Vitamin D and Cancer: Diversity, Complexity, and Still a Ways to Go
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Abstract

Vitamin D has taken a center-stage role in our basic and population research quest for the panacea for all human maladies, including cancer, yet sufficient evidence for a beneficial role has existed only for bone health. This Commentary discusses and places into a broader context the report of Chandler and colleagues that found a protective association for higher vitamin D status in colorectal cancer in women, consistent with most other cohort studies but not with limited supplementation trial data. Little human evidence exists for the preventive potential in other malignancies, including breast cancer, with the exception of possible benefit in bladder cancer and an adverse serologic association with prostate cancer (pancreatic cancer risk may be similarly influenced) that is supported by vitamin D genetic data. Current vitamin D trials are examining high-dose supplementation (i.e., 1,600–3,333 IU daily) for effects on multiple outcomes, but they may not have sufficient power to test efficacy in colorectal or other specific malignancies and are unlikely to inform any benefit for higher physiologic levels. A more complete understanding of vitamin D and human carcinogenesis will come from multifaceted lines of research, including elucidation of organ site-specific biologic mechanisms, prospective serologic analyses, testing of vitamin D–related genetic variation, and short-term clinical–metabolic biomarker studies of multidose vitamin D supplementation, including metabolomic profiling of controlled supplementation in these and past or ongoing trials. Cancer Prev Res; 8(8); 657–61. ©2015 AACR.

See related article by Chandler et al., p. 675

The relatively new “kid” on the chemoprevention “block,” vitamin D, has taken a center-stage role in our basic and population research quest for the panacea for all human maladies, from cardiovascular diseases and diabetes, to cancer and rheumatoid arthritis. A beneficial role in bone health and prevention of osteoporosis is the one health outcome singled out by the most recent National Academy of Sciences Institute of Medicine Dietary Reference Intake report, with evidence for all other health outcomes being deemed insufficient and inconclusive (1). Other August panels and review groups have concluded essentially the same (e.g., ref. 2). The study of Chandler and colleagues (3) in this issue of the journal is the latest to grow the already sizeable literature that has provided actionable data specifically with respect to colorectal cancer at a time when the area has gained substantial research, public health, and media attention. Based on a nested case–control sample of the Women’s Health Study (WHS) that originally tested supplementation with aspirin, beta-carotene, and vitamin E for prevention of cardiovascular disease and malignancies, including breast cancer (4), the authors found a protective association for higher vitamin D status, with women whose plasma 25-hydroxy-vitamin D (25(OH)D) concentration was 74 nmol/L or greater (i.e., representing the top ~24%–32% of U.S. women; ref. 5) having approximately one half of the colorectal cancer risk compared with women with concentrations of <44 nmol/L. The added-value of this analysis derives from the relatively long time from blood collection to diagnosis (average of 16 years—a strength of the study that helps minimize the influence of undiagnosed colorectal cancer on circulating 25(OH)D status) and being a study of women, who compared with men have been underinvestigated with respect to the role of vitamin D in cancer. (In this regard, it is of interest and in need of further evaluation that one recent report indicated the vitamin D–colorectal cancer association may be stronger in women than in men; see ref. 6.) Even though the intervention period represented only the initial portion of WHS follow-up for the present analysis, examination of possible interactions between colorectal cancer, 25(OH)D status and the vitamin E and beta-carotene trial components could be informative; the authors reported no such interaction for the aspirin intervention, although the vitamin D association may have been weaker in the aspirin group (3).

The findings are in line with a large number of colorectal cancer investigations that have been summarized through meta-analyses of cohort-based data, yielding relative risk estimates such as 0.66 for high versus low of 25(OH)D status (7, 8). On the basis of approximately 4,500 cases, and as represented in Fig. 1, the totality of this observational evidence seems to have settled this hypothesis for the most part; an apparent “ad in” for vitamin D status and cancer prevention. The underlying biology requires elucidation, however, as does a more robust confirmation of the protective association in non-Caucasians, including particularly African Americans. Further comparison of the risk associations for higher dietary intake versus low-dose supplementation is also needed.

But wait—not so fast, and not that easy: What do randomized controlled trials, our “gold standard” of scientific evidence for

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doi: 10.1158/1940-6207.CAPR-15-0207
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modifying disease outcomes in humans, have to say about this? One small, 5-year, high-dose trial (effective 833 IU daily) in men and women showed no effect on the incidence of colon cancer (9), whereas the Women's Health Initiative (WHI) found a nonsignificant 8% increase in colorectal cancer incidence in those supplemented daily with both vitamin D3 (400 IU) and calcium (1 g) for an average of 7 years (10). Nonsignificantly lower incidence was, however, suggested among the subset of women not self-supplementing with either vitamin D or calcium in the latter trial, as reported most recently (11). What are we to make of the fact that limited controlled trial data for vitamin D supplementation have not supported efficacy for colorectal cancer prevention? Certainly, we cannot ignore the relatively consistent evidence from nearly 20 cohort studies, and new vitamin D trials may provide additional data. But as we have learned from the controlled trial testing of some similar hypotheses (e.g., beta-carotene, folic acid, and vitamin E), effective nutrient exposure levels, trial durations, population risk, and preexisting tumors would all appear germane to the question and to the disconnect. In this case, women and men with higher vitamin D status, within the physiologic range—likely contributed to not only by sun exposure and diet (mainly from consumption of fatty fish, fortified foods, including especially dairy and fruit juices, and eggs), but by hereditary variation in genes related to vitamin D metabolism (12) and some supplement use—appear to be at lower colorectal cancer risk in long-term prospective cohorts with no appreciable overall additional benefit for daily supplementation with 400 or 833 IU.

Vitamin D Status and Other Cancers

What about the preventive potential of vitamin D for other cancers? There is a growing critical mass and consensus of prospective vitamin D data for adenocarcinoma of the prostate. Yet in this case, we see a likely preventive potential for lower vitamin D status; that is, a positive overall association, with risk increasing along with circulating 25(OH)D concentrations in a large number of studies as evidenced by a 2014 meta-analysis (13) and as depicted in Fig. 2. On the basis of 21 nested case-control serologic studies of nearly 12,000 cases, the authors estimated a combined risk estimate of 1.17 [95% confidence interval (CI), 1.05–1.30] for high versus low quantiles of circulating 25(OH)D. Our own analysis of 1,000 cases and 1,000 controls in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study exemplifies the available data, with 40% to 50% higher risk for the highest serum vitamin D categories.
that appeared stronger in men with higher circulating vitamin D binding protein (DBP) concentrations (15). In support of these prospective serologic data is a large pooled analysis of 10,000 cases and 11,000 controls in the Breast and Prostate Cancer Cohort Consortium (BPC3) that used a polygenic vitamin D score and confirmed a direct association with aggressive prostate cancer, with estimated relative risks of 1.0, 0.99, 0.88, 0.90, 0.78, and 0.66 for six decreasing vitamin D categories with median serum 25(OH)D concentrations of 65, 61, 58, 54, 53, and 43 nmol/L, respectively (16). Such “Mendelian randomization” analyses of genetic variants, which likely reflect chronic, lifetime, biologic exposures, represent a complementary approach to testing vitamin D–cancer hypotheses, as well as other potential preventive strategies, nutritional or otherwise.

Vitamin D studies of breast cancer include a large number of retrospective case–control analyses (17), with the attendant reverse causality resulting in vitamin D insufficiency or deficiency after diagnosis. The impact of treatment effects, decreased physical activity and sun exposure, and altered diet on the vitamin D status of these women has only recently been acknowledged as factors likely to bias such studies. Most meta-analyses reflect this substantial retrospective–prospective study heterogeneity (e.g., risks of 0.6 and 0.9 for high vs. low vitamin D in the two classes of studies, respectively; ref. 17), although a new study points to a possible modest inverse association in prospective studies of postmenopausal (but not premenopausal) women (18). Yet the WHI trial of vitamin D and calcium supplementation showed no effect on invasive postmenopausal breast cancer (19), and the aforementioned vitamin D genetic score was unrelated to breast cancer risk based on 9,500 cases and 11,000 controls in the multicohort analysis (20). The Vitamin D Pooling Project of Breast and Colorectal Cancer, a large international pooling project of cohorts for vitamin D serologic status and risk involving nearly 10,000 and 6,000 cases of the two sites, respectively, should help resolve the vitamin D question for these malignancies, but based on currently available data, including the WHI intervention findings, the preventive potential for higher vitamin D status in breast cancer seems unlikely.

Prospective data for nearly all other cancer sites are also consistent with null associations for vitamin D status, including kidney, esophagus, stomach, endometrium, ovary, and

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<th>Author</th>
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<td>Tuohimaa</td>
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Figure 2. Forest plot of ORs and 95% CIs for high versus low 25-hydroxyvitamin D categories from prospective nested case–control studies of prostate cancer.
lymphoma (21). Two possible exceptions are bladder cancer, for which a recent meta-analysis of five prospective studies demonstrated a summary relative risk of 0.75 (P < 0.001) for high versus low serum 25(OH)D (22), and pancreas, which has shown evidence of elevated risk for concentrations of ≥100 nmol/L (relative risk = 2.24) in the Vitamin D Pooling Project of Rarer Cancers (23). A subsequent pooled analysis failed to confirm the latter finding, however (24), placing pancreatic cancer back into the "deuce" column for vitamin D, with further studies needed. One lead worth pursuing for pancreas is the possible interaction with circulating DBP that appeared opposite to that in prostate cancer; that is, a possible harmful association for higher 25(OH)D status in persons with lower DBP concentrations (25), supporting the "free hormone" hypothesis for vitamin D, in this case, a deleterious relation.

Current Vitamin D Supplementation Trials

The latest round of vitamin D trials is examining several outcomes, including fractures, cardiovascular diseases, infections, respiratory disease, and cancer (26). They will be helpful to some degree, although with sample sizes ranging from 2,150 to 26,000 available to test the multiple primary hypotheses, efficacy for specific cancer sites would seem difficult to establish unless large effects are observed. Also, these trials are all administering only high-dose supplementation (i.e., 1,600–3,333 IU daily), with any potential impact of lower, more physiologic dosages not being tested. In addition, unanticipated adverse effects cannot be ruled out. One of these is the VITamin D and OmegA-3 TRIal (VITAL) of nearly 26,000 adult women and men in the United States that is testing the potential efficacy of daily vitamin D3 (2,000 IU) or omega-3 fatty acid (1 g as fish oil) supplementation for prevention of total major cardiovascular events (myocardial infarction, stroke, and others) and cancers (27). Prevention of incident breast, prostate, and colorectal cancers and total cancer mortality are secondary aims, and an average intervention period of 5 years is planned. One key feature of the trial is that all participants are permitted to self-supplement with up to 800 IU vitamin D3, 1,200 mg calcium, or both daily. In the case of vitamin D, this design feature will permit substantial vitamin D supplementation among participants not receiving the trial vitamin D3 supplement, thus potentially attenuating any observable intervention effect. Furthermore, the known preventive action of calcium supplementation on colorectal cancer could either overshadow any vitamin D3 or fish oil effects, or create an opportunity to detect biologically based interactions through secondary analyses. Barring any large intervention group differences that warrant early termination, we will have to wait several more years for results from this and the other trials.

Biologic Mechanisms and Future Directions

Further progress in this area will require multifaceted lines of research, including especially ones aimed at elucidating organ site–specific biologic mechanisms for vitamin D and human carcinogenesis. This is particularly relevant for colorectal and prostate (and possibly pancreatic) cancers, which appear to have substantial supportive observational evidence. Possible mechanisms for colorectal cancer include, for example, effects of vitamin D on cell proliferation and differentiation, inflammation, apoptosis, and bile acid metabolism (see ref. 6). How higher vitamin D status might confer benefit for colorectal cancer and harm for prostate cancer is presently unknown, although higher vitamin D status and controlled supplementation have been shown to increase circulating androgens in men (28, 29). We have recently incorporated measurement of circulating DBP in our studies to estimate bound and unbound (or "free") 25(OH)D in circulation, which appear to variably modulate vitamin D–cancer associations (15, 25, 30). This would be a useful addition to available and future colorectal cancer studies. The plasma membrane megalin–cubulin receptor complex is also relevant to 25(OH)D–DBP cellular uptake and may vary functionally across organ sites. The aforementioned vitamin D–related genetic variation and proxy SNP scores can be further exploited in studies or consortia with available GWAS or sequencing data (e.g., 16, 20), and studies of genomic vitamin D response elements would be useful. Short-term clinical–metabolic biomarker studies of multidose vitamin D supplementation aimed at providing deeper insights into its biologic actions at both the blood and tissue levels are needed, as is metabolic profiling of the controlled supplementation in these studies, or in past or ongoing randomized controlled trials (as was done recently for beta-carotene supplementation in the ATBC Study; ref. 31). Finally, examination of vitamin D in relation to cancer survival is a relatively uncharted area that deserves much greater attention.

Conclusions

Greater specificity and less generalization are needed with regard to the current evidence relevant to the role of vitamin D in human cancer risk. We need to openly accommodate, and make further meaningful advances in this field based on, divergent data for vitamin D associations across cancer sites. Admittedly speculative, it is likely that adaptive advantage for higher vitamin D status in human evolution derived from effects on increased bone mineral density, whereas any impact on biologic susceptibility to carcinogenesis and malignancies in older adults may have evaded the test of evolutionary selection. That is, how the complex interactions of human exposures, metabolism, and genetics related to the development of colorectal, breast, prostate, and other cancers in the 21st century might actually be influenced by vitamin D status is not yet known.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

This work was supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS.

Received May 22, 2015; accepted May 22, 2015; published OnlineFirst July 28, 2015.
Vitamin D Status and Human Cancer Risk


