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Response

RESPONSE

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We thank Raimondi et al. for their alternative interpretation of our results on the prognostic value of 25-hydroxyvitamin D3 (25[OH]D3) serum level in melanoma patients. With the observation that standardized value of 25(OH)D3 at diagnosis was not a prognostic factor, our major finding was that a change of 25(OH)D3 serum level upon time in both directions was associated with worse disease-free and overall survivals, with U-shaped curves. We postulated that this latter result was unlikely to be a direct consequence of vitamin D biological actions but rather reflected a global instability in patients' metabolisms, which finally impact 25(OH)D3 serum level by any of the multiple pathways involved in the vitD3 regulation (1).

The alternative explanation proposed by Raimondi et al. links our finding with their own hypothesis that vitamin D mediates the lower risk of relapse this team found in melanoma patients who had sunny holidays before and after diagnosis (2). They speculate that just after announcement of this dreadful diagnosis most of our patients refrained from exposing their skin to the sun, inducing a reduction of the production of 25(OH)D3. As patients' ultraviolet exposures were not measured directly in our study, we cannot exclude this hypothesis. However, should this hypothesis be true, then patients with high exposition to the sun before diagnosis (and thus with higher 25(OH)D3 serum level) should have a better prognosis, a result we did not find in our study, which included far more patients and was a long follow-up prospective study. Secondly, should a brutal reduction of sun exposure habits have occurred in our patients, such changes usually fade with time (3). We would expect a decrease over time of sun exposure–induced variations of 25(OH)D3 levels and a reduction of the U-shaped curves linking survival to the variation of 25(OH)D3 levels over time. On the contrary, some of the multiple sensitivity analyses, which resulted in similar results as in the main analysis, are not in line with this expectation. The hazard ratios for the effect of variation of standardized 25(OH)D3 serum levels remained of similar magnitude when using different initial periods for standardization or restricting the sample to individuals with a short delay between diagnosis and first 25(OH)D3 measurement. We also took into account the number of 25(OH)D3 measures performed, partly reflecting the length of follow-up. Finally, this hypothesis of transient change would imply a progressive increase of 25(OH)D3 levels with time while we observed a median decline of -0.30 nmol/L/year.

Thus the hypothesis proposed by Raimondi et al., although attractive, seems not confirmed by our data. There are multiple parameters outside of sun exposure that control 25(OH)D3 serum levels, such as inflammation (4). Melanoma progression is also associated with poorer global health, thus possibly limiting sun exposure, then resulting in reduction of 25(OH)D3 serum levels. Further studies are needed to link findings originating from sun exposition questionnaires, which are prone to memory bias and somewhat imprecise, to more objective measures such as standardized 25(OH)D3 serum levels, which directly depend on sun exposure, but also diet, inflammation, sex, body mass index, smoking, and finally global health.

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