CHAPTER 3

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. Based on this observation, Peller and Stephenson hypothesized that acquiring skin cancer conferred immunity against other cancers. Several years later, Apperley 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.” 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. Initially, the hypothesis was centered on colon cancer, but later it was extended to breast cancer, ovarian cancer, prostate cancer, and to multiple cancer types.

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 1α-hydroxylase which can convert 25(OH)D to the active 1,25(OH)2D 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. 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. 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. 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. 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) and Spain. 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, 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