Chapter

Vitamin D Status and Cancer Incidence and Mortality

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Introduction

The role of excessive sun exposure in increasing risk of skin cancers is well established. Less known, less established and more controversial is the potential role of sun exposure in reducing risk of several types of internal cancers. The hypothesis that sunlight may be beneficial against several types of cancer extends back almost seven decades. Initially, Peller and Stephenson observed higher rates of skin cancer, but lower rates of other malignancies in United States Navy personnel in the 1930s.[1] Based on this observation, Peller and Stephenson hypothesized that acquiring skin cancer conferred immunity against other cancers. Several years later, Apperly observed an association between latitude and cancer mortality rate, which led him to state that "The presence of skin cancer is really an occasional accompaniment of a relative cancer immunity in some way related to the exposure to solar radiation".[2] However, no plausible mechanism was proffered and these observations were essentially ignored for about four decades. In 1980, Garland and colleagues hypothesized that the potential benefit of sun exposure was attributed to vitamin D.[3] Initially, the hypothesis was centered on colon cancer,[3] but later it was extended to breast cancer,[4] ovarian cancer,[5] prostate cancer,[6,7] and to multiple cancer types.[8]

When Garland and colleagues hypothesized a role of vitamin D, the hypothesis was premised on the fact that sun exposure increases vitamin D levels, but the varied actions of vitamin D were not well understood at the time. Subsequently, the potential benefit of vitamin D on cancer risk has received substantial experimental support. These laboratory studies have suggested the following model: many cells types, normal as well as neoplastic, express vitamin D receptors, express 1-α-hydroxylase which can convert 25(OH)D to the active 1,25$(OH)_2$D and activation of the vitamin D receptor induces a number of anti-cancer properties, including reduced proliferation, invasiveness, angiogenesis and metastatic potential and increased differentiation and apoptosis.[9] Such data suggest that autocrine or paracrine influences of 25(OH)D could potentially help retard cancer causation or progression in some tissues. If the 25(OH)D level is rate limiting for these actions, associations with indicators of vitamin D status and cancer incidence and mortality should be observable in human populations, depending on the dose-response relation and on the range of vitamin D status in the specific population considered.

Since Garland's initial hypothesis, a number of epidemiologic studies have generated evidence regarding the role of sun exposure or vitamin D on risk of various cancers. In these studies, the measurement of sun exposure is assumed to be a determinant of vitamin D status. The basis of this assumption is that the vast majority of vitamin D in most human populations is made through exposure to solar UV-B radiation. However, it is possible that sun exposure has other yet to be identified effects. Limited randomized trial data to test the vitamin D-cancer hypothesis are currently available. This chapter provides a review and synthesis of these studies, focusing on the

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relative strengths and limitations of the various approaches that have been utilized to evaluate the relationship between vitamin D status and cancer occurrence or progression.

Ecologic Studies of Sun Exposure

Latitude or region UV-B radiation has been examined in relation to various cancers.[3-8,10] In general, lower incidence and mortality rates of various cancer have been noted in regions with greater solar UV-B exposure. For example, Grant showed that regional UV-B radiation in the United States correlated inversely with mortality rates of numerous cancers, especially for cancers of digestive organs.[8] In Grant's analysis, the strongest associations were observed for cancers of the colon and rectum; out of all the preventable cancers estimated attributable to living in a low sun area, 60% were due to colorectal cancer in men; in women, 35% were due to colorectal cancer and 42% were attributable to breast cancer. In total, at least 15 types of cancers have been correlated with low sun exposure.[11] Those of the colorectum and breast appear to be most important quantitatively.

An important limitation of these ecologic studies is that other potentially confounding factors related to regional differences in solar UV-B radiation could account for the associations; thus, a cause-effect association is not secure. However, corroborating evidence that an inverse association between regional solar UV-B exposure and cancer risk may be causal is that this association is observed in regions outside of the United States. Indeed, similar relationships have been observed in diverse populations such as in Japan for digestive organ cancers (esophagus, stomach, colon, rectum, pancreas and gallbladder and bile ducts)[10] and Spain.[12] Thus, a putative confounding factor would have to have similar relationships with regional solar UV-B exposure in diverse populations such as in the United, Spain and Japan. This possibility cannot be excluded, but appears somewhat remote.

The capability of region to act as a surrogate of solar UV-B radiation and vitamin D status is prone to a number of complexities. These include increasing urbanization over time and more time spent indoors, winter vacations to sunny climates and altered sun exposure behavior such as sun avoidance or use of sun-screen. These factors could vary among populations and could change over time within the same population. Of note, in a study in Spain,[12] the rates a number of cancers correlated inversely with rates of nonmelanoma skin cancer. This finding confirms that region is a good surrogate of actual UV-B exposure, at least in some circumstances, because rates of nonmelanoma skin cancer (especially squamous cell cancer) are very likely associated with cumulative sun exposure. A potential strength of ecologic studies is that they may provide some indication of sun exposure during childhood and adolescence; such an assessment may be difficult in typical cancer cohort or case-control studies, which are usually conducted in adulthood. Even cancers that are diagnosed in middle-aged or elderly individuals may have been initiated during childhood.

Case-Control and Cohort Studies of Sun Exposure

Ecologic data examine hypotheses at the population level. Case-control and cohort studies, called analytic epidemiologic studies, assess exposure and outcome at the individual level. In principle, confounding may be better controlled because typically more detailed information can be assessed on other covariates in analytic studies. In addition, the study population may be relatively homogenous, which may reduce the potential for residual or uncontrolled confounding that may not be captured by multivariate analysis. An additional strength of such studies is that exposure is actually assessed for the individual, whereas in ecologic studies exposure is inferred—for example, presumably living in sunnier regions may allow for greater opportunity for sun exposure, but actual exposure will depend on the individuals' behaviors. Because the strengths and potential limitations of ecologic and analytic epidemiologic studies differ, these two sources of data can be considered complementary.

Several case-control and cohort studies have assessed surrogates of sun exposure in relation to cancer risk. Prostate cancer appears to be the most studied cancer through this method. In a cohort study of 3414 white men, among whom 153 developed prostate cancer based on NHANES I data, residence in the South at baseline (relative risk (RR) = 0.68), state of longest residence in

the South (RR = 0.62) and high solar radiation in the state of birth (RR = 0.49) were associated with significant reductions in prostate cancer risk.[13] In a recent population-based cohort study conducted in the Netherlands, male skin cancer patients diagnosed since 1970 (2,620 squamous cell carcinomas, 9,501 basal cell carcinomas and 1,420 cutaneous malignant melanomas) were followed up for incidence of invasive prostate cancer until 2005.[14] Skin cancer patients had an 11% reduction in total prostate cancer and a 27% reduction in advanced prostate cancer relative to expected population rates. The reduction was especially seen in patients with skin cancers that were located in the chronically ultraviolet radiation-exposed head and neck area.

An innovative approach has been to use a reflectometer to measure constitutive skin pigmentation on the upper underarm (a sun-protected site) and facultative pigmentation on the forehead (a sun-exposed site) to calculate a sun exposure index.[15] The difference between facultative skin pigmentation and constitutive pigmentation is a function of overall sun exposure, at least on the forehead. This measurement predicted risk of advanced prostate cancer in a case-control study. Specifically, a reduced risk of advanced prostate cancer was associated with high sun exposure determined by reflectometry (RR = 0.51) and high occupational outdoor activity level (RR = 0.73). Others have used factors such as childhood sunburns, holidays in a hot climate and skin type in case-control studies to predict prostate cancer risk. In a study in the United Kingdom, subgroups stratified by childhood sunburns, holidays in a hot climate and skin type displayed a remarkable 13-fold gradient in prostate cancer risk across extremes of sun and skin type exposure.[16,17]

Freedman et al[18] conducted a large death certificate based case-control study of mortality from five cancers: female breast, ovarian, colon, prostate and nonmelanoma skin cancer as a positive control to examine associations with residential and occupational exposure to sunlight. The cases consisted of all deaths from these cancers between 1984 and 1995 in 24 states of the United States. The controls were age frequency matched to a series of cases and excluded deaths from cancer and certain neurological diseases because of possible relationships with sun exposure. The investigators found that residential exposure to sunlight was inversely associated with mortality from female breast, ovarian, prostate and colon cancer. However, only female breast and colon cancer also were significantly inversely associated with jobs with the highest occupational exposure to sunlight (RR = 0.82 for breast cancer and RR = 0.90 for colon cancer). For both of these cancers, the inverse association with occupational sunlight was greatest in the geographical region of highest exposure to sunlight. Also, these associations were independent of occupational physical activity level. Nonmelanoma skin cancer, acting as a "positive control", was positively associated with both residential and occupational sunlight.

In the Health Professionals Follow-Up Study, men living in the northeastern and mid-Atlantic states had a statistically significant 24% higher rate of cancers of the digestive system compared to those living in the southern states.[19] This result was adjusted for multiple cancer risk factors, including age, tobacco use, body weight, physical activity, various dietary factors and alcohol. In a sample of the cohort, men living in these states were shown to have lower levels of 25(OH)D by 6.4 nmol/L compared to men living in the South. In a United States population-based case-control study of colon cancer limited to Northern California, Utah and Minnesota, estimated sun exposure by residence was only weakly and non-significantly associated with a reduced cancer risk (RR = 0.9).[20]

Prospective Studies of Circulating 25(OH)vitamin D and Cancer Risk

A relatively small number of studies have examined plasma or serum 25(OH) level in relation to cancer risk, especially for colorectal cancer and for prostate cancer. The circulating 25(OH)D level accounts not only for skin exposure to UV-B radiation, but also for total vitamin D intake and for factors such as skin pigmentation that all affect vitamin D status. 25(OH)D has a relatively long half-life ($t_{1/2}$) in the circulation of about 2-3 weeks and thus can provide a fairly good albeit imperfect indicator of long-term vitamin D status. For example, in one study of middle-aged to elderly men, the correlation of two 25(OH)D measures approximately three years apart was 0.7[21] In epidemiologic studies, circulating 25(OH)D has typically been based on a measure in archived

blood samples in a nested case-control study. Because the sample is taken before the diagnosis of cancer, in some cases over a decade before, it is unlikely that any association observed is spuriously due to the cancer influencing the blood level, a phenomenon referred to as reverse causation. Several studies have been based on the measurement of 25(OH)D in individuals already diagnosed with cancer; these studies need to be interpreted very cautiously because of the potential for the phenomenon of reverse causation. Results for studies of colorectal cancer, prostate cancer and breast cancer are briefly reviewed here.

Studies that have examined 25(OH)D levels prospectively in relation to risk of colorectal cancer or adenoma have generally supported an inverse association.[22-29] In a recent systematic review of the colorectal cancer studies, individuals with ≥33 ng/mL (82 nmol/L) serum 25-hydroxyvitamin D had 50% lower incidence of colorectal cancer ($p < 0.01$) compared to those with relatively low values of less than or equal to 12 ng/mL (30 nmol/L).[30] The total number of colorectal cancer cases was 535. The two largest studies were based on the Nurses' Health Study (NHS) and the Women's Health Initiative (WHI) In the NHS,[24] the multivariable RR, controlling for the known risk factors for colorectal cancer, decreased monotonically across quintiles of plasma 25(OH)D concentration, with an RR of about 0.5 for those with the highest compared to the lowest levels of 25(OH)D. In the WHI, a similar inverse association was observed between baseline 25(OH)D level and colorectal cancer risk. The WHI was primarily a randomized placebo-controlled trial of 400 IU vitamin D plus 1,000 mg a day of calcium in 36,282 postmenopausal women; however, as discussed below, the interventional component of this study did not support a protective role of vitamin D intake.[29] A similar reduced risk of colorectal cancer has been confirmed in the Health Professionals Follow-Up Study (submitted manuscript). Thus, based on multiple studies of circulating 25(OH)D and colorectal cancer risk, individuals in the high quartile or quintile of 25(OH)D had about half the risk of colorectal cancer as did those in the lowest group. The dose-response appears fairly linear up to a 25(OH)D level of at least 35-40 ng/mL and controlling for multiple covariates have had little influence on the findings.

Although ecologic studies of regional UV-B exposure and of sun exposure in case-control studies tend to support an association for sun exposure and prostate cancer risk, higher 25(OH)D level has not been clearly associated with a reduced risk for prostate, although some of the studies suggest weak inverse associations.[31-36] In addition, four studies that have evaluated dietary or supplemental vitamin D have not found substantial protection for prostate cancer.[37-40] Only two studies,[41,42] which were conducted in Nordic countries, supported an inverse association for 25(OH)D. However, one of these studies also found an increased risk in men with the highest 25(OH)D values.[42] Although $1,25(OH)_2D$ that is produced intracellularly is believed to be more important than circulating $1,25(OH)_2D$, several studies found supportive[32] or suggestive[33] inverse associations for circulating 25(OH)D and aggressive prostate cancer, particularly in older men. With further follow-up in the Physicians' Health Study, men with both low 25(OH)D and $1,25(OH)_2D$ were at higher risk of aggressive prostate cancer (RR = 1.9).[43] In the Health Professionals Follow-up Study, both lower 25(OH)D and $1,25(OH)_2D$ appeared to be associated surprisingly with lower (mostly early stage) prostate cancer risk[35] but possibly with higher risk of advanced prostate cancer, although numbers of advanced cases were limited (n = 60).[35] Thus, overall the studies of circulating 25(OH)D have been equivocal for prostate cancer; the association has not been as clear as that for colorectal cancer.

In one study, breast cancer cases had lower 25(OH)D levels than did controls.[44] Another study found that serum levels of 25(OH)D were significantly higher in patients with early-stage breast cancer than in women with locally advanced or metastatic disease.[45] However, the possibility of reverse causation cannot be ruled out in these two studies because 25(OH)D levels were assessed in women who already had breast cancer. In the Nurses' Health Study, stored plasma samples were assessed in 701 breast cancer cases and 724 controls.[46] Cases had a lower mean 25(OH)D level than controls (P = 0.01) and women in the highest quintile of 25(OH)D had a RR of 0.73 (P trend = 0.06) compared with those in the lowest quintile. The association was stronger in women ages

60 years and older, suggesting that vitamin D may be more important for postmenopausal breast cancer. There have been no other prospective studies of 25(OH)D level and breast cancer risk.

There is one report of a prospective study of serum 25(OH)D in relation to pancreatic cancer risk. This study was based on the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention cohort of male Finnish smokers.[47] Contrary to expectation, this study found a significant positive association between higher 25(OH)D levels and increased risk of pancreatic cancer. This association persisted in multivariate analysis and after excluding cases early in follow-up (to avoid reverse causation).

One analysis based on the Health Professionals Follow-up Study used a surrogate of 25(OH)D to examine risk of total cancer.[19] The analysis was based on a two-stage approach. First, in a sample of 1,095 men in this cohort circulating 25(OH)D levels were measured. Then, geographical region, skin pigmentation, dietary intake, supplement intake, body mass index and leisure-time physical activity (a surrogate of potential exposure to sunlight UV-B) were used to develop a predicted 25(OH)D score using multiple linear regression. This score can be interpreted as an estimate of 25(OH)D level. Secondly, the score was calculated for each of approximately 47,000 cohort members and then this variable was examined in relation to subsequent risk of cancer incidence and mortality using multivariate analysis. In the cohort analysis, a 25 nmol/L increment in predicted 25(OH)D was associated with a 17% reduction in total cancer incidence and an even greater 29% reduction in total cancer mortality. Additionally, digestive cancers (colorectal, pancreatic, stomach and esophageal cancers) were considered as a group, as these had been considered a priori to be most likely to be "vitamin D sensitive" based on ecologic geographic data in the United States and in Japan.[8,10] The risk reduction of total cancer incidence and mortality was largely though not solely due to a the reduction in digestive organ cancers; specifically, a 43% reduction in incidence and 45% reduction in mortality for these cancers was associated with a 25 nmol/L increment in 25(OH)D. A strong inverse association overall was also found for oral/pharyngeal cancers and for leukemias. Multivariate analysis of the major known risk factors for cancer risk had little influence on the findings.

The predicted 25(OH)D approach may have some advantages and disadvantages compared to the use of a single measurement of circulating 25(OH)D in epidemiologic studies. The measurement of 25(OH)D is more direct, intuitive and encompasses some of the sources of variability of 25(OH)D not taken into account by the score. The most important of these is actual sun exposure behaviors, such as type of clothing and use of sunscreen. However, in some aspects, the predicted 25(OH)D measure may provide a comparable or superior estimate of long-term vitamin D status over a single measurement of circulating 25(OH)D. Most importantly, some factors accounted by the predicted 25(OH)D score are immutable (skin color) or relatively stable (region of residence, body mass index). In contrast, circulating 25(OH)D level has a half-life of two to three weeks and thus a substantial proportion of variability picked up by a single blood measure would likely be due to relatively recent exposures that are not necessarily representative of long-term exposure. Of interest, in the Health Professionals Follow-Up Study, for colon and advanced prostate cancer, an actual measure of 25(OH)D and the score provide similar (approximately 40-50% reduction in colon cancer risk and suggestive but nonsignificant 20% reductions in advanced prostate cancer risk. These finding suggest that as a measure of long-term vitamin D status, presumably the exposure of interest, the predicted score provides a comparable assessment as does a single measurement of circulating 25(OH)D.

Studies of Vitamin D Intake

Vitamin D intakes are relatively low in general and in most populations much more vitamin D is made from sun exposure than is ingested. Nonetheless, vitamin D intake is an important contributor to 25(OH)D levels, especially in winter months in regions at high latitudes when it may be the sole contributor. A number of case-control and cohort studies have examined vitamin D intake in relation to risk of colorectal cancer or adenoma. These studies, which have been reviewed in detail previously, have generally found an inverse association between vitamin

D intake and risk of colorectal cancer or adenoma.[9,48,49] Many of the studies controlled for known or suspected risk factors for colorectal cancer. However, because calcium and vitamin D intakes tend to be correlated, the independent effects of vitamin D and calcium intakes may be difficult to separate entirely. The magnitudes of the risk reductions have been relatively modest in the range of 20 to 30% reductions in studies in the United States, where supplement use is higher and milk is fortified with vitamin D. Yet, even with added vitamin D from supplementation and fortification, vitamin D intake at typical levels currently do not raise 25(OH)D levels substantially and most variability in populations comes generally from sun exposure.

In contrast to colorectal cancer, studies of vitamin D intake and prostate cancer risk have generally not supported an association with prostate cancer incidence.[37-40] One report, which combined data from the Nurses' Health Study and the Health Professionals Follow-Up Study examined total vitamin D intake (from diet and supplements) in relation to pancreatic cancer risk based on 365 incident cases over 16 years of follow-up.[50] This study found a linear inverse association, with a significant 41 percent reduction in risk comparing high (≥600 IU/day) to low total vitamin D intake (<150 IU/day). There is some suggestive but limited evidence of a potential relationship between higher vitamin D intake and lower risk of breast cancer. [51-53]

Randomized Trial of Vitamin D Intake and Colorectal Cancer

Only one adequately powered randomized controlled trial has examined vitamin D intake in relation to cancer risk, specifically colorectal cancer. The WHI, a randomized placebo-controlled trial of 400 IU vitamin D plus 1000 mg a day of calcium in 36,282 postmenopausal women, did not support a protective role of calcium and vitamin D over a period of seven years, with 332 colorectal cancer cases diagnosed.[30] However, this study likely had important limitations. First, the vitamin D dose of 400 IU/day was probably inadequate to yield a substantial contrast between the treated and the control groups. Specifically, the expected increase of serum 25(OH)D level following an increment of 400 IU/day would be approximately 3 ng/ml. In comparison, in the epidemiologic studies of 25(OH)D, the contrast between the high and low quintiles was generally at least 20 ng/mL. This wide range is likely due primarily to differences in sun exposure. Further, the adherence was sub-optimal and a high percentage of women took nonstudy supplements, so the actual contrast of 25(OH)D tested between the treated and the placebo group in the intent-to-treat analysis was further reduced. An additional factor is that it is unclear if the duration of seven years was sufficiently long to show an effect. In fact, the epidemiologic data on duration, although limited, suggest that any influence of calcium and vitamin D intakes may require at least 10 years to emerge for colorectal cancer as the endpoint.[54] Thus, this WHI trial was probably not a robust test of the hypothesis that improving vitamin D status would lower the incidence of colorectal cancer.

Solar Radiation, Vitamin D and Survival Rate of Colon Cancer

Some recent studies have examined seasonal variation of the time of cancer diagnosis and treatment in relation cancer prognosis. The populations studied were in areas of high latitude, where vitamin D production does not occur during the winter months. The first study was conducted in Norway, where all cancer diagnoses since 1953 have been registered in the Cancer Registry. The investigators examined the influence of season of diagnosis on survival from colon, prostate and breast cancers.[55,56] No significant annual variation in the incidence rates of these cancers was found, suggesting that there was no seasonal bias in the diagnosis of cancers. The death rates at 18 months, 36 months and 45 months were 20 to 30% lower in the cancers diagnosed in autumn months compared with those diagnosed in the winter months. The findings were very statistically robust, being based on over 40,000 breast, colon and prostate cancer cases. Subsequently, some potential benefit of autumn season of diagnosis was observed for lung cancer with an approximately 15% lower case fatality for young male patients diagnosed during autumn versus winter.[57] Finally, in this population, season of diagnosis was examined in relation to survival from Hodgkin's lymphoma.[58]

A 22% improved survival was observed for autumn versus winter diagnosis and a 63% improved survival was noted for patients younger than 30 years.

A study of surgery season and vitamin D intake with recurrence-free survival in 456 early-stage nonsmall cell lung cancer patients was conducted in Boston, Massachusetts.[59] Patients who had surgery in the summer had a better recurrence-free survival than those who had surgery in the winter (adjusted hazard ratio, 0.75), with 5-year recurrence-free survival rates of 53% and 40%, respectively. Furthermore, patients who had surgery during summer with the highest vitamin D intake had better recurrence-free survival (adjusted hazard ratio, 0.33) than those who had surgery during winter with the lowest vitamin D intake, with the 5-year recurrence-free survival rates of 56% and 23%, respectively. Surgery season and vitamin D intake were similarly associated with overall survival. Subsequently, levels of 25(OH)D at the time of surgery were taken for these patients and similar results suggesting a survival benefit associated with high 25(OH)D levels was found.[60]

Recently, a large study of season of diagnosis and sunlight exposure in cancer survival for cancers of the breast, colorectum, lung, prostate and at all sites combined was conducted of over a million cancer patients from the United Kingdom.[61] The investigators found evidence of substantial seasonality in cancer survival, with diagnosis in summer and autumn associated with improved survival compared with that in winter, although the associations tended to be weaker than those observed in the Norwegian study. Reductions in the hazards ratio were observed for female breast cancer patients (hazard ratio, 0.86) and both male and female lung cancer patients (hazard ratio, 0.95). Cumulative sunlight exposure in the months preceding diagnosis was also a predictor of subsequent survival, although season of diagnosis was a stronger predictor than cumulative sunlight exposure.

The findings from these three studies indicate that summer/autumn season of diagnosis may improve survival for multiple cancers. The mechanism behind this influence of season is unclear, but could possibly relate to vitamin D status. In the late summer in Norway, 25(OH)D levels are about 50% higher than that in late winter. Wintertime vitamin D production is also minimal in Boston and in the United Kingdom, where the other studies were conducted. Effects of vitamin D in late carcinogenesis stages such as reduction in metastases are observed in numerous animal models. In some animal studies, vitamin D may improve tumor control by radiation treatment, possibly by promoting apoptosis.[62]

Vitamin D and Cancer Rates in United States Black Men

Melanin efficiently blocks UV-B induced production of vitamin D in the skin. Not surprisingly, darker skinned individuals, such as African-Americans, have been documented to have markedly lower vitamin D levels.[63-68] In African-Americans, low levels of vitamin D had been hypothesized to account for their higher prostate cancer rates,[6] more aggressive prostate and breast cancer,[69] and higher total cancer incidence and mortality.[9] In addition, an inverse association between regional solar UV-B radiation and mortality rate of breast, colon, esophageal and gastric cancers was demonstrated for African-Americans in one study.[70] In the Health Professionals Follow-Up Study cohort, a prospective study which consists of highly educated, generally health conscious male health professionals, even after adjusting for multiple dietary, lifestyle and medical risk factors, Black men were at 32% higher risk of total cancer incidence and 89% higher risk of total cancer mortality compared to Whites.[71] In multivariate analyses, Black men also had especially high risk of digestive organ malignancies (colon, rectum, oral cavity, esophagus, stomach and pancreas), the group of cancers that had been identified most strongly associated with low predicted vitamin D by other studies. The increased risk of these cancers in Black men was especially marked if they had additional risk factors for vitamin D deficiency, such as low vitamin D intake or living in the northeastern part of the United States.

The higher rates of these cancers in Blacks do not prove a cause and effect relationship because other factors could be relevant. Nonetheless, one cannot ignore that that African-Americans have a particularly high prevalence of hypovitaminosis D and they have higher rates of the types of malignancies that appear to be most associated with low sun exposure or vitamin D levels. Moreover,

the relationships appear stronger for mortality than for incidence. These patterns suggest that the high prevalence of vitamin D deficiency in African-Americans could potentially contribute to their substantially higher rates of cancer mortality.

Synthesis of Evidence Regarding Sun Exposure, Vitamin D and Cancer Incidence and Mortality

Since Garland and Garland initiated the hypothesis that vitamin D reduces cancer incidence and mortality in 1980, a number of epidemiologic and mechanistic studies have been conducted to test this hypothesis. This chapter has reviewed the major studies that have examined the vitamin D-cancer hypothesis. Many of the initial studies were based on correlation between incidence or mortality rates of various cancers with estimations of solar UV-B by region. In addition, a number of case-control and cohort studies have found that individuals with higher exposure to sun (measured in a variety of ways) have a reduction in cancer incidence and cancer mortality rates. Quantitatively, malignancies of the large bowel and breast appear to be the most important.

There are two major limitations in interpreting these studies; first, a confounding factor may account for the association with solar UV-B radiation and second, if one assumes the association is real, a factor other than vitamin D could be the causal protective factor. Confounding could occur if regions with more solar UV-B have a higher prevalence of a protective factor and/or a lower prevalence of a causal risk factor. Some of the ecologic analyses have accounted for some of the likely major confounding factors for cancer incidence (e.g., tobacco use, alcohol) and these do not seem to account for the association. Perhaps the strongest argument against confounding is that these associations have been observed in diverse populations, such as in the United States, Japan and Spain. It is not impossible, but appears unlikely that a consistent confounding factor would be operative in all these diverse populations. The second consideration is whether vitamin D does indeed account for the association. This is impossible to prove through such studies, though the mechanistic evidence for vitamin D appears strong and no other strong candidates for cancer protective effects of sunlight have been offered. Other lines of evidence are required to evaluate whether vitamin D is the causal agent.

Probably the most direct evidence for a role of vitamin D is from serum or plasma based studies of vitamin D status. To date, colorectal cancer and prostate cancer have received the most study. The studies have been relatively consistent for colorectal cancer and support about a doubling of risk of this malignancy associated with low levels of 25(OH)D. For prostate cancer, the data on circulating 25(OH)D have been equivocal, suggesting no association, or at least an association of a much weaker magnitude as has been observed for colorectal cancer. It is plausible that for prostate cancer, vitamin D level much longer before the time of diagnosis is most relevant, consistent with the notion that the process of prostate carcinogenesis encompasses a very long time period. Prostate cancer cells appear to lose 1-alpha-hydroxylase activity early in carcinogenesis, so it is plausible that exposure to vitamin D early in life is most relevant. In addition, determinants of prostate cancer incidence may differ from prostate cancer progression and ultimately mortality and most of the available data have assessed incident prostate cancer, as opposed to aggressive or fatal prostate cancer.

In the plasma- or serum-based studies, the best single indicator of vitamin D status, 25(OH)D, is assessed at the individual level and examined in relation to subsequent risk of cancer. Potentially confounding factors such as body mass index and physical activity are accounted for in the statistical analyses. A limitation is that although the $t_{1/2}$ in the circulation is only about 2-3 weeks, studies have been based on a single measurement throughout the year and the correlation with long-term (for example, over decades) vitamin D status is unclear. An important feature of these studies is that they are conducted in a single region or controlled for region so the variation in 25(OH)D levels is completely independent of region. This fact is critically important because if an association with cancer is shown, these results can be considered as completely independent supporting evidence from the studies based on regional solar UV-B level. It is unlikely that the same confounding factors would occur for region UV-B and for individual vitamin D levels in individuals in the same region.

At the ecologic level, the overall potential for sun exposure is assessed based on how much UV-B radiation is falling in that region. At the individual level within a specified region, this variable in not variant and behaviors and skin pigmentation determine actual exposure.

In regards to dietary studies, it is important to understand that in most populations diet contributes a relatively small proportion to vitamin D stores. For example, a glass of fortified milk, though generally perceived as being a good source of vitamin D contains only 100 IU vitamin D, whereas being exposed to enough UV-B radiation to cause a slight pinkness to the skin with most of the skin uncovered (1 minimal erythemal dose) produces vitamin D equivalent to an oral dose of 20,000 IU vitamin D.[72,73] On the other hand, in higher latitudes during the winter months no vitamin D is made from sun exposure so diets and supplements become relatively more important sources. One important issue is that ergocalciferol (D2) is often used in supplements and ergocalciferol has been estimated to be only one-fourth as potent as cholecalciferol (D3) in raising 25(OH)D.[74] Only colorectal cancers and adenomas have been reasonable well studied in relation to vitamin D intake and as a whole, the literature is suggestive of a moderate inverse association associated with higher intakes (i.e., about a 20 to 25% risk reduction). From epidemiologic studies, it has not been possible to study the effects of intakes above 600 IU per day, because few individuals have had such high intakes in the populations that have been studied to date. In addition, adequate calcium intake is a likely protective factor for colorectal cancer and in populations that fortify milk with vitamin D and that consume abundant milk products, calcium intake will tend to be correlated with vitamin D intake. Thus, it has not been possible to disentangle the independent effect of vitamin D from these studies.

In the past several years, some studies have found that prognosis of various cancers, including colon, breast, lung, prostate and Hodgkin's lymphoma may be better in those diagnosed and presumably treated in the summer months than in the winter months. These studies were conducted in northern latitudes (Norway, United Kingdom, northeastern United States) in which 25(OH)D levels differ markedly between summer and winter months. It is possible that a confounding factor accounts for these results, but they suggest the intriguing possibility that vitamin D status at the time of treatment may influence outcome of various cancers. Given that many patients are vitamin D deficient at the time of diagnosis, randomized intervention trials can be feasibly conducted in which high doses or vitamin D are provided to the randomized subjects to rapidly increase vitamin D stores at the time shortly before treatment.

Implications for Future Research

The data on vitamin D and cancer incidence or mortality are intriguing, but many important questions remain. Although not definitive at this point, the epidemiologic and supporting mechanistic and animal evidence indicate that vitamin D may have a role in reducing cancer incidence and progression. The "gold standard" study would be a randomized intervention that unequivocally demonstrates a reduction in cancer risk. The only relevant randomized study to date, the WHI, did not show a benefit of vitamin D, but several important limitations of that study cannot be ignored. Based on hypotheses suggested by the current evidence, several types of trials may be considered. A primary prevention trial with the endpoint of cancer incidence may be most difficult to achieve, because the time period needed and the required dose are unknown. Doses much higher than 400 IU/day of vitamin D and periods longer than seven years may be required to observe an effect. Trials of established intermediate endpoints, such as colorectal adenoma recurrence, may be useful. One such trial is currently being conducted (Baron J, personal communication). Other intermediate endpoints, such as cell proliferation and apoptosis in specific tissues would not be definitive, but such studies could provide useful complementary mechanistic evidence. Probably the most feasible trial design would be to enhance vitamin D status at the time of cancer diagnosis with high doses of vitamin D to test the hypothesis that vitamin D status may favorably interact with treatment. Such a trial may achieve a result within a relatively short time frame.

Beyond randomized trials, further observational studies would be useful in testing the hypothesis that vitamin D may help prevent cancer. Serum or plasma-based studies of a wider spectrum of

cancers than has been studied would be useful. Such studies could help establish the dose-response, what level of 25(OH)D is optimal and what intakes of vitamin D would be required to achieve this level. These studies can also help establish the role modifying factors, such as genetic variants in the vitamin D pathway and other factors such as retinol intake, which may antagonize the actions of vitamin D. In addition, the evidence for a causal association between sun exposure or enhanced vitamin D status and cancer risk can be fortified if these relationships are observed in a variety of diverse populations worldwide. If a relevant genetic polymorphism in the vitamin D pathway were consistently associated with a cancer, the evidence for causality would be increased. To date, only the vitamin D receptor has received substantial study and the functionality of polymorphisms studied have been unclear. Thus, perhaps not surprisingly, the results have been equivocal.

Confirming that vitamin D reduces risk of cancer incidence or mortality is critical because current health recommendations typically do not encourage high intakes of vitamin D and they tend to discourage sun exposure. Current dietary recommendations are geared only to prevent quite low vitamin D levels and if the association between vitamin D and reduced cancer risk is causal, such levels are almost definitely inadequate. While messages to avoid excessive sun exposure, which may cause skin aging and cancer, are appropriate, one cannot ignore that extreme avoidance of sun exposure, if not countered by relatively high intakes of vitamin D, may be associated with hypovitaminosis D, a potential risk factor for numerous cancers. Defining what are optimal levels of vitamin D for general health status remains a challenge and further study should be a high priority because of the great potential for cancer prevention achievable through vitamin D.

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