The Role of Vitamin D in Cancer Prevention

Vitamin D status differs by latitude and race, with residents of the northeastern United States and individuals with more skin pigmentation being at increased risk of deficiency. A PubMed database search yielded 63 observational studies of vitamin D status in relation to cancer risk, including 30 of colon, 13 of breast, 26 of prostate, and 7 of ovarian cancer, and several that assessed the association of vitamin D receptor genotype with cancer risk.

The majority of studies found a protective relationship between sufficient vitamin D status and lower risk of cancer. The evidence suggests that efforts to improve vitamin D status, for example by vitamin D supplementation, could reduce cancer incidence and mortality at low cost, with few or no adverse effects. (*Am J Public Health.* 2006;96: XXX–XXX. doi:10.2105/AJPH.2004.045260)

Cedric F. Garland, DrPH, Frank C. Garland, PhD, Edward D. Gorham, PhD, MPH, Martin Lipkin, MD, Harold Newmark, ScD, Sharif B. Mohr, MPH, and Michael F. Holick, PhD, MD

ALTHOUGH VITAMIN D deficiency is known mainly for its association with fractures and bone disease,[1–7] its newly recognized association with risk of several types of cancer is receiving considerable attention.[8–11] The high prevalence of vitamin D deficiency, combined with the discovery of increased risks of certain types of cancer in those who are deficient, suggest that vitamin D deficiency may account for several thousand premature deaths from colon,[12] breast,[13,14] ovarian,[15] and prostate[16] cancer annually.[17] This discovery creates a new impetus for ensuring adequate vitamin D intake in order to reduce the risk of cancer.

PREVALENCE OF VITAMIN D DEFICIENCY

A low serum level of 25(OH)D, the principal form of vitamin D circulating, is the main marker of vitamin D deficiency.[18–20] High prevalence of vitamin D deficiency is present in all races, even in temperate areas,[19–36] and is particularly high among Black Americans.[19,21–24] A recent survey found, for example, that 42% of Black women had seriously deficient 25(OH)D levels (<15 ng/mL).[19]

Residents of the northern tier of the United States receive considerably less solar ultraviolet B (UVB) radiation than those in the South, owing to the longer length and severity of northern winters.[37–39] UVB is needed to make vitamin D, which cannot be photosynthesized by the skin in the Northeast from November through March.[40] Although some sunscreens, such as zinc or titanium oxides, may reduce risk of some skin cancers,[41–43] everyday use of sunscreens that offer a high level of protection against the sun, which currently are used periodically by about half the US population,[44] completely blocks photosynthesis of vitamin D[45,46] and reduces circulating vitamin D metabolites.[46] This results in 25(OH)D deficiency unless there is adequate oral intake.[47]

A clinical laboratory test is available to identify 25(OH)D deficiency; it is most useful during the fall and winter, when deficiency is prevalent[29,30] owing to the 3-week half-life of 25(OH)D.[18,48] With respect to osteoporosis, the range of 25(OH)D considered deficient is less than 15 to 20 ng/mL,[49] whereas serum levels below 30 ng/mL are associated with increased risk of colon cancer.[50–52] Levels above 150 ng/mL suggest potential toxicity.[53–55]

EPIDEMIOLOGICAL EVIDENCE

Most observational studies have reported that vitamin D has a beneficial effect on risk of colon, breast, prostate, and ovarian cancer. A PubMed search (in December 2004) for epidemiological studies of vitamin D, sunlight, ultraviolet radiation, and latitude in association with these cancers yielded 63 studies, including 30 of colon cancer, 13 of breast cancer, 26 of prostate cancer, and 7 of ovarian cancer (some studies included more than one site).

Of the 30 studies of colon cancer or adenomatous polyps, 20 found a statistically significant benefit of vitamin D, its serum metabolites, sunlight exposure, or another marker of vitamin D status on cancer risk or mortality[12,13,50–52,56–66] and incidence of adenomatous polyps,[67–70] including 1 study in which the association was limited to men[65]; 5 studies reported a beneficial effect (of borderline statistical significance) of vitamin D or its markers on risk of colon or rectal cancer,[71–75] and 5 reported no association.[76–80]

Of the 13 studies of breast cancer, 9 reported a favorable association of vitamin D markers or sunlight with cancer risk,[13,14,57,64,75,81–84] including 1 where the association was limited to premenopausal women[84]; 1 study reported a favorable trend of borderline statistical significance[85] and 3 found no association.[66,80,86] None reported adverse effects.

Thirteen of the 26 studies of prostate cancer found a statistically significant favorable association,[16,17,64,75,87–95] 1 reported a favorable trend for serum 25(OH)D of borderline significance,[96] and 11 reported no statistically significant association.[66,80,97–105] One reported a U-shaped association[106] and 1 reported a significant inverse correlation with latitude, with a weaker correlation with UVB.[94] Five of the 7 studies of ovarian cancer found higher mortality associated with lower regional sunlight[15,17,64,75] or lower vitamin D intake,[107] although 2 reported no association with sunlight.[66,80]

The consistency of the findings of dietary and serum studies with those of geographic studies allowed triangulation on vitamin D as a common factor in risk of colon cancer,[12,13,17,50–52,56–59,61–64] colonic adenomas,[67–70] breast cancer,[14,17,57,64,75,81,82,84] prostate cancer,[16,17,64,75,87–95,108,109] and ovarian cancer.[15,17,64,94,107]

Dietary studies[56,58,60–63,71–74,76–79,84,100–102,105,107] had certain limitations that contrasted with studies of serum.[50–52,59,67,68,82,86,88,90,97,98,110] Dietary studies in the United States were somewhat limited because it was difficult to fully separate associations of vitamin D from those of calcium, because both are in milk. There are many foods, however, that contain substantial amounts of vitamin D but little calcium, including fatty ocean fish.[111,112] Higher intake of fatty fish was associated with lower mortality rates of colon[113,114] and breast[114,115] cancer in international comparisons, and of prostate cancer in cohort studies.[116,117]

Although serum studies have the advantage of measuring vitamin D status regardless of source, they can be confounded by associations with physical activity, particularly in studies of colon cancer. An association between greater physical activity and lower risk of colon cancer has been reported,[118–120] although this was not always found.[121] A common link could be that physical activity raises serum levels of 1,25(OH)$_2$D, the most biologically active metabolite of vitamin D.[122]

Six of 7 prediagnostic serum studies of colon cancer or adenomas reported significantly higher risk of colon cancer[50–52] and adenomas[67–69] in those with low 25(OH)D levels, whereas 1 reported a trend suggestive of higher risk in those with low serum 25(OH)D.[59] Both studies of the role of vitamin D in breast cancer analyzed 1,25(OH)$_2$D, rather than 25(OH)D.[82,86] One reported that the risk of breast cancer was markedly higher in women with low prediagnostic 1,25(OH)$_2$D,[82] but the other found no association.[86] Lower levels of 25(OH)D[90] or 1,25(OH)$_2$D[88] were associated with higher risk of prostate cancer in 2 studies, but not in others.[97,98,103,110] Some of the latter may not have detected an association with 1,25(OH)$_2$D because its serum concentration is homeostatically regulated.[123,124] On the other hand, some individuals with prolonged poor vitamin D status have below-average levels of 1,25(OH)$_2$D,[125,126] possibly accounting for the studies that found that individuals with low serum 1,25(OH)$_2$D had high risk of breast[82] and prostate[88] cancer.

Vitamin D synthesis[127] and serum 25(OH)D levels[128–130] are inversely correlated with latitude and positively correlated with sunlight, consistent with higher incidence or mortality rates for colon[12,13,17,57,75] and breast cancer,[13,14,17,57,75,81] especially in areas 37° or more from the equator. There are also north–south gradients for ovarian[15,17,64,75] and prostate[16,17,64,75,87,92,94] cancer. Some of the gradient for breast cancer may be associated with reproductive factors.[131,132]

UVB exposure and vitamin D intake increase serum 25(OH)D levels in a dose-dependent manner[133–135] by providing a higher concentration of 25(OH)D as substrate for synthesis of 1,25(OH)$_2$D. Normal colon,[136–138] breast,[139,140] and prostate[141] epithelial cells have a vitamin D receptor (VDR) that is highly sensitive to 1,25(OH)$_2$D. This could provide a mechanism of anticarcinogenic action for either circulating or locally synthesized 1,25(OH)$_2$D.

Because synthesis of circulating 1,25(OH)$_2$D is regulated in the kidney by parathyroid hormone,[133] increased UVB exposure usually does not elevate circulating 1,25(OH)$_2$D. 1,25(OH)$_2$D is the most active vitamin D metabolite, although its concentration in serum is one thousandth that of 25(OH)D.[142] It is synthesized from 25(OH)D by 1-α-hydroxylase enzymes in the colon,[143] prostate,[144] breast,[145] and other tissues[146] through an autonomous mechanism not homeostatically regulated by parathyroid hormone.

The fact that 1,25(OH)$_2$D is synthesized in colon epithelium provides a possible explanation for lower incidence rates of colon cancer[50–52] and adenomatous polyps[67–69] in individuals with higher levels of serum 25(OH)D. It also helps explain the association of residence at sunnier latitudes with lower mortality rates from colon,[12,17,56,64] breast,[13,14,17,64,85] ovary,[15,17,64] and prostate[16,17,64,87,90,91] cancer, because sunlight increases 25(OH)D levels, thereby providing more substrate for these tissues to make 1,25(OH)$_2$D.

RACIAL FACTORS

Blacks have levels of 25(OH)D approximately half those of Whites.[19,20,23,147–150] Blacks in northern cities with large Black populations (Chicago, Minneapolis, Detroit, Buffalo, Cleveland, and Toledo) have colon cancer mortality rates substantially higher than those of Whites.[151] Case-fatality rates are higher among Blacks for colon,[152–154] breast,[154] prostate,[154] and ovarian[155] cancer. Colon cancer mortality rates are 33% higher among Blacks, and incidence rates are 19% higher.[156] Breast cancer mortality rates are 28% higher among Blacks, although incidence rates are slightly lower.[156]

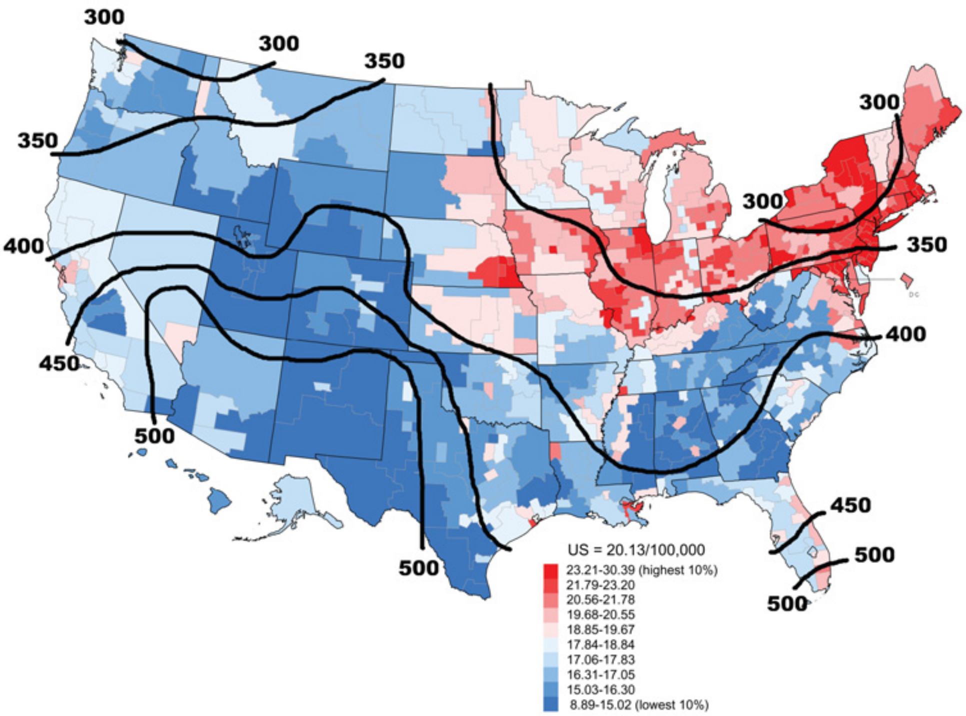
There is a possibility of confounding by stage at diagnosis, since breast cancer tends to be diagnosed in more advanced stages in Blacks than in Whites.[157] However, differences in stage at diagnosis persisted after adjustment for socioeconomic status.[158] Blacks have substantially poorer survival rates,[159] even when mammographic screening rates are similar to those of Whites.[160] Prostate cancer mortality rates are more than twice as high among Blacks as among Whites, and incidence is 1.6 times higher.[156,159] Ovarian cancer mortality and incidence rates are higher among Whites, although they are rising among Blacks.[156]

GENETIC FACTORS

There are several VDR genotypes.[161] The most important of these regarding cancer is Bsm I,[162,163] which has 3 variants: BB, Bb, and bb. The bb genotype occurs in 35% of the US population[164] and is associated with lower circulating concentrations of 1,25(OH)$_2$D.[162] Men with the bb genotype were found to have twice the incidence of colon cancer[162] as those with the BB genotype. In men below the median serum 25(OH)D level, those with the bb genotype had more than twice the incidence of prostate cancer as other men.[162,165] Risk of breast cancer in women with the bb genotype was twice that of women with the BB genotype,[166,167] although breast cancer findings have been mixed.[168] Women with the bb genotype were 4 times more likely to develop metastases than those with the BB genotype.[169] Approximately 40% of colon and prostate cancer may be related to the bb genotype, interacting adversely with low 25(OH)D.[162]

VDR polymorphisms also are associated with a more severe form of malignancy. Men with the VDR Taq I TT genotype, for example, were found to be 5 times more likely to develop a severe (Gleason grade$\geq$5) prostate malignancy than those with other genotypes.[170] This differs from previous inconclusive studies of associations of VDR genotypes with prostate cancer.[171,172] Breast cancer cases with the TT genotype were twice as likely to have lymphatic metastases.[173] The population prevalence of the TT genotype is 35%.[174]

These studies have helped define the role of vitamin D in cancer,[162,163,165,167] although most were exploratory, and only a few of the known VDR genotypes have been shown to be associated with risk of cancer.



Source. Developed through use of National Cancer Institute and National Oceanic and Atmospheric Administration data (available at http:// www3.cancer.gov/atlasplus/charts.html and http:// www.noaa.gov).

FIGURE 1—Age-adjusted colon cancer mortality rates by county, United States, 1970–1994.

VITAMIN D AND COLON CANCER

Age-adjusted death rates for colon cancer tend to be high in areas with low levels of winter sunlight and low in sunny areas (Figure 1).

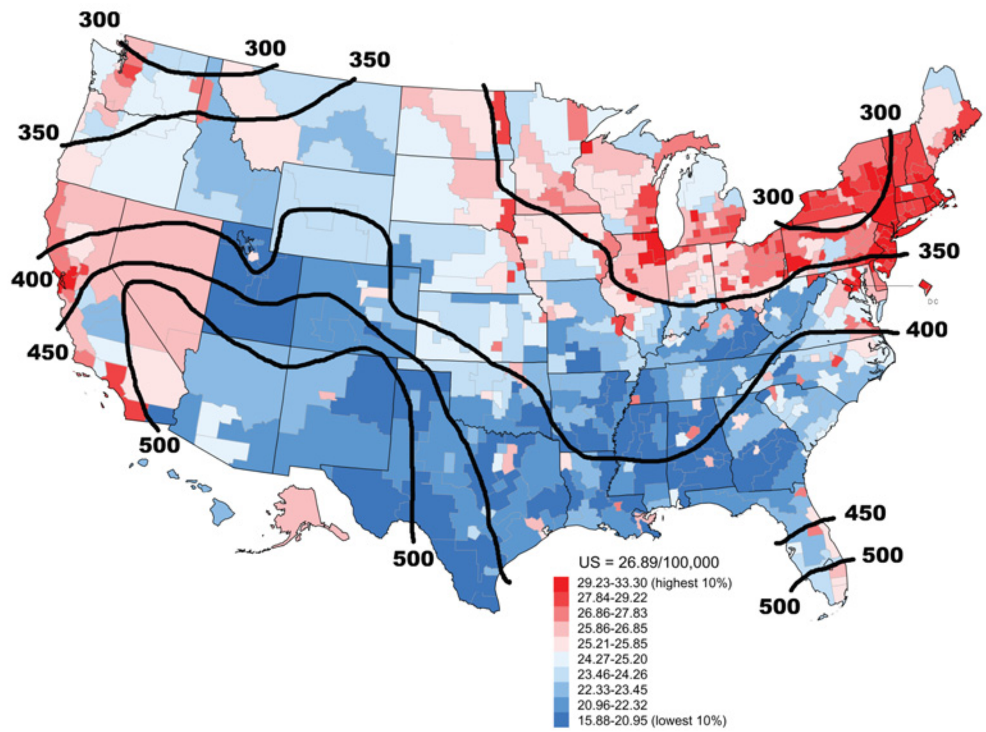
Individuals with circulating 25(OH)D levels below 30 ng/mL had approximately twice the risk of colon cancer as those with higher levels in 2 studies,[50,52] with doubling of incidence for those with less than 20 ng/mL in another.[51] There was a consistent favorable, although nonsignificant, trend in a fourth.[59] Individuals with 25(OH)D levels below 30 ng/mL also had higher incidence of colonic adenomas.[68,69] The association of 25(OH)D with risk of colon cancer was present both early and late in follow-up,[50,59] suggesting that vitamin D metabolites may have effects at all stages of carcinogenesis.[175–177]

Seven epidemiological studies reported higher risk of colon cancer in individuals who consumed lower amounts of vitamin D, including the Western Electric Cohort Study,[56] the Nurses' Health Study,[60] the Male Health Professionals' Follow-Up Study,[62] the Iowa Women's Health Study,[71] and the American Cancer Society Cancer Prevention Study II (CPS II) Cohort Study,[65] and 2 case–control studies.[63,73] The association in the CPS-II Cohort was limited to men.

One study reported a trend toward higher risk of colon cancer with lower vitamin D intake,[71] and another reported an inverse association of vitamin D and calcium intake with risk of rectal cancer.[72] Another found that lower vitamin D intake was associated with higher risk of adenomas.[70] The findings of one study of colon cancer were no longer statistically significant after multivariate analysis.[71] Five studies found no association.[76–79,178] Two of these were performed in sunny climates,[76,178] where they could have been influenced by solar vitamin D synthesis. Although the latitude gradient helps to isolate the role of vitamin D, confounding is still possible.

VITAMIN D AND BREAST CANCER

Breast cancer death rates tended to be higher in areas with low winter sunlight levels and lower in sunny areas (Figure 2).[13,14] Women regularly exposed to sunlight, and consumers of above-average amounts of vitamin D, had significantly lower incidence rates of breast cancer.[85] Women in the lowest quartile of serum $1,25(OH)_2D$ had a risk of breast cancer 5 times higher than those in the highest quartile.[82] Low $1,25(OH)_2D$ levels were also associated with faster



Source. Developed through use of National Cancer Institute and National Oceanic and Atmospheric Administration data (available at http://www3.cancer.gov/atlasplus/charts.html and http:// www.noaa.gov).

FIGURE 2—Age-adjusted breast cancer mortality rates by county, United States, 1970–1994.

progression of metastatic breast cancer.[179] Mortality rates of perimenopausal ovarian cancer also were lower in sunny regions,[15,17,64,75] although one study found no geographic association within a single country.[80] High intake of vitamin D and calcium markedly reduced incidence of mammary cancer in mice and rats consuming high-fat diets.[9,180] Incidence of mammary cancer was only one quarter as high in rats that received high levels of vitamin D and calcium.[181]

VITAMIN D AND PROSTATE CANCER

Residents of sunny areas,[16,87] and those with a history of exposure to high levels of sunlight,[92,95,108] had lower risk of prostate cancer. In a study of 19 000 men, those with 25(OH)D levels below 16 ng/mL had a 70% higher incidence rate of prostate cancer than those with levels above 16 ng/mL.[90] For younger men with 25(OH)D levels below 16 ng/mL, incidence of prostate cancer was 3.5 times higher than for those with levels of 16 ng/mL or above and incidence of invasive cancer was 6.3 times higher.[90] However, other studies have not found associations.[80,97–102,104–106]

MECHANISM OF VITAMIN D EFFECTS

Vitamin D and its metabolites reduce the incidence of many types of cancer by inhibiting tumor angiogenesis,[182–185] stimulating mutual adherence of cells,[186] and enhancing intercellular communication through gap junctions,[187] thereby strengthening the inhibition of proliferation that results from tight physical contact with adjacent cells within a tissue (contact inhibition). Vitamin D metabolites help maintain a normal calcium gradient in the colon epithelial crypts,[188] and high serum levels of 25(OH)D are associated with markedly decreased proliferation of noncancerous but high-risk epithelial calls in the colon.[189] $1,25(OH)_2D$ inhibits mitosis of breast epithelial cells.[190] Pulsatile release of ionized calcium from intracellular stores, including the endoplasmic reticulum, induces terminal differentiation and apoptosis,[176] and $1,25(OH)_2D$ enhances this release.[191]

RECOMMENDATIONS FOR VITAMIN D INTAKE

The National Academy of Sciences recommends the following daily intakes of vitamin D: 1 to 50 years of age, 200 IU; 51 to 70 years, 400 IU; older than 71 years, 600 IU.[192] In one study, 500 IU per day was associated with a 25(OH)D level of 30ng/mL, although this included photosynthesized vitamin D.[193] Sufficient vitamin D intake to achieve 30 to 35 ng/mL of 25(OH)D in serum was associated with reduced incidence of colonic adenomas,[67,69] the latter in combination with adequate calcium intake. On the basis of the studies of serum 25(OH)D and risk of colorectal cancer cited in this article, the target range for serum 25(OH)D should be at least 30 ng/mL, but no more than 150 ng/mL.[149,194] The National Academy of Sciences does not recommend a different intake of vitamin D by Blacks, although it suggests a need for further research on racial differences.[192] On the basis of the markedly higher prevalence of 25(OH)D deficiency in Blacks,[19,147] a higher level of supplementation is probably needed. Althought adverse VDR genotypes[162,165–167,169] are present in a large proportion of the population,[164,174] different intakes according to genotype would not be practical.

Older adults need higher amounts of vitamin D owing to decreased absorption,[195] and at any age, serum 25(OH)D rises as an inverse power function of vitamin D intake.[196] Intake of 800 international units (IU) of vitamin D_3 per day, for example, would increase serum 25(OH)D by only 6 ng/mL,[193] so there is no reasonable concern about inducing toxicity with daily intake of 800 to 1000 IU per day.[197] The latter intake would be consistent with maintaining the serum 25(OH)D level at or above 30 ng/mL in most individuals.[69,198] New vitamin D analogs have promising cellular effects, but are not currently used for prevention.[199]

Throughout the United States, the estimated daily solar exposure to maintain a serum 25(OH)D level of 30 ng/mL is 15 minutes in summer and 20 minutes in early fall or late spring, from 11:00 AM to 2:00 PM under clear skies,[18,40,200] assuming exposure of arms, shoulders, and back. Blacks require twice as long.[147] During November to March, north of 37° latitude in the Northeastern and mid-Atlantic regions, no amount of solar exposure is sufficient,[40] partly owing to a slightly thicker regional stratospheric ozone layer[201] and denser tropospheric sulfate aerosol.[202,203] In the Northwest and most other regions, some UVB is available during winter, although low ambient temperatures limit duration and area of exposure.[37,38,40,127,147,200]

Moderation is needed concerning sunlight exposure. Actinic changes are associated with exposure to ultraviolet radiation, and there is considerable evidence for its role in skin cancer.[42,43] If sunlight is used as a source of vitamin D, exposure should be scrupulously monitored so that no reddening of the skin occurs,[200,204] and intentional exposure of the face should be minimized. Individuals with skin type I or II, who tend to burn easily and tan poorly,[205] should not exceed 20 minutes per day in the sun. Exposure times much longer than 20 minutes would not appreciably increase vitamin D synthesis and could increase risk of skin cancer.[206] Oral vitamin D_3 supplementation, rather than solar exposure, should be used by fair-skinned or sun-sensitive persons, or by individuals taking medicines causing photosensitivity.

POTENTIAL TOXICITY

Vitamin D dosages of up to 1000 IU per day have no reasonable likelihood of producing toxicity. Serum 25(OH)D levels of at least 30 ng/mL[207] to 45 ng/mL[143,208] are the minimum necessary to maintain normal parathyroid hormone levels, and at least 400 IU of supplemental vitamin D_3 per day is needed to maintain serum 25(OH)D at a range consistent with normal parathyroid hormone levels in young and middle-aged adults; intake of at least 600 IU per day is required to maintain normal levels in adults aged older than 70 years.[192] The National Academy of Sciences–Institute of Medicine has indicated that 2000 IU per day is the safe upper limit of vitamin D intake.[192] Typical recommended intakes are far below this.[192,209]

Potential toxic effects of vitamin D overdosage, such as bone demineralization, hypercalcemia, hypercalciuria, or nephrocalcinosis with renal failure, are encountered rarely, generally only when the daily dose exceeds 10 000 IU of vitamin D on a chronic basis.[55] Concerns about vitamin D toxicity in the past have been because of massive overdoses in the range of 50 000 to 150 000 IU per day on a long-term basis.[54,133] According to the National Academy of Sciences, no known health risks are associated with dosages of vitamin D in the normally encountered range of intake (up to 2000 IU/day).[55,192,197,198,210,211]

Relatively high oral intakes of vitamin D or serum levels of 25(OH)D are not a concern from a cardiovascular viewpoint, because most studies suggest that higher levels of 25(OH)D are associated with reduced cardiovascular risk. For example, higher serum 25(OH)D,[212] $1,25(OH)_2D$,[213,214] and oral vitamin D[215] were associated with moderately but significantly lower blood pressure.

There also was a beneficial association between serum 25(OH)D and risk of myocardial infarction,[216] ischemic heart disease mortality,[217] and congestive heart failure,[218] although other cardiovascular results have been mixed.[219,220]

Vitamin D supplementation was also associated with reduced incidence of type I diabetes[221,222] and with improvement in type II diabetes.[223,224] In Finland, vitamin D supplementation of infants was associated with reduction by four fifths in incidence of type I diabetes.[221] Higher regional UVB levels have also been linked with lower age-adjusted death rates from endometrial and kidney cancers, Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma, and other malignancies.[75]

ADOPTION OF VITAMIN D FOR CANCER PREVENTION

Supplemental vitamin D intake could address the high prevalence of vitamin D deficiency in the United States.[1,55,198,225] Strong evidence indicates that intake or synthesis of vitamin D is associated with reduced incidence and death rates of colon, breast, prostate, and ovarian cancers. More than 1000 laboratory and epidemiological studies have been published concerning the association between vitamin D and its metabolites and cancer. Long-term studies have demonstrated the efficacy of moderate intake of vitamin D in reducing cancer risk and, when administered with calcium, in reducing the incidence of fractures.[226] Despite these reassuring studies, the public health and medical communities have not adopted use of vitamin D for cancer prevention.

The cost of a daily dose of vitamin D_3 (1000 IU) is less than 5 cents, which could be balanced against the high human and economic costs of treating cancer attributable to insufficiency of vitamin D. Leadership from the public health community will provide the best hope for action. ■

About the Authors

Cedric F. Garland, Frank C. Garland, and Edward D. Gorham are with the Department of Family and Preventive Medicine, University of California, San Diego. Cedric F. Garland, Frank C. Garland, Edward D. Gorham, and Sharif B. Mohr are with the Naval Health Research Center, San Diego, Calif. Martin Lipkin is with the Strang Cancer Prevention Center, New York, NY. Harold Newmark is with the Laboratory for Cancer Research, Department of Chemical Biology, Rutgers University, Piscataway, NJ. Michael F. Holick is with the Vitamin D Laboratory, Section of Endocrinology, Nutrition and Diabetes, Department of Medicine, Boston University School of Medicine, Boston, Mass.

Requests for reprints should be sent to Cedric Garland, DrPH, Department of Family and Preventive Medicine, 0631C, University of California, San Diego, 9500 Gilman Dr, La Jolla, CA 92093-0631 (e-mail: cgarland@ucsd.edu).

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Contributors

C.F. Garland, F.C. Garland, and E.D. Gorham jointly developed the plan and outline of the article, prepared the first draft, and reviewed and edited subsequent drafts. S.B. Mohr and C.F. Garland jointly performed the literature review, and S.B. Mohr edited drafts of the article. M. Lipkin, H. Newmark, and M.F. Holick reviewed and edited drafts.

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