	0.0, 94	0.0, 94.1	54.4, 88.3	58.4, 88.8	58.2, 88.1	-1.23, 0.57	-1.19, 0.4	-1.2, 0.4	178.5, 341.4	0.0, 4679.2
New Mexico	34	0.0, 96.4	0.0, 97.2	0.0, 95.6	54.9, 86.0	62.4, 88.2	64.7, 88.6	-1.52, 4.18	-1.49, 4.7	-1.6, 5.3	112.1, 286.0	0.0, 956.5
Seattle-Puget Sound	13	0.0, 91.9	0.0, 94.2	0.0, 96.3	48.6, 79.1	53.6, 81.3	62.6, 82.5	-0.48, 0.29	-0.87, 0.7	-0.8, 0.8	145.5, 330.5	0.0, 3256.6
Utah	29	0.0, 99.1	0.0, 99.4	0.0, 98.8	47.0, 82.1	59.7, 86.4	59.4, 84.3	-0.78, 3.39	-0.65, 4.6	-1.0, 4.7	30.4, 371.6	0.0, 1754.7
Metropolitan Atlanta	5	69.9, 97.5	86.4, 97.5	97.4, 99.6	56.9, 76.6	57.7, 71.4	61.5, 66.3	-0.85, 1.35	-0.87, 0.8	-0.6, 0.8	270.0, 406.8	179.2, 361.5
San Jose-Monterey†	4	45.9, 97.7	52.4, 97.9	77.4, 98.8	67.0 75.2	69.8, 77.8	71.2, 79.2	-0.35, 0.98	-0.25, 0.5	-0.2, 1.0	200.3, 231.2	192.3, 416.2
Los Angeles†	1	98.9	99.1	99.3	82.9	83.0	87.7	0.74	0.94	1.6	229.1	347.3
Rural Georgia†	10	0.0, 47.0	0.0, 33.5	0.0, 40.2	81.9, 93.8	73.2, 90.6	72.4, 88.0	1.24, 3.73	0.69, 2.9	0.2, 3.2	305.9 - 436.9	217.6 – 416.0
Mean (1 S.D.) ††		44.8 (30.3)	45.6 (31.0)	47.8 (31.8)	77.3 (8.7)	80.0 (7.1)	78.7 (6.5)	0.0 (1)	0.0 (1)	0.0 (1)	233.14 (66.6)	259.6 (595.4)

Notes: Average month = sum of values for (January to December), divided by 12.
† Joined SEER in 1992; all other registries in this table in SEER by 1978.
†† Mean values and standard deviations prior to transformation. 1990 values were used in all analysis, centered around mean and divided by one standard deviation.

Sources:
Census data, including data used to create the deprivation indexes, retrieved from: *Social explorer*. New York, NY : Oxford University Press. (Computer file). Available at: http://www.socialexplorer.com/pub/home/home.aspx;
Age-Adjusted County Lung Mortality Rate per 100,000 1975-2004, retrieved from: National Cancer Institute. (2011) *Cancer Mortality Maps*. Retrieved on November 1, 2011, from: http://ratecalc.cancer.gov/ratecalc/

Table 4. Range, mean values and standard deviations for environmental D exposure in the First Primary Prostate, Colon and Rectal Cohorts.

Environmental D Range Max, Min (Mean, SD)	**Prostate Cohort**	**Colon Cohort**	**Rectal Cohort**
Vitamin D Radiation†			
Average Month	491.6, 1201.5 (769.0, 198.7)	491.6, 1201.5 (749.5, 187.8)	491.6, 1201.5 (741.0, 185.6)
June	960.8, 1829.3 (1316.3, 241.7)	960.8, 1829.3 (1292.7, 230.6)	960.8, 1829.3 (1284.0, 229.4)
December	44.7, 489.5 (196.9, 115.9)	44.7, 489.5 (186.1, 107.4)	44.7, 489.5 (180.7, 105.2)
Minimum Exposure Minutes††			
Average Month	6.7, 105.7 (20.1, 12.5)	6.7, 105.7 (19.3, 11.0)	6.7, 105.7 (19.1, 10.3)
June	3.6, 18.6 (6.2, 3.1)	3.6, 17.9 (6.0, 2.7)	3.6, 18.0 (5.8, 2.4)
December	13.4, 385.7 (57.7, 42.4)	13.4, 385.7 (55.3, 37.6)	13.4, 385.7 (55.0, 35.9)

Notes: Average month = sum of values for (January to December), divided by 12. This table presents the mean values and standard deviations prior to transformation. For analysis, all values were centered around their mean and divided by one standard deviation.
†The vitamin D action spectrum-weighted UV (VDR) in J/m^2 at the noon hour.
†† Minimum Exposure minutes represent the average time required for White and Black patients in these cohorts given their county of residence at diagnosis for 1 SDD (Standard vitamin D Dose) equal to approximately 1000 I.U., achieved using ¼ MED (personal Minimal Erythemal Dose) using hands face and arms. See text for manuscript #2 for methods.

Source: Environmental D values calculated using data from Fioletov, V.E., McArthur, L. J. B., Mathews, T. W., & Marrett, L. (2010b). Estimated ultraviolet exposure levels for a sufficient vitamin D status in North America. *Journal of Photochemistry and Photobiology B-Biology*, 100(2), 57-66. doi:10.1016/j.jphotobiol.2010.05.002.

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Epidemiology. School of Public Health, University of Medicine and Dentistry of New Jersey, 2004 to present.
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Thesis advisor: Dr. Kitaw Demissie.

MPH Epidemiology. School of Public Health, University of Medicine and Dentistry of New Jersey, 2000 - 2004. Degree awarded May 2004.
Fieldwork project: "*Population Density as a Marker for an Infectious Origin of Childhood Leukemia*." Fieldwork advisor and site supervisor: Dr. Daniel Wartenberg. Public Health Traineeship 2000-2001.

MA Education. School of Education, New York University, 1995-1996.
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Areas: Teaching English to Speakers of Other Languages, electives in health education.

MA Performance Studies. Graduate School of Arts and Sciences/Tisch School of the Arts, New York University, 1989-1994. Degree awarded January 1995.
Areas: anthropology, cultural theory, visual and performing arts.

MLS Librarianship. School of Communication, Information and Library Service, Rutgers University, 1984-1986. Degree awarded May 1986.
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Librarianship

Reference and Instruction Librarian; Reference Resources Coordinator
Skillman Library, Lafayette College, Easton PA, August 2000 to present.

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Anthropology and Women's Studies Librarian
Bobst Library, New York University, New York, NY, September 1989 to August 1997.

PUBLICATIONS

A. Refereed Original Articles in Journals

Abruzzi A and Fried B. (2011). Coinfection of trematodes with other organisms in vertebrate hosts. *Advances in Parasitology* 77:1-85. doi: 10.1016/B978-0-12-391429-3.00005-8.

Fried B and Abruzzi A. (2010). Food-borne trematode infections of humans in the United States of America. *Parasitology Research* 106:1263–1280. doi: 10.1007/s00436-010-1807-0.