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LETTER TO THE EDITOR

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In defense of the UVB–vitamin D–cancer hypothesis

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To the Editor:

Ronald Brown proposes the vitamin D– de–phosph orus–cancer hypotheses to replace the UVB–vitamin D–cancer hypothesis [1]. I will not evaluate his two hypotheses. However, I will defend the UVB–vitamin D–cancer hypothesis.

Brown cited ~17 papers reporting evidence that vitamin D fails to reduce the risk of cancer incidence and approximately four reporting that vitamin D does reduce the risk of cancer incidence. A quick search at pubmed.gov (July 7, 2019) finds that there are 5372 publications with "vitamin D" and "cancer" in the title and/or abstract. Thus, Brown apparently selectively searched for papers that did not support the UVB–vitamin D–cancer hypothesis.

The strongest evidence for beneficial effects of agents generally comes from randomized controlled trials (RCTs). Brown argued that vitamin D RCTs failed to support the UVB–vitamin D–cancer hypothesis based on statements reported in the abstracts. Journals such as the *New England Journal of Medicine* restrict abstracts from reporting more than one major result per RCT. However, deeper inspection reveals that such RCTs did find reductions in cancer incidence and/or death from vitamin D supplementation in secondary analyses. In the Creighton University vitamin D–cancer RCT (ref. 6 in [1]), the online supplement reported that when the results were analyzed with respect to achieved 25-hydroxyvitamin D [25(OH)D] concentration, "Compared with 25(OH)D level of 30 ng/ml as baseline, the estimated HR [hazard ratio] for cancer incidence for 25(OH)D levels between 30 and 55 ng/ml was 0.65 (95% CI, 0.44–0.97)."The VITAL study (ref. 2 in [1]) reported that cancer incidence was significantly reduced in the treatment arm by 25% for those with BMI <25 kg/m^2, and by 23% for blacks ($P = 0.06$). Cancer mortality rates were reduced significantly in the treatment arm by 21 and 25% when the first 1 year or 2 years of data, respectively, were omitted. Thus, RCTs do support the role of vitamin D supplementation in reducing both cancer incidence and mortality rates.

There are a number of reasons for failures of vitamin D RCTs to find reductions in cancer incidence for the entire group. It is not short-term vitamin D intake per se, but, rather, 25(OH)D concentration that is related to cancer risk. Thus, clinical trials of vitamin D should be based on serum 25(OH)D concentrations at baseline in terms of selecting participants with lower concentrations, and measuring achieved 25(OH)D in order to compare more directly with the results from observational studies [2].

This paper [2] also presents the 25(OH)D concentration-breast cancer incidence relationship derived from 11 case–control studies conducted in seven countries. Incidence rates decrease rapidly as 25(OH)D concentration increases to 20 ng/ml, then more slowly to above 60 ng/ml. Case–control studies of breast cancer are appropriate since breast cancer can develop rapidly, and there is no evidence that 25(OH)D concentrations are affected by breast cancer in the early stages prior to diagnosis. The predictive power of baseline 25(OH)D concentrations in prospective studies of breast cancer incidence with follow-up periods longer than 3 years is greatly reduced, rendering such studies unreliable. Several of the references in ref. [2] also provide support for the UVB–vitamin D–cancer hypothesis, including that the mechanisms, whereby vitamin D reduces incidence, progression, and metastasis of tumors, are well known.

With regard to lower cancer rates in the tropics, that finding appears to be related to a lower ratio of dietary animal-based products to plant-based products than at higher latitudes. A multi-country ecological study found that country dietary energy supply from animal products was directly correlated with ten types of cancer for data from the 87 countries with high-quality data, with eight for smoking (index = lung cancer incidence rate), while six were directly correlated with latitude, an index of UVB dose [3]. As noted

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in ref. [3], ecological studies conducted on solar UVB doses and cancer incidence and/or mortality rates in several single midlatitude countries, as well as a study of occupation and cancer incidence in Nordic countries, strongly support the UVB–vitamin D–cancer hypothesis. Use of data from single midlatitude countries is preferred, since solar UVB doses have a large range in these countries, and many factors, such as diet, are similar country wide, while other factors, such as smoking, and in the United States, ethnic background, can be included in the model.

Thus, the UVB–vitamin D–cancer hypothesis does have strong support, and cannot be dismissed, based on accepting studies with flaws and by ignoring studies supporting the hypothesis.

Compliance with ethical standards

Conflict of interest The author received funding from Bio-Tech Pharmacal, Inc. (Fayetteville, AR).

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