Commentary: Additional strong evidence that optimal serum 25-hydroxyvitamin D levels are at least 75 nmol/l

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The study by Ford et al.¹ offers further evidence that higher serum 25-hydroxyvitamin D [25(OH)D] levels are associated with reduced mortality rates. They found a 7% reduction [95% confidence interval (CI): −1 to 14] in hazard ratio per 10-nmol/l increase in serum 25(OH)D level. However, if one plots the data in that paper’s Table 2, assuming a mean value of 35 nmol/l for the first quartile, the reduction is ~17% per 10 nmol/l for the lowest three quartiles [25(OH)D < 75 nmol/l]. Data for levels >75 nmol/l show evidence of a slight, non-statistically significant, increase in hazard ratio.

Other studies have reported similar dose–response relations. For example, odds ratios for breast cancer incidence and for colorectal cancer in observational studies declined rapidly from 15 to 40 nmol/l, fell more slowly to 70 or 80 nmol/l and showed little additional change for higher 25(OH)D levels.² Further study found that as the follow-up period after blood draw increased beyond 3 years, results for breast cancer were no longer statistically significant, although those for colorectal cancer were.³ A single value of 25(OH)D level apparently loses prognostic value over time, as levels can change with changes in lifestyle. For breast cancer, previous work discussed by Grant² found that detection rates show seasonality, with highest values in spring and autumn, and that rapid tumour growth beyond 1–3 mm requires angiogenesis. One mechanism whereby vitamin D reduces cancer risk is antiangiogenesis. Evidently, colorectal cancer tumours grow more slowly. Also, the follow-up period does not seem to be an issue with studies of...
cardiovascular disease outcomes. In cardiovascular disease, the atherosclerotic process apparently progresses slowly over several years, with no rapid progression phase.

The long follow-up periods may have been the reason that the Vitamin D Pooling Project failed to find inverse correlations between the prediagnostic serum 25(OH)D level and any of seven types of cancer. The follow-up periods ranged from 1.7 to 10.8 years, with a median value of 4.5 years. In addition, few cases had serum 25(OH)D levels >75 nmol/L, so the 95% CIs for the highest quantile were generally about ±50%. Further evidence of a beneficial role of vitamin D is that survival rates after diagnosis have been reported for seven types of cancer: breast, colorectal, lung and prostate cancer, as well as melanoma, non-Hodgkin’s lymphoma and chronic lymphocytic leukaemia.

One issue that the Ford et al. paper raised was the recent vitamin D recommendations by the Institute of Medicine (IOM) of the National Academies: 600–800 IU/day. The IOM also stated that the only benefit of vitamin D with strong scientific support was for bones, and that 50 nmol/L was an adequate serum 25(OH)D level. The report also raised concerns about health risks of higher serum 25(OH)D levels, but admitted that no adverse effects have been reported for vitamin D intakes of <10000 IU/day. As several journal publications commenting on the IOM recommendations have pointed out, the IOM report was deeply flawed in terms of logic, science and guidance, and the evidence that vitamin D has many health benefits beyond those for the bones is very strong. The basic problem with the IOM report seems to be the committee’s understanding of ‘evidence’ in an era of evidence-based medicine. The federal sponsors of the study specified that it could use randomized controlled trials (RCTs) and observational studies using prediagnostic serum 25(OH)D levels—but not ecological studies, which often use indices of solar ultraviolet B doses as the proxy for vitamin D, or case-control studies, in which serum 25(OH)D level is measured at the time of diagnosis. Vitamin D is not a pharmaceutical drug but is a natural substance that plays a key role in all human and animal life, so requiring evidence from RCTs is unnecessary. Observational studies are abundant, such as the one by Ford et al., as are ecological studies of cancer, most of which carefully control for other risk-modifying factors.

In other disciplines, such as atmospheric sciences, in which I spent most of my salaried career, all peer-reviewed published evidence is taken into account when making scientific assessments. Analogies exist between vitamin D studies and atmospheric studies of constituents: ecological studies are analogous to satellite mapping studies; nested case-control studies are analogous to Lagrangian studies, in which aircraft follow a parcel of the atmosphere for several hours to observe atmospheric processes; case-control studies are analogous to many measurements of the atmospheric constituents at one location, and cross-sectional studies are analogous to survey flights sampling many different air masses. Also, laboratory studies are similar in both fields, and modelling studies—such as the estimate of the reduction in mortality rate if serum 25(OH)D levels were increased from 60 to 105 nmol/l at the population level, as in Ref. 45 in Ford—are similar to modelling studies of ozone depletion and climate change. Furthermore, when scientific assessments are made, they generally include the best scientists in the field, are made in an open fashion, invite reviewers’ comments and respond to comments, as done by the Intergovernmental Panel on Climate Change. The IOM followed only one of these steps, inviting comments, but is unwilling to release the comments.

Finally, if we assume that serum 25(OH)D levels should be >75 nmol/l for optimal health, how can people achieve those levels? Although solar UVB irradiance is the primary source for most people, most people do not get enough sunlight because of such factors as lifestyle and use of sunscreen. Another option is to supplement with vitamin D3 (cholecalciferol). The conventional rule is that serum 25(OH)D levels increase by ~15–25 nmol/l for each 1000 IU/day of vitamin D. However, as a recent paper showed, considerable individual variation occurs in the USA between oral vitamin D intake and serum 25(OH)D level. This work found that the serum 25(OH)D level for White Americans with zero oral vitamin D intake was 83.5 nmol/l, with a 95% CI of ±45 nmol/l. Thus, testing of serum 25(OH)D levels before supplementing and after supplementing for a few months seems to be required to permit individuals to achieve the desired serum 25(OH)D level.

The health benefits of higher serum 25(OH)D levels appear to be significant and at little cost or risk of adverse health effects.

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**References**


Grant WB. Effect of interval between serum draw and follow-up period on relative risk of cancer incidence with respect to 25-hydroxyvitamin D level; implications for meta-analyses and setting vitamin D guidelines. *Dermato-Endocrinology* in press.


Grant WB. An ecological study of cancer mortality rates in the United States with respect to solar ultraviolet-B doses, smoking, alcohol consumption, and urban/rural residence. *Dermatoendocrinol* 2010; *2*:68–76.


Heaney RP, Holick MF. Why the IOM recommendations for vitamin D are deficient. *J Bone Miner Res* 2011; *26*:455–57.

