Response

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List of abbreviations:

25 hydroxy-vitamin D3: 25(OH)D3

Counts:

Letter: 500 words, not counting title and reference list.

We thank S 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.[1] 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 a direct consequence of vitamin D biological actions, but rather reflected a global instability in patient's metabolisms, which finally impact 25(OH)D3 serum level by any of the multiple pathways involved in the vitD3 regulation.[2]

The alternative explanation proposed by S 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 holydays before and after diagnosis.[3] They speculate that just after announcement of this dreadful diagnosis, most 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 occurred in our patients, such changes usually fades with time.[4] We would expect a decrease over time of sun-exposure induced variations of 25(OH)D3 level and a reduction of the U-shaped curves linking survival to the variation of 25(OH)D3 level 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 level 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 sun exposure that control 25(OH)D3 serum level, such as inflammation.[5] Melanoma progression is also associated with poorer global health, thus possibly limiting sun-exposure, then reduction of 25(OH)D3 serum level. Further studies are needed to link findings originating for sun exposition questionnaires, which are prone to memory bias and somewhat imprecise, to more objective measures such as standardized 25(OH)D3 serum level, which directly depends on sun exposures, but also diet, inflammation, sex, body-mass index, smoking, and finally global health.[1]

[1]Saiag P, Aegerter P, Vitoux D, *et al*. Prognostic value of 25-hydroxyvitamin D3 levels at diagnosis and during follow-up in melanoma patients. J Natl Cancer Inst (2015) 107 (12): djv264.

[2]Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. Am J Physiol Renal Physiol 2005;289(1):F8-28.

[3]Gandini S, De Vries E, Tosti G, et al. Sunny holidays before and after melanoma diagnosis are respectively associated with lower Breslow thickness and lower relapse rates in Italy. PLoS One. 2013;8(11):e78820.

[4]Idorn LW, Datta P, Heydenreich J, Philipsen PA, Wulf HC. A 3-year follow-up of sun behavior in patients with cutaneous malignant melanoma. JAMA Dermatol. 2014 Feb;150(2):163-8.

[5]Autier P, Boniol M, Pizot C, *et al.* Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol 2014;2(1):76-89.