ELSEVIER

Vitamin D and Cancer Incidence in the Harvard Cohorts

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Since the hypothesis that vitamin D reduces the risk of some cancers was initiated in 1980, this hypothesis has been studied in the Harvard cohort studies, including the Nurses' Health Study (NHS), the Health Professionals Follow-Up Study (HPFS), and the Physicians' Health Study (PHS). Three approaches have been used, the study of circulating 25(OH)vitamin D (25(OH)D) level, of dietary and supplementary intake, and of predicted 25(OH)D. These cohorts strongly support an inverse association with colorectal cancer, because this association has been viewed in both the NHS and HPFS cohorts, for cancers and adenomas, and for plasma, diet, and predicted 25(OH)D analyses. In the NHS, about a 30% reduction in risk was observed for breast cancer comparing the highest with lowest quintiles of 25(OH)D levels. Vitamin D intake also was associated with a lower risk of pancreatic cancer in both men and women, but studies of plasma or predicted 25(OH)D level or dietary intake have generally not been supportive of a major role of vitamin D status in middle-age or elderly men on prostate cancer risk. Results from the HPFS also suggest that the poor vitamin D status generally in African-Americans contributes to their higher incidence and mortality from various malignancies.
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INTRODUCTION

In 1980, Garland and colleagues hypothesized that greater levels of vitamin D are associated with a reduced risk of colon cancer (1). Subsequently, this benefit of vitamin D was proposed for breast cancer (2), ovarian cancer (3), prostate cancer (4, 5), and to multiple cancer types (6) based on evidence from ecologic studies. This hypothesis was premised on the facts that sun exposure increases vitamin D levels and that residence in higher latitudes was associated with greater rates of these cancers. Subsequently, it was demonstrated that many normal and neoplastic cells express vitamin D receptors; express 1-α-hydroxylase, which can convert 25(OH)vitamin D (25(OH)D) to the active metabolite $1,25(OH)_2D$; and that activation of the vitamin D receptor by $1,25(OH)_2D$ induces a number of anticancer properties, including reduced proliferation, invasiveness, angiogenesis and metastasis, and increased differentiation and apoptosis (7). Since Garland's initial hypothesis, a number of epidemiologic studies, including the Nurses' Health Study (NHS), the Health Professionals Follow-Up Study (HPFS), and the Physicians' Health Study (PHS), have examined vitamin D levels or intakes on risk of various cancers. The results from the Harvard studies are briefly summarized here.

COLORECTAL CANCER AND ADENOMA

The first report concerning the vitamin D hypothesis from the Harvard cohorts was based on risk of colorectal adenoma in the NHS and HPFS cohorts (8). In that study, cases were participants with a diagnosis of adenoma of the left colon or rectum (331 men, 1986–1990; 350 women, 1980–1988), and controls were cohort members with endoscopic findings negative for adenoma (9159 men and 8585 women) over these time periods. The results did not yield strong evidence of an association between vitamin D intake and adenoma risk. For men, there was a linear inverse trend for total vitamin D intake through the fourth quintile, but vitamin D was unrelated to the risk for adenoma when comparing the highest quintile to the lowest quintile (multivariable relative risk (RR) 1.29, 95% confidence interval [95% CI] 0.87–1.93). For women, the results were equivocal; an inverse association was observed in the 1980-1988 analyses (RR 0.68, 95% CI 0.41-1.13, p (trend) = 0.09), which was mainly attributable to the intake of multivitamin supplements. However, an analysis of four-year data (1984–1988) using a more detailed dietary assessment showed no association with vitamin D (RR 1.04; 95% CI 0.65–1.67).

These cohorts have been followed with multiple dietary questionnaires, which allow for a more detailed assessment of long-term diet. In a recent updated analysis of the NHS (9) involving 2747 cases of adenoma diagnosed in 48,115 nurses who had had an endoscopy by 2002, total vitamin

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Selected Abbreviations and Acronyms

NHS = Nurses' Health Study
HPFS = Health Professionals Follow-Up Study
PHS = Physicians' Health Study
25(OH)D = 25(OH)vitamin D
RR = relative risk
95% confidence interval = 95% CI

D intake was moderately associated with a reduced risk of distal colorectal adenoma (RR.79; 95% CI 0.63–0.99; p (trend) = 0.07) and distal colon adenoma (RR 0.67; 95% CI 0.52–0.87; p (trend) = 0.004). Interestingly, retinol intake, which is hypothesized to antagonize the actions of the vitamin D receptor (7), appeared to modify the association with vitamin D. If retinol intake was high (>4784 IU/day), high (>399 IU/day) versus low vitamin D (<240 IU) had no effect (RR = 1.10; 95% CI 0.82–1.49), but if retinol intake was low (<2646 IU), greater levels of vitamin D were associated with lower risk of distal colorectal adenoma (RR 0.55; 95% CI 0.28–1.10) and especially distal colon adenoma (RR 0.34; 95% CI 0.13–0.86). Also, vitamin D was associated with lower risk only in post-menopausal women not currently taking postmenopausal hormones, and not in premenopausal women or postmenopausal women taking hormones.

Next in the NHS and HPFS cohorts, intake of vitamin D was studied in relation to colorectal cancer outcomes. In the HPFS, 203 new cases of colon cancer were documented between 1986 and 1992. For total vitamin D intake, the highest versus lowest quintile group showed a suggestive inverse association (multivariate RR highest vs. lowest quintile 0.66, 95% CI 0.42–1.05). The inverse association was weaker for dietary vitamin D (RR 0.88. 95% CI 0.54–1.42) and strongest for vitamin D from vitamin supplements (RR 0.48, 95% CI 0.22–1.02). In the NHS, from 1980 to 1992, 501 incident cases of colorectal cancer were documented. On the basis of the data from the 1980 questionnaire alone, the multivariate RR for colorectal cancer for women in the upper versus the lower quintile were 0.84 (95% CI 0.63–1.13) for dietary vitamin D and 0.88 (95% CI 0.66–1.16) for total vitamin D intake. Use of multiple dietary questionnaires and questions designed to assess long-term intake allowed an examination of these associations among long-term consistent users. The corresponding RRs for the consistency analyses were 0.59 (95% CI 0.30–1.16) for dietary vitamin D and 0.33 (95% CI 0.16–0.70) for total vitamin D.

Plasma 25(OH)D 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. Intake accounts for a minority of vitamin D (10), although it is a relatively important source in the winter in northern latitudes. In 1989 in the NHS and 1993 in the HPFS, blood samples were collected in a segment of the study population. This resource allowed us to examine circulating 25(OH)D levels in relation to cancer or adenoma risk in nested case-control studies. For adenomas in the NHS, based on 326 cases from 1989 to 1996 no association was observed with plasma 25(OH)D (11). However, with further follow-up to 1998, a modest nonsignificant inverse association emerged (unpublished data). We then examined 25(OH)D in relation to colorectal cancer risk in 193 cases from 1989 to 2000 (12). A linear inverse association was observed (p (trend) = 0.02). Among women in the highest quintile, the multivariable RR was 0.53 (95% CI 0.27–1.04). A parallel analysis in the HPFS based on 139 cases yielded similar results for colon cancer (RR 0.46; 95% CI 0.24–0.89; p (trend) = 0.005), though no association was observed for rectal cancer based on only 40 cases (13).

Using an alternative approach in the HPFS, first, in a sample of 1,095 men who had 25(OH)D levels measured, we used multiple linear regression to develop a predicted 25(OH)D score based on 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) as the independent variables (14). Then, the score was calculated for each of approximately 47,000 cohort members, and this variable was examined in relation to subsequent risk of cancer. For colorectal cancer, based on 691 cases diagnosed from 1986 to 2000, a 25 nmol/L increment in 25(OH)D was associated with a reduced risk (multivariable RR 0.63; 95% CI 0.48–0.83).

BREAST CANCER

In the NHS, 25(OH)D was assessed in stored plasma samples in 701 breast cancer cases from 1989 to 1996 and 724 controls in cancer cases (15). 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 multivariable RR of 0.73 (95% CI 0.49–1.07; p (trend) = 0.06) compared with those in the lowest quintile. The association was stronger in women ages 60 years and older (RR 0.57; 95% CI 0.31–1.04; p (trend) = 0.03), suggesting that vitamin D may be more important for post-menopausal breast cancer. In a prior analysis in the NHS, vitamin D intake was assessed in relation to breast cancer based on 3482 women with breast cancer diagnosed from 1980 and 1996; up to 5 food frequency questionnaire assessments were used to assess long-term intake (16). In multivariable analysis, total vitamin D was associated with a reduced risk of breast cancer in premenopausal women (>500 vs. ⩽150 IU/day; RR 0.72, 95% CI 0.55–0.94, p (trend = 0.01), but no association was observed in postmenopausal women.

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PANCREATIC CANCER

A prospective analysis of pancreatic risk by intake of vitamin D was conducted in the NHS and HPFS (17). Through the year 2000, 365 incident cases of pancreatic cancer were identified in these cohorts combined. In pooled analysis, compared with participants in the lowest category of total vitamin D intake (<150 IU/day), the pooled multivariate RR was 0.59 (95% CI 0.40–0.88) for ⩾600 IU/day; (p (trend) = 0.01). The association appeared to be stronger in men than women. In an analysis of predicted vitamin D status in the HPFS (see above) (14), an increment of 25 nmol/L of 25(OH)D was associated with a significantly reduced risk of pancreatic cancer (multivariable RR 0.49; 95% CI 0.28–0.86).

PROSTATE CANCER

Plasma 25(OH)D has been examined in relation to risk of prostate cancer in the HPFS and PHS cohorts. In the PHS, plasma samples from 14,916 participants were collected and frozen in 1982–1983. The prostate cancer analysis in the PHS included 232 cases diagnosed up to 1992 and 414 age-matched control participants (18). No association was observed between high versus low quartile for 25(OH)D (RR 0.92; 95% CI 0.56–1.50), and a modest, nonsignificant inverse association was observed for aggressive cases (RR 0.82; 95% CI 0.42–1.61). In the HPFS 460 men were diagnosed with prostate cancer through 1998 after providing a blood specimen in 1993/95 (19). The RR of prostate cancer comparing the top and bottom quartiles of plasma 25(OH)D level was 1.19 (95% CI 0.79–1.79; p (trend) = 0.59). There were too few cases of advanced prostate cancer to examine, as the vast majority of cases diagnosed were prostate-specific antigen detected, early stage cases. However, no association was observed with predicted 25(OH)D based on 461 advanced cases in the HPFS (14). Further, vitamin D intake was not associated with risk of total prostate cancer (multivariable RR 1.21; 95% CI 0.92–1.58) for intake ⩾800 versus <150 IU/day nor with advanced prostate cancer (RR 1.48; 95% CI 0.91–2.39) (20). These analyses were based on 1369 total cases and 423 advanced prostate cancer cases.

VITAMIN D AND CANCER RATES IN AFRICAN-AMERICAN MEN

Melanin efficiently blocks UV-B induced production of vitamin D in the skin and darker skinned individuals, such as African-Americans, have been documented to have markedly lower vitamin D levels. In the HPFS cohort, even after adjusting for multiple dietary, lifestyle and medical risk factors, African-American men were at 32% greater risk of total cancer incidence and 89% greater risk of total cancer mortality compared with white men (21). In multivariate analyses, African-American 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 most strongly associated with low predicted 25(OH)D in this cohort (14). The increased risk of these cancers in African-American men was especially marked if they had additional risk factors for vitamin D deficiency. 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.

CONCLUSIONS AND FUTURE DIRECTIONS

The hypothesis that better vitamin D status may lower risk of several types of cancer has been extensively examined in the Harvard cohort studies. Three approaches have been used, the study of circulating 25(OH)D level, dietary and supplementary intake, and use of predicted 25(OH)D. These cohorts have provided varying degrees of support for specific cancers. These studies strongly support an association with colorectal cancer, as this association has been seen in both the NHS and HPFS cohorts, for cancers and adenomas, and for plasma, diet, and predicted 25(OH)D analyses. These results are consistent with the literature, for which support for an association for colorectal neoplasia has been relatively consistent (22). In the NHS, about a 30% reduction in risk was observed for breast cancer comparing the highest to lowest quintiles of 25(OH)D levels. Vitamin D intake was also suggestively associated with a lower risk, but this was observed only for premenopausal women. No other prospective data for vitamin D levels are available for breast cancer.

The clearest evidence thus far for a role of vitamin D for colorectal and breast cancer in these cohorts is consistent with ecologic data on regional UV-B exposure. For example, in Grant's analysis, out of all the preventable cancers he estimated attributable to living in a low sun area, 60% were due to colorectal cancer in men; in women, 35% were caused by colorectal cancer and 42% were attributable to breast cancer (6). Thus, even though at least 15 types of cancers have been correlated with low sun exposure (23), cancers of the large bowel and breast appear to be most important quantitatively.

The NHS and HPFS also suggest a benefit of vitamin D on pancreatic cancer risk. However, a recent study based in the Alpha-Tocopherol Beta-Carotene cohort surprisingly found a positive association between 25(OH)D level and pancreatic cancer risk in Finnish men (24). There could be some population differences that account for these differences; for example, the Alpha-Tocopherol Beta-Carotene

study was composed entirely of heavy lifelong smokers whereas the HPFS had very few current smokers (<10%). Although the data on pancreatic cancer are intriguing, more study is obviously needed before any conclusions can be made with confidence.

The HPFS and PHS do not provide support of a relation between vitamin D and prostate cancer risk based on plasma levels and intake. The literature on prostate cancer in general is puzzling. A number of studies indicate that sun exposure may be protective (25–29), but studies based on blood levels of 25(OH)D (18, 19, 30–33) or intake (20, 34–36) generally do not support an association. The only two studies that seemed to support an increased risk with lowest levels of 25(OH)D were conducted in Nordic countries (37, 38), where vitamin D levels get very low in the winter months. However, even so, one of these studies also found an increased risk in men with the highest 25(OH)D values (38). A complexity with prostate cancer is that risk factors for incidence, which is most frequently studied, may be different for those for aggressive or fatal disease (39). Other considerations may be that high intake of milk (a major source of dietary vitamin D when fortified) or calcium may increase risk of prostate cancer (20). Also, neoplastic prostate cancer cells may lose the ability to convert 25(OH)D to $1,25(OH)_2D$ (40). Because neoplastic prostatic cells may be present for decades before diagnosis, it is possible that vitamin D status many years prior to diagnosis may be most relevant for prostate carcinogenesis.

The analyses of vitamin D and cancer in the Harvard cohorts also suggest several areas worthy of further study. First, the dose-response for 25(OH)D levels and vitamin D intakes and cancer risk need to be better understood, and the influence of vitamin D on rarer cancers (beyond colorectal, prostate and breast) needs to be evaluated. Analyses in the HPFS suggest that vitamin D deficiency may contribute to the higher risk of some cancers, especially those of the digestive system, in African-Americans. In addition, high intake of retinol from supplements should be evaluated in relation to potential antagonistic effects on the vitamin D receptor. Because of the high correlation between vitamin D and retinol intakes (attributable ot common supplementary and dietary sources), we could achieve adequate power only when several thousand of cases of adenomas were accrued. For colorectal neoplasia, interacting effects of hormonal replacement in postmenopausal women should be evaluated. Finally, these cohorts have begun to assess known polymorphisms with the vitamin D receptor (41, 42), but more extensive vitamin D pathway analyses are planned.

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