Reply: Vitamin D in Oncology

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The recent article ‘Vitamin D in Oncology’ [1] reviewed the evidence that vitamin D reduced the risk of cancer and increased rates of survival after diagnosis. The article acknowledged strong support for the ultraviolet-B-(UVB)-vitamin D-cancer hypothesis from ecological, laboratory, and observational studies. But the evidence was deemed inconclusive for several reasons:

- i) Possible confounding by other cancer risk-modifying factors with the vitamin D index
- ii) Some observational studies found direct correlations between prediagnostic serum 25-hydroxyvitamin D (25(OH)D) levels and cancer incidence rates
- iii) A general lack of randomized controlled trials (RCTs) with vitamin D and cancer outcomes.

This letter addresses these 3 concerns.

The concern about confounding factors was raised in [2]. The factors stated were obesity, solar exposure, and skin legitimate modifiers of serum 25(OH)D that should not be considered confounding factors. In fact, 1 study of cancer incidence used solar exposure and skin pigmentation to develop a vitamin D index [3]. However, an analysis from the Women’s Health Initiative (WHI) study found that the predictive model for 25(OH)D explained 21% of the variation in 25(OH)D concentrations [4]. Another study found large variations of serum 25(OH)D level for any oral vitamin D intake [5]. Thus, because serum 25(OH)D levels cannot be predicted based on known factors, it seems unlikely that confounding factors would affect the serum 25(OH)D levels in cancer studies systematically rather than randomly. As for the reverse causality also mentioned, people generally do not know that they have cancer until it is diagnosed; so having cancer before diagnosis is unlikely to affect serum 25(OH)D levels.

Most recent ecological studies of the UVB vitamin D cancer hypothesis include many cancer risk-modifying factors in the analysis [6]. Some ecological studies also used non-melanoma skin cancer incidence or mortality rates as the index of solar UVB irradiance [7]. Solar UVB irradiance

is the strongest risk factor for non-melanoma skin cancer deaths. Other than vitamin D production, researchers have proposed no credible mechanism to explain the findings of ecological studies of solar UVB and cancer rates in Australia, China, France, Japan, Russia, Spain, and the USA.

As to direct correlations between serum 25(OH)D and cancer incidence rates, a systematic problem appears with prospective studies of cancer outcome with respect to serum 25(OH)D levels determined at time of enrollment: as follow-up time increases, the prognostic value of the single serum 25(OH)D level decreases. This effect is most apparent for breast cancer. Breast cancer has 2 peaks in detection, spring and fall [8]. The explanation is that melatonin levels are higher in winter, when daylight hours are shorter, and vitamin D levels are higher in summer. A review of breast cancer risk with respect to follow-up time found that case control studies with no follow-up time found strong inverse correlations with respect to serum 25(OH)D, but as follow-up time increased in nested case control studies, the risk ratio tended toward unity [9]. Another study found inverse correlations between serum 25(OH)D level and breast cancer incidence for follow-up times up to 10 years, but it found a direct correlation for follow-up times between 15 and 20 years [10]. For non-Hodgkin’s lymphoma, an inverse correlation of incidence with respect to serum 25(OH)D level was found for follow-up times up to 7 years, with a direct correlation for longer follow-up times [11]. The observational studies mentioned in [1] reporting no correlation or a direct correlation between serum 25(OH)D level and cancer incidence rates had follow-up times between 6 and 17 years.

One RCT used a high enough level of vitamin D₃ (1,100 IU/day) to be effective [12]. It found a 77% reduction (relative risk = 0.23; CI: 0.09, 0.60; $p < 0.005$) in all-cancer incidence between the ends of the 1st and 4th years for vitamin D plus calcium. In the calcium arm, the trial found a 41% non-significant reduction (relative risk = 0.59; CI: 0.29, 1.21; $p = 0.15$).

A recent analysis of a subset of those in the WHI found that women not taking calcium or vitamin D supplements at the start had a 14–20% reduction of breast cancer and a 17% non-significant reduction of colorectal cancer, whereas those taking either supplement at the start had no significant change in cancer incidence rates [13]. This finding is consistent with the fact that the relationship between serum 25(OH)D level and cancer incidence rates changes rapidly at lower serum 25(OH)D levels and then more slowly at levels higher than 100 nmol/l or so [14].

Thus, the concerns raised in [1] have explanations that counter the doubts regarding the UVB vitamin D cancer hypothesis. Increasing serum 25(OH)D levels to 110 nmol/l globally would reduce cancer rates by an estimated 20–25% and increase life expectancy by 2 years [15]. Because vitamin D supplementation up to 4,000 IU/day is associated with limited risks [16], waiting another 5 years or so for ‘definitive’ RCTs to demonstrate efficacy and lack of harm does not make sense. Although RCTs are required for pharmaceutical

drugs, they should not be required for vitamin D for cancer prevention: solar UVB is the primary source of vitamin D, and abundant evidence from ecological and observational studies indicates i) that higher UVB doses and serum 25(OH)D levels are associated with reduced risk and increased survival and ii) that causality of vitamin D for cancer risk reduction is largely established [17]. In addition, conducting RCTs without measuring serum 25(OH)D level at time of enrollment and every year or 2 of the study will reduce the ability of the study to determine the effect of vitamin D because cancer risk is related to serum 25(OH)D levels, not oral vitamin D intake per se [13].

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