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RESPONSE TO LETTER

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

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Dear editor

We thank Dr. Rastmanesh for his interest in our paper and appreciate the opportunity to respond to his concerns.[1]

We found an association between low vitamin D (25-hydroxyvitamin D (25(OH)D)) status and worse bladder cancer (BC) prognosis, most pronounced in non-muscle invasive BC. Dr. Rastmanesh's concern is that the association could be confounded by limited functional hydroxylation steps in the liver and kidneys due to cellular abnormalities within the hepatic and renal cells that can result from ongoing BC itself. Thus, a reanalysis of our data was requested, taking information about renal and hepatic disease as well as other possible confounders into consideration.

Our study utilizes data from the Janus serum bank, which constitutes data and serum samples from individuals who participated in population-based health surveys when they were in their early 40s.[2] At this age the incidence of bladder cancer is low.[3] As shown in Table 1 in our paper,[4] the mean duration between serum sampling (used for vitamin D measurement) and the subsequent BC diagnosis was more than 20 years. Moreover, all serum samples were collected at least five years prior to the diagnosis. Thus, it is not reasonable to believe that ongoing BC could have influenced the vitamin D measurements and that the association between low 25(OH)D status and worse prognosis of BC is confounded by limited hydroxylation function due to the BC diagnosis. Also, we do not have information about liver and kidney or other diseases, and a reanalysis is thus not possible. In our analysis, all available lifestyle factors were taken into consideration, but we cannot exclude the possibility that residual and/or unmeasured confounding from diet and other clinical conditions/diseases still persist, as emphasised as a weakness in our paper.

Secondly, Dr. Rastmanesh commented the wide latitude of Norway and the potential impact season for blood sampling.

Although Norway covers a wide latitude range (the mainland extend from 58 to 71°), the levels of 25(OH)D do not seem to vary by latitude possibly as suggested due to the diet and supplementary intake.[5] However, in the Norwegian population, the 25(OH)D levels vary by season, with the lowest levels during December-February. Therefore, the

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impact of season for serum sampling was acknowledged and the 25(OH)D concentrations were season-standardized as described in the method section.[4]

Thirdly, the authors were criticised for giving a conclusion that potentially could give a misleading message to BC patients.

We concluded that our results suggest vitamin D deficiency to play a more critical role in survival of early stage BC patients. This is in agreement with another study that found associations between 25(OH)D status and survival in low stage non-small lung cancer, but not in advanced stage.[6,7] We did not in any way consider an interaction between vitamin D use and treatment in our study, and did not either draw any conclusions regarding treatment of BC in clinical practice. We also rely on a 25(OH)D level in serum samples collected years prior to the BD diagnosis. Overall, it is not likely that our conclusion would be interpreted in a way that patients would prefer treatment for their vitamin D status at diagnosis instead of treatment according to the clinical guidelines for BC, in order to improve their prognosis.

Disclosure

The authors have no conflicts of interest in this communication.

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