

**EDITORIAL**

# Vitamin D<sub>3</sub> for reducing mortality from cancer and other outcomes before, during and beyond the COVID-19 pandemic: A plea for harvesting low-hanging fruit

## INTRODUCTION

Vitamin D<sub>3</sub>, also known as cholecalciferol, is a fat-soluble secosteroid whose key role in calcium and phosphate homeostasis and bone health has been recognized for long. In recent years, evidence has accumulated on multiple other biological effects, such as immunomodulatory and anti-inflammatory effects. The main source of vitamin D for humans is its production in the skin under sunlight exposure, which is often insufficient to ensure adequate vitamin D supply, particularly at high latitudes during fall, winter and spring. This editorial aims to draw attention to the underused potential of enhancing vitamin D<sub>3</sub> supply for reducing cancer mortality and other adverse health outcomes, which might be a most valuable low-hanging fruit before, during and after the Coronavirus Disease 2019 (COVID-19) pandemic.

## VITAMIN D AND CANCER MORTALITY

Each year, approximately 10 million people die from cancer globally [1]. Due to population growth and aging, this number is expected to rise substantially in the current and next decades. A large body of epidemiological research has demonstrated a high prevalence of vitamin D deficiency and insufficiency, defined by blood levels of 25-hydroxyvitamin D (25(OH)D) < 30 nmol/L and < 50 nmol/L, respectively, in many countries around the globe, especially in older adults [2]. Particularly, a high prevalence of vitamin D deficiency and insufficiency has been consistently found among cancer patients [3]. Furthermore, low 25(OH)D levels have been shown to be consistently associated with increased cancer mortality in

general population cohorts [4] and with poorer survival rates among cancer patients [5, 6]. A recent meta-analysis of randomized controlled trials (RCTs) has estimated a 13% reduction in cancer mortality by vitamin D<sub>3</sub> supplementation in daily doses between 400 and 2000 International Units among older adults from the general population [7]. Few RCTs with cancer patients, looking into cancer survival, have been conducted so far, but for colorectal cancer, the second most common cause of cancer-related deaths globally, there is preliminary evidence from RCTs that vitamin D<sub>3</sub> supplementation may increase survival rates [8]. Taken together, current evidence suggests a large potential for vitamin D<sub>3</sub> supplementation to reduce deaths from cancer globally.

The very low costs of vitamin D<sub>3</sub> supplementation would make such an approach very appealing for both high- and low-income countries. Recent model calculations for Germany estimated that saved costs for end-of-life cancer care would be expected to exceed the costs of population-wide vitamin D<sub>3</sub> supplementation of older adults (age 50 and older), suggesting the latter to be not only cost-effective but also a cost-saving approach to reduce the burden of cancer deaths [9]. Further analyses suggest that similar effects could be achieved at even a fraction of the costs of vitamin D<sub>3</sub> supplementation by food fortification [10], pointing to an enormous but largely underused potential to reduce both the global burden of cancer mortality and the global burden of cancer care costs. This is highly relevant as cancer care costs are rising rapidly for many cancers, even those with limited progress in cancer treatment and survival. For example, overall expenditure on pharmaceuticals for colorectal cancer patients in the European Union increased by more than 200% from 2009 to 2015 [11], even though therapeutic breakthroughs have remained relatively limited for this cancer. Notwithstanding the need for further high-quality studies on the effectiveness of vitamin D<sub>3</sub> supplementation or fortification in reducing mortality from specific cancer types, and despite substantial hetero-

**Abbreviations:** COVID-19, Coronavirus Disease 2019; 25(OH)D, 25-hydroxyvitamin D; RCT, randomized controlled trial; UVB, ultraviolet B.

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generality in cancer treatments and corresponding treatment costs across cancers and across countries, the overall picture of vitamin D<sub>3</sub> reducing cancer mortality as a whole, at very low costs, is fairly clear.

## VITAMIN D AND OTHER MORTALITY OUTCOMES

When considering vitamin D<sub>3</sub> supplementation or food fortification as preventive measures to reduce the burden of cancer mortality in the general population, their effects on outcomes other than cancer require equal attention. One obvious key outcome to be considered is all-cause mortality. Again, observational epidemiological studies have consistently demonstrated vitamin D deficiency and insufficiency to be associated with increased all-cause mortality and cardiovascular disease mortality, the most common cause of death globally [12, 13]. Particularly strong associations (3-fold increase among those with vitamin D deficiency) have been observed for respiratory disease mortality [14].

Nevertheless, evidence on lowering total mortality by vitamin D<sub>3</sub> supplementation from RCTs remains controversial. Although meta-analyses have consistently pointed to the beneficial effects of vitamin D<sub>3</sub> supplementation, this association did not consistently reach statistical significance. However, several of the largest trials were conducted in the United States, where the prevalence of vitamin D insufficiency and deficiency is much lower than in most other countries due to food fortification and widespread supplement intake. Given the reverse J-shaped dose-response relationship between 25(OH)D levels and total and cause-specific mortality, with a strong increase of mortality at low 25(OH)D concentrations and absence of associations at higher levels (or even a slight increase at very high levels), much stronger beneficial effects might be expected in populations with lower baseline 25(OH)D levels [15]. This suggestion is supported by most recent evidence from a large Mendelian Randomization Study that suggested a strong causal inverse relationship between 25(OH)D concentrations and mortality for individuals with low vitamin D status but not for those with adequate vitamin D status [16]. Furthermore, several RCTs included in the meta-analyses employed supplementation by single or intermittent non-physiological high doses (“bolus”), such as doses of 100,000 or 200,000 International Units, which seems to be far less effective [17], possibly due to the triggering of countervailing factors such as 24-hydroxylase (CYP24A1), that results in the downregulation of the active vitamin D metabolite 1,25-dihydroxyvitamin D.

## VITAMIN D IN TIMES OF THE COVID-19 PANDEMIC

Most recently, a large number of studies have addressed the potential use of vitamin D<sub>3</sub> supplementation for preventing COVID-19 infections and/or adverse outcomes in those who were infected [18]. A large body of studies consistently found 25(OH)D levels to be critically low among those with acute COVID-19 infections, and the low levels to be associated with poor outcomes such as hospitalization, intensive care unit admission, and need for mechanical ventilation or death [19].

If and to what extent the latter reflects causal associations, confounding or even reverse causation remains to be determined. Several studies with “quasi-experimental” designs have reported very encouraging results, but the results are yet to be corroborated by RCTs [19]. A number of RCTs have been initiated to address the potential benefits of vitamin D<sub>3</sub> supplementation on the acquisition and outcomes of the infection. Although several RCTs administering single or intermittent high bolus doses yielded null results, this may again be due to the inadequate, non-physiological application scheme. Large RCTs with more rational daily dosing schemes over an extended period of time are ongoing, and results are awaited.

A recent meta-analysis has demonstrated that cancer patients are at more than a 2-fold increased risk of adverse outcomes of COVID-19 infections (severe course of the disease, intensive care unit admission and mortality) [20]. A potential positive impact of vitamin D<sub>3</sub> supplementation on those outcomes could therefore be of particularly high relevance for cancer patients, especially in the light of additional adverse outcomes of the pandemic on cancer care, such as delayed diagnosis and treatment.

## PUBLIC HEALTH AND CLINICAL IMPLICATIONS

Notwithstanding many remaining open questions regarding the benefits of vitamin D<sub>3</sub> supplementation or food fortification, their established benefits for a number of health outcomes, such as bone health and respiratory infections, along with emerging evidence of beneficial effects on reducing cancer mortality, their low cost and proven safety (unless extremely overdosed), call for their more widespread use. We are not aware of any other single pharmacological measure that could potentially reduce total cancer mortality by as much as 13% within just a few years, at costs far below those of saved end-of-life cancer care.

Although large benefits of widespread vitamin D<sub>3</sub> supplementation or food fortification would be expected even in the absence of the COVID-19 pandemic, such benefits are likely to be further augmented in times of the pandemic, in which patients with low vitamin D status, to which most cancer patients belong, are at particularly high risk of severe course of the diseases.

Food fortification, a measure already employed in a number of countries, might be the most powerful and economic public health measure, particularly for countries with a high prevalence of vitamin D deficiency and insufficiency. Even though the benefits of food fortification are expected to outweigh costs and potential harms by far, a comprehensive fortification program should always go along with measures to avoid hypervitaminosis D, which may cause hypercalcemia. Such measures could include upper limits in fortified foods and surveillance of serum 25(OH)D levels in representative population samples. For countries with higher average 25(OH)D levels, targeted supplementation of those with vitamin D insufficiency or deficiency might be a more rational way to go, even though that might still include large proportions of the elderly and of cancer patients in particular. In clinical care of cancer patients, measurement of 25(OH)D levels and calcium, and vitamin D<sub>3</sub> supplementation in case of vitamin D deficiency or insufficiency should be strongly encouraged. Such supplementation should be done by physiological regular (such as daily) doses rather than single or intermittent high dose (bolus) supplementation.

An even more economic way to increase vitamin D status could enhance the self-production of vitamin D metabolites in the skin under ultraviolet B (UVB) exposure from sunshine. With increasing time spent indoors by most populations in history of mankind, along with increasing use of sunscreens to prevent potential carcinogenic effects of ultraviolet radiation in recent years, vitamin D supply from this “natural source” most likely has decreased over time and is likely one main reason for the high prevalence of vitamin D deficiency and insufficiency in many countries. Insufficient “natural supply” is of particular concern for people with dark skin living at latitudes where UVB exposure from sunshine is insufficient for adequate vitamin D synthesis. Also, the ability of the skin to synthesize vitamin D diminishes at old age, which contributes to the particularly high prevalence of vitamin D deficiency and insufficiency in the elderly. Nevertheless, promoting well-dosed sunshine exposure, ideally combined with outdoor physical activity, might be a particularly powerful tool to enhance the health outcomes of populations in general and older people and cancer patients in particular. However, as UVB radiation from sunshine is too limited in autumn and winter in higher latitude regions, this “natural supply” strategy only works in spring and summer in many coun-

tries. As vitamin D depots in fat tissue only have a reservoir for about 2 months and vitamin D intake from diet is very limited, vitamin D<sub>3</sub> supplementation or food fortification would still be required to avoid temporary vitamin D insufficiency in winter/early spring, in particular for high-risk patients for vitamin D insufficiencies, such as older adults and cancer patients.

## FURTHER RESEARCH NEEDS

Notwithstanding the plea for an immediate move towards more widespread use of beneficial effects of vitamin D<sub>3</sub> in public health and clinical practice, which are expected to by far outweigh potential harms, further research is needed to substantiate the evidence for designing and choosing the most rational and effective measures. Such research might include comprehensive observational epidemiological studies and community or clinical intervention trials. Like in other fields of medicine, including oncology, RCTs may include novel approaches to personalized interventions, such as supplementation of cancer patients with personalized loading and maintenance doses that best match individual patients' needs. Due to the fact that vitamin D<sub>3</sub> is a patent-free, very low-cost drug, the pharmaceutical industry has no incentive to sponsor such RCTs. Research on vitamin D<sub>3</sub> should therefore be promoted and supported with priority by non-profit-making sponsors, such as governmental sponsors.

## CONCLUSION

Enhanced supply of vitamin D<sub>3</sub> by supplementation, food fortification, carefully-dosed sunlight exposure or a combination of these approaches might be a most powerful and cost-effective, if not cost-saving, approach for reducing the burden of cancer mortality and many other adverse health outcomes. Public health action and further research are warranted to best harvest this low-hanging fruit during and beyond the COVID-19 pandemic.

## DECLARATIONS

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None.

### CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

### AUTHOR CONTRIBUTIONS

HB wrote the manuscript, BS and TN critically reviewed the manuscript and contributed to its finalization. All authors read and approved the final manuscript.

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Not applicable.

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Not applicable.

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Not applicable.

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