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A Brief History of Vitamin D and Cancer Prevention

SHARIF B. MOHR, MPH

PURPOSE: To review the history of vitamin D and its use in cancer prevention.
METHODS: The literature on published studies of vitamin D and its role in human health was reviewed and summarized.
RESULTS: The modern history of vitamin D began in the mid-1800s, when it was noticed that city children were more likely to have rickets than rural children. Half a century later, Palm reported that children raised in sunny climates virtually never developed rickets. McCollum isolated vitamin D, and Windaus its precursors, receiving the Nobel Prize. Other scientists later observed that people with skin cancer had lower prevalence of nonskin cancers, and that lower overall mortality rates from all internal cancers combined existed in sunnier areas. These observations went largely unnoticed, and the field stagnated until 1970, when maps were created of cancer mortality rates. Through study of these maps, Cedric and Frank Garland of Johns Hopkins University reported a strong latitudinal gradient for colon cancer mortality rates in 1980, and hypothesized that higher levels of vitamin D compounds in the serum of people in the south were responsible, and that calcium intake also would reduce incidence. Edward Gorham and colleagues carried out cohort and nested studies, including the first study that found an association of a serum vitamin D compound with reduced cancer risk. William B. Grant then carried out numerous ecologic studies that extended the vitamin D-cancer theory to other cancers.
CONCLUSIONS: The history of the role of vitamin D in human health is rich and much of that history is yet to be written not only by scientists, but by policy makers with the vision and leadership necessary to bridge the gap between research and policy.
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KEY WORDS: Vitamin D, Calcium, 25-Hydroxyvitamin D, Colon Cancer, Breast Cancer, History.

INTRODUCTION

The first known recognition of the importance of sunlight in promotion of human health was made by Hippocrates in ancient Greece. He expressed the belief that the south face of a hill, which receives the most daily sunlight in the northern hemisphere, was the healthiest place to live. More than 2000 years later, Sniadecki noticed in 1922 that children living on farms in Poland did not develop rickets, in contrast to children living in the city of Warsaw, who had high incidence of the disease (1). He hypothesized that increased exposure to sunlight in the children living in rural areas prevented them from developing rickets.

In 1890, a British medical missionary and epidemiologist, Theodore Palm, noted through his travels that children living in equatorial countries did not develop rickets (2). This prompted him to write to other medical missionaries throughout the world inquiring about whether children in their areas had rickets. He attributed the geographic differences in rickets incidence to differences in sunlight exposure (2).

The works of Sniadecki (1), and Palm (2) remained largely unnoticed until 1918, when Sir Edward Mellanby, searching for a cure for rickets, carried out over 100 experiments on dogs. In these experiments, Mellanby kept dogs indoors, away from sunlight, and fed them a diet consisting exclusively of oats (3). The combination of lack of sunlight and an exclusively oat diet induced rickets (3). He then fed the rachitic dogs cod liver oil, and cured them of rickets within a few months. Through these experiments, cod liver oil was confirmed as a scientific model for an essential micronutrient.

In the following years, Elmer V. McCollum, a chemist at the University of Wisconsin, discovered the compound that is now known as vitamin D. McCollum took the Mellanby study a step farther by investigating the chemical composition of cod liver oil. At that time, it was known that cod liver oil could prevent night blindness and fractures. McCollum wanted to know if cod liver oil retained its properties with respect to fractures and night blindness after being heated. In a series of experiments, McCollum et al. (4) tested this hypothesis by heating and oxygenating cod liver oil. They discovered that cod liver oil still prevented fractures after heating and oxygenation, but it no longer prevented night blindness (4). This led them to conclude that there were

From the Department of Family and Preventive Medicine, University of California San Diego, La Jolla, California 92093-0631.
Address correspondence to: Dr. Sharif B. Mohr, University of California San Diego, Department of Family and Preventive Medicine, La Jolla, California 92093-0631. E-mail: mohr.sharif@med.navy.mil
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Selected Abbreviations and Acronyms

UV = Ultraviolet
7-DHC = 7-dehydrocholesterol
NCI = National Cancer Institute

two different active compounds. The compound that was destroyed by the heating and oxygenation was named vitamin A, and the heat-stable component of cod liver oil became known as vitamin D.

Until 1937, the use of cod liver oil or ultraviolet (UV) light in the prevention of rickets were two competing concepts on independent tracks. Several scientists were able to show that rickets could be cured by exposure to sunlight or ingestion of UV irradiated food (5–8). Because only foods containing cholesterol could cure rickets after being irradiated with UV light, investigators were able to isolate and identify a form of cholesterol as the precursor of vitamin D_3. The discovery of 7-dehydrocholesterol (7-DHC), the precursor of vitamin D_3, was made by Windaus and colleagues in 1937. They isolated 7-DHC from animal skin and induced formation of vitamin D_3 by irradiating 7-DHC with ultraviolet radiation (9). Windaus received a Nobel Prize for this work, which unified two apparently disparate lines of evidence through the discovery that exposure to UV was responsible for vitamin D synthesis.

The emergence of the epidemiologic role of sunlight in cancer prevention began in 1936, when Peller observed that U.S. Navy personnel who experienced skin cancer had a much lower incidence of nonskin cancers (10). This led him to hypothesize that the development of skin cancer conferred protection against other cancers (10). Then, in 1942, Apperly first observed that there were lower overall mortality rates from internal cancers in sunnier regions of the United States (11). The observations of Peller and Apperly went largely unnoticed and the field remained stagnant until the U.S. government launched the War on Cancer in 1970. As a part of this effort, the National Cancer Institute (NCI) published maps of mortality rates according to cancer site. The goal was to better understand the geographical distribution of cancer mortality in the United States, and identify counties with unusually high incidence rates.

Through study of the cancer maps, Cedric Garland and Frank Garland of Johns Hopkins University noticed a strong latitudinal gradient within the United States for colon cancer mortality rates. They observed that mortality rates were much higher in the Northeastern and Northern parts of the country than in the South and Southwest. This observation led to them to hypothesize that differences in exposure to ultraviolet B (UVB) and consequently differences in serum vitamin D levels may have been responsible for increased risk of developing colon cancer. Vitamin D had not been proposed previous to this study as a compound that could prevent cancer in humans. Their study also proposed, possibly for the first time, that calcium also could prevent cancer in humans. The dominant paradigm in cancer research at that time was the search for exposures that were believed to cause the cancers. The idea that cancer might be due to a deficiency, namely of vitamin D, was a bold departure from the prevailing ideology.

In pursuit of testing their hypothesis, the Garlands published the seminal article on the relationship between vitamin D, calcium and colon cancer risk in the International Journal of Epidemiology in 1980 (12). In this ecologic analysis, Garland and Garland proposed that vitamin D and calcium were protective factors against colon cancer (12).

The next step by Garland et al. was to test the observations from the ecologic analysis in an observational study carried out in the Western Electric Cohort (13). This was a prospective study of oral vitamin D intake and colon cancer risk in a cohort of 1,954 men followed for 19 years (13). The main finding of the study was that men who consumed at least 150 IU per day of vitamin D had only half the risk of developing colorectal cancer than men who consumed less (13).

The Western Electric Cohort study also found a protective effect of calcium on risk of colon cancer, that was almost immediately replicated in a case-control study (14). In the same year that the Western Electric study was published, a study by Lipkin and Newmark that proposed a mechanism for a protective effect of calcium on colorectal cancer, was published in the New England Journal of Medicine (15). Although the Lipkin and Newmark study focused on calcium, it was important for vitamin D epidemiology as well, because it generated interest in the role of vitamin D in cancer prevention, since vitamin D influences calcium absorption. However, the calcium hypothesis would also prove to be a substantial barrier to acceptance of the vitamin D theory by the scientific community. Subsequent research would show that the effect of calcium and vitamin D in reducing colorectal cancer risk do not occur in isolation (16), but that the two work in tandem in maintaining colon, breast, and other epithelial cells in a differentiated state (16, 17). A recent study found that the effect of calcium in preventing cancer was dependent on serum vitamin D levels and that the effect was absent at low levels of serum 25(OH)D (18).

A key development in the advancement of the theory was when Samuel S. Broder, then Director of the NCI, took a serious interest in the role of vitamin D in the prevention of colorectal cancer. As a result, a vitamin D arm was incorporated into the largest ever clinical trial consisting of over 60,000 women, the Women's Health Initiative. Data from a nested case-control study in this cohort showed that women in the lowest quartile of vitamin D intake had an odds ratio of 2.53 ($p < 0.05$) compared with women in

the highest quartile (19). The dose of vitamin D (400 IU/day) used in the study apparently was too low to produce an overall effect, although there was a trend favoring benefit among women who had not been simultaneously assigned to the hormone replacement therapy arm of the study.

Since 1985, the year of the Western Electric Cohort study, a total of 16 (20) studies of the effect of oral vitamin D on risk of colorectal cancer have been published. Nine (20) of these studies have found a statistically significant protective effect of oral vitamin D intake on colorectal cancer risk and one found a beneficial effect of borderline significance (21). Of the remaining studies that did not find a statistically significant effect, three (22–24) adjusted for calcium intake, which is highly correlated highly with oral vitamin D intake, and two (25, 26) studied very small doses of oral vitamin D that would not have a detectable effect on risk. Another study that did not find a statistically significant beneficial effect was conducted in a population where, according to authors of the study, the result may have been due to high levels of consumption of salted and smoked fish, which could have a carcinogenic effect on the colon and rectum due to processing, and also contain some vitamin D (27). None of the studies found an adverse effect.

The relationship between serum 25-hydroxyvitamin vitamin D levels as a biomarker for cancer risk was first determined by Garland et al. in 1989 using the Johns Hopkins University Operation Clue Cohort (28). This research used a nested case-control design to examine the relationship between prediagnostic serum levels of 25-hydroxyvitamin D and subsequent risk of colon cancer in a cohort of 25,620 men and women residing in Washington County, Maryland who were followed for 8 years (28). This research advanced the study of vitamin D and colon cancer risk beyond ecologic associations or dietary studies and found an association between high pre-diagnostic serum levels of circulating 25-hydroxyvitamin D, the main circulating vitamin D metabolite and reduced risk of colon cancer. Four more studies of pre-diagnostic serum 25(OH)D and colorectal cancer risk were carried out over the following years (20), all of them finding a beneficial effect on risk.

In 1989, Gorham et al. postulated an association between ultraviolet-B blocking air pollution and increased risk of breast and colon cancer, based on inhibition by sulfur-related air pollution of cutaneous vitamin D photosynthesis, resulting in vitamin D deficiency (29). They examined the association between sulfur dioxide air pollution and other ultraviolet-B-blocking aerosols in 20 Canadian cities, and age-adjusted breast and colon cancer mortality rates. They found statistically significant positive associations between measures of air pollution and age-adjusted mortality rates for colon cancer in men and women and for breast cancer in women. It had been well-recognized that rickets, another vitamin D deficiency condition, was associated with the industrial revolution, but the important role of sulfur-related, ultraviolet-B blocking air pollution in vitamin D deficiency is still not appreciated fully.

Garland et al. (30) continued their geographic exploration of the inverse association between sunlight and breast cancer in two other studies. In 1990, they found an inverse association between total average annual sunlight energy striking the ground and age-adjusted breast cancer mortality rates in 87 regions of the United States (30). Gorham et al. (31) examined breast cancer incidence rates from the former Union of Soviet Socialist Republics in relation to sunlight levels. Breast cancer had a three-fold range of incidence across the 15 former republics, and total sunlight energy varied from 210 to 400 calories/cm^2/day. They found a negative association between total average annual sunlight energy striking the ground and age-adjusted breast cancer incidence rates in the Union of Soviet Socialist Republics (31).

Gorham et al. (32) continued to focus primarily on the role of vitamin D and cancer, advancing the research in recent years by helping to quantify the dose-response relationship of vitamin D with reduction in risk of colon and breast cancer. In a meta-analysis, they further defined the dose-response relationship of serum levels of 25-hydroxyvitamin D and subsequent risk of colon cancer (32). The analysis combined results of five studies in which blood was collected and tested for 25-hydroxyvitamin D levels in healthy volunteer donors who were then followed for up to 25 years for development of colorectal cancer. The dose-response data from 1,448 individuals were ranked by serum 25-hydroxyvitamin D level and then divided into five equal groups, from the lowest serum levels to the highest. Through this meta-analysis, the authors found that an increase in the serum level of 25-hydroxyvitamin D to 34 ng/ml was associated with a 50% reduction in incidence rates of colorectal cancer. This corresponds to a daily intake of about 2,000 IU of vitamin D3.

Garland et al. also published a breast cancer dose-response meta-analysis (33) that pooled serum data from two previous studies, the Harvard Nurses Health Study and the St. George's Hospital Study, and found that individuals with the highest blood levels of 25-hydroxyvitamin D had reduced risk of breast cancer. They divided the 1,760 records of individuals in these two studies into five equal groups, from the lowest blood levels of 25-hydroxyvitamin D to the highest. The results showed a very clear dose-response relationship in which individuals in the group with the lowest serum levels ($<$13 ng/ml) had the highest rates of breast cancer, and the breast cancer rates were successively lower as serum levels of 25-hydroxyvitamin D increased (up to 52 ng/ml). The serum level associated

with a 35% reduction in risk could be maintained by taking about 2,000 IU of vitamin D3 daily.

The Garlands and Gorham, joined by Mohr and Grant, have continued research in geographic epidemiology by exploring the association of latitude and age-adjusted incidence rates of renal cancer (34), ovarian cancer (35), endometrial cancer (36), and lung cancer (37) using the World Health Organization cancer database, GLOBOCAN. The model the team has developed includes cancer data for 175 countries as well as solar UVB irradiance, stratospheric ozone thickness, cloud cover, and other environmental and demographic factors. Solar UVB irradiance was inversely associated with age-adjusted renal and lung cancer incidence as well as ovarian and endometrial cancer incidence on a world-wide basis. These studies also included regression analyses for examination of relevant confounding factors, including smoking, alcohol intake, and body mass index.

The history of vitamin D in human health is rich, and much of that history is yet to be written. Since the publication in 1980 of the Garland study entitled "Do sunlight and vitamin D reduce the likelihood of colon cancer?," five epidemiologic studies of the effect of serum 25(OH)D (20) and 15 studies (20) of the effect of oral intake of vitamin D on risk of colorectal cancer have been carried out, providing strong evidence that vitamin D prevents colorectal cancer.

Since publication by Gorham et al. of a manuscript on the role of vitamin D deficiency in increasing the risk of breast cancer, two studies of serum 25(OH)D have further quantified the dose-response relationship (38); these are supported by a major population-based case-control study of oral intake of vitamin D and solar exposure history (39). The association of vitamin D deficiency with ovarian cancer proposed by Garland et al. (40) and Lefkowitz (41) was recently supported by a study of serum 25(OH)D (42). Similar associations proposed by Grant (43) and Garland et al. for renal (34) and lung (37) cancer have been replicated in a cohort study based on modeled serum 25(OH)D levels in a large cohort of male health professionals by Giovannucci and colleagues (44), and are awaiting further confirmation by nested case-control studies of prediagnostic serum 25(OH)D. A similar association proposed by Grant (42) and Garland et al. (36) for endometrial cancer awaits support from studies of prediagnostic serum 25(OH)D levels; in the meantime, a dietary case-control study has reported 60% lower incidence rates of this cancer in association with higher than average oral intake of vitamin D (45).

The next important pages in the history of vitamin D and colorectal cancer will not necessarily be written solely by the scientific community, but by health policy makers with the vision and leadership necessary to bridge the gap between research and public health policy.

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