

## Letters to the Editor

### RE: "CIRCULATING 25-HYDROXYVITAMIN D AND RISK OF PANCREATIC CANCER"

In their study on circulating 25-dihydroxyvitamin D (25(OH)D) and the risk of pancreatic cancer, Stolzenberg-Solomon et al. found that a high 25(OH)D concentration ( $\geq 100$  nmol/L) was associated with a statistically significant increase in pancreatic cancer risk. On the basis of these results, the authors concluded, "... recommendations to increase vitamin D concentrations in healthy persons for the prevention of cancer should be carefully considered" (1, p. 81). However, there are potential health implications of chronic vitamin D deficiency in healthy persons, particularly in populations inhabiting higher geographic latitudes (2) and in those with darker skin pigmentation (3).

At 156 nmol/L, the highest 25(OH)D concentration observed in this study cannot be considered as potentially toxic. The authors acknowledge that the range of 25(OH)D levels associated with the cancer risk in this study was below that considered to reflect hypervitaminosis D. In addition, a half-hour skin exposure under the summer sun in a bathing suit can initiate the release of up to 50,000 IU (1,250  $\mu$ g), 30,000 IU (750  $\mu$ g), and 10,000 IU (250  $\mu$ g) of vitamin D into the circulation within 24 hours of the exposure in white, tanned, and dark-skinned individuals, respectively (4).

A dose of 250  $\mu$ g of vitamin D/day for up to 5 months is not expected to elevate circulating 25(OH)D to concentrations greater than 90 ng/mL (225 nmol/L), while doses of less than 25  $\mu$ g of vitamin D/day are inadequate for maintaining physiologically normal circulating 25(OH)D concentrations of 15–80 ng/mL (37–200 nmol/L) (5). Considering that vitamin D plays an important role in modulating the immune response (4, 6), it is likely not plausible to even suspect a causal relation between moderately elevated levels of circulating 25(OH)D and an increased incidence of pancreatic or other cancers. It may be useful to establish the difference between concentrations of total and free serum 25(OH)D and its active metabolite, 1,25-(OH)<sub>2</sub>D, among the selected subjects. Pettifor et al. (7) found that, despite normal or near-normal total 1,25-(OH)<sub>2</sub>D values, most of the patients in their study had elevated free 1,25-(OH)<sub>2</sub>D suspected to play a role in the pathogenesis of hypercalcemia and vitamin D toxicity.

Further research is needed to determine if the observed elevated 25(OH)D levels in pancreatic cancer patients could be associated with genetic variants of vitamin D receptors or abnormal vitamin D metabolic pathways. Ramagopalan et al. (8) provide a comprehensive high-resolution map of numerous vitamin D receptor binding sites with influence on the immune and other functional pathways, and they discuss observed significant enrichment in regions near autoimmune and cancer-associated genes. An unbalanced metabolic transformation or inadequate receptor binding may lead to plasma accumulation of active/inactive vitamin D

metabolites and an impaired immune response, which could increase the probability of developing not only pancreatic but also other cancers. Hence, although seemingly paradoxical, the elevated levels of circulating 25(OH)D observed by Stolzenberg-Solomon et al. (1) may indicate a functional vitamin D hypo- rather than hypervitaminosis.

#### ACKNOWLEDGMENTS

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