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LETTER

Prediagnostic Serum 25-Hydroxyvitamin D and Mortality Among Bladder Cancer Patients in the Janus Serum Bank Cohort: A Short Comment [Letter]

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Dear editor

I read with interest the article by Hektoen et al.[1] The authors have concluded that: 1) 25 (OH)D deficiency prior to a bladder cancer (BD) diagnosis is associated with increased risk of BC-specific mortality, when compared to insufficient levels; and 2) results were pronounced among non-muscle invasive BC (NMIBC) patients only, suggesting a more critical role of vitamin D deficiency in an early stage of the disease. While their results can be partly true, their interpretation and conclusion suggesting a more critical role of vitamin D deficiency in an early stage of the disease is subject to many biases and meanwhile can be clinically/epidemiologically misleading.

Firstly, vitamin D status is a function of many factors, including the 7-dehydrocholesterol concentration in epidermis (which in turn is a function of dietary cholesterol intake and serum cholesterol concentration), and melanin pigmentation, skin melanin pigmentation, sunscreen use, clothing, season, time of day, aging and latitude.[2] To become active, vitamin D underwent two hydroxylation steps in the liver and kidneys, as the authors acknowledge. This simply means that sufficient/proper/functional hydroxylation is critically associated with the expression and serum levels of 1-alpha hydroxylases and 25-alpha hydroxylases[2] in functional/healthy liver and kidneys, respectively.

Indeed, multiple deregulated metabolic changes result in bladder cancer,[3–5] namely impaired hepatic cytochrome P450 oxidoreductase,[5] dysregulation of MMP-1 expression in response to hypoxia, which in turn is dependent on the intracellular redox status of metastatic bladder cancer cells,[4] and altered cellular metabolism, drastic changes in glycolysis and mitochondrial metabolism,[3] just to mention a few.

This means that insufficient vitamin D status—besides insufficient dietary vitamin D intake—is indicative of multiple cellular abnormalities within the hepatic and renal cells, directly leading to BC, not vitamin D status per se de facto.

Secondly, their cohort study is carried out in Norway, with a wide latitude and, it is not indicated in which season the blood samples are taken.

Thirdly, they suggest a more critical role of vitamin D deficiency in an early stage of the disease, like many other authors. Extreme caution should be taken here, as many readers may interpret this as an encouraging note to focus correction of serum vitamin D levels, instead of individualized clinical evaluation strategy and practice guidelines.

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These imply that their conclusion emphasizing that a more critical role of vitamin D deficiency in an early stage of the disease could be either an artifact, or association in some patients might be more pronounced (ie, in participants who had renal or hepatic disease or both), while in some samples, associations might be attenuated (ie, in patients who had not renal/hepatic diseases). Authors might choose to re-analyze their data, particularly if they could adjust for confounding factors such as data on renal and hepatic diseases (and other confounders), in case data were available. A mediation analysis performed to support the conclusion is also recommended.

Disclosure

The author reports no competing or conflicts of interest for this communication.

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