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Vitamin D status in relation to non-skeletal disease outcomes: findings from the EPIC study

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Vitamin D is an established regulator of calcium homeostasis and bone metabolism. Currently, relationships between vitamin D deficiency and increased risks of various non-skeletal health outcomes, especially cancer and cardiovascular diseases (CVD), are under debate. The aim of the present work was to contribute to the evidence base on vitamin D and breast cancer as well as myocardial infarction (MI) and stroke by means of a prospective cohort study, the European Prospective Investigation into Cancer and Nutrition (EPIC).

First, it was assessed whether vitamin D status, i.e. circulating concentrations of 25-hydroxyvitamin D (25(OH)D) were associated with breast cancer risk in a Europe-wide prospective case-control analysis nested within the EPIC study. This analysis was motivated by the fact that the evidence on the relationship between pre-diagnostic 25(OH)D levels and breast cancer risk from longitudinal studies was inconclusive, in contrast to the evidence on vitamin D status and other cancer types. Due to results from laboratory based mechanistic studies implying protective properties of vitamin D mediated through an interplay with estrogen signaling, particular attention was given to possible differential associations between 25(OH)D and breast cancer risk by estrogen receptor (ER) status.

Second, the link between pre-diagnostic 25(OH)D, its genetic determinants and the risks of MI and stroke was investigated in a case-cohort study nested in the German arm of the EPIC study. While several pathways through which vitamin D may affect CVD risk have been identified in experimental studies, and inverse associations between vitamin D status and CVD risk have been detected in epidemiological studies, it remains unclear if vitamin D is a causal factor in the etiology of CVD or if 25(OH)D is simply an unspecific marker of overall health related to outdoor activity. Thus, analyses on genetic predictors of 25(OH)D and the risk of CVD were conducted applying the Mendelian randomization approach in order to rule out reverse causation and to limit the possibility of confounding.

The latter analysis on 25(OH)D and CVD risk was part of an interdisciplinary collaborative project, which also covered an assessment of vitamin D deficiency in German adults, and an evaluation of the potential of vitamin D fortified fish as a food vehicle to improve vitamin D status. Further, based on data generated by project partners from the fields of inland fishery and clinical nutrition research, the impact of an increased vitamin D intake via fortified fish on the incidence of CVD was simulated.

Regarding breast cancer risk, the present work revealed no association with 25(OH)D in a prospective case-control study of 1391 incident cases and the same number of controls during a follow-up time of 4.1 years, neither in analyses stratified by ER status nor overall, the odds ratio between extreme quartiles of 25(OH)D being 1.07 (95% confidence interval: 0.85-1.36). These findings are contrary to those of classical case-control studies that have consistently shown inverse associations between vitamin D status and the odds ratio of breast cancer, which may point to reverse causation as underlying phenomenon of such associations. Moreover, in obvious contrast to previous experimental research, the present results do not suggest that vitamin D might be involved in the early development

of breast cancer. Lastly, the findings from the EPIC study, that was the first epidemiological study on 25(OH)D and breast cancer risk including well-powered analyses stratified by ER status, do not support the notion of an interaction between vitamin D and estrogen signaling, as opposed to results from cell culture and animal models.

Analyses on 25(OH)D and CVD risk were conducted based on data of a random subcohort of 2132 subjects, as well as 559 incident cases of MI and 471 incident cases of stroke, respectively, that occurred during an average of 7.6 years of follow-up. While the risks of MI, stroke and overall CVD, i.e. a composite endpoint of both MI and stroke, in vitamin D deficient subjects were significantly increased compared to vitamin D replete subjects (hazard ratio for overall CVD: 1.53, 95% confidence interval: 1.12-2.09), there were no linear inverse associations. Further, even though several genetic variants significantly associated with vitamin D status were identified, a genetic score based on these variants was not related to the risks of MI, stroke, or overall CVD, the hazard ratio for CVD being 1.0 (95% confidence interval: 0.71-1.42). These results, and the negative results of a similar study on 25(OH)D and MI risk that have been published recently, do not point to a causal role of vitamin D in the development of CVD, but rather indicate that residual confounding or reverse causation drive inverse associations between 25(OH)D and CVD risk in observational studies.

Simulations on the impact of an increased consumption of cultured fish with optimized vitamin D content suggested that up to 3.9% of the incident CVD cases in the middle-aged population of the EPIC-Germany study may have been avoided by fortifying fish with vitamin D without increasing the risk of vitamin D toxicity. However, given that the present work and two further Mendelian randomization studies on MI and CVD mortality conducted in parallel have not provided evidence for a causal relationship between vitamin D and CVD, and that data from intervention trials will become available by 2017 at the earliest, vitamin D fortification schemes may not seem indicated for the prevention of CVD in the general population at this time, despite promising observational data. Also, fish might not be an appropriate food vehicle for added vitamin D in view of low consumption levels and technical constraints to vitamin D “bio-addition”. Nevertheless, proportions of 25(OH)D levels of 60% in the range below 50 nmol/L reflecting insufficiency and 13% in the range below 25 nmol/L reflecting deficiency (<25 nmol/L), respectively, that were observed in the random subcohort of EPIC-Germany study might suggest a need for measures to improve vitamin D status in Germany in order to prevent fractures. Therefore, a combination of campaigns to increase moderate sun exposure, targeted vitamin D supplement use in risk groups, and enrichment of foods with a population-wide reach with vitamin D may have to be considered by public health bodies.

In summary, the present findings are not in line with the notion of a key function of vitamin D in the development of CVD. Also, whereas results from basic science research and epidemiological studies may be supportive of a role of vitamin D in the prevention of colorectal cancer, the present findings do not suggest that vitamin D protects against breast cancer. As vitamin D status might even be positively related to the risk of prostate cancer, and no clear associations with other cancer types have been shown to date, possible anti-cancer actions of vitamin D may be specific for particular tissues at best. Considering that inverse associations between vitamin D status and the risks of colorectal cancer and CVD from prospective observational studies have not been replicated by first Mendelian randomization studies, it cannot be ruled out that reverse causation or confounding by factors such as visceral obesity and outdoor activity have driven associations in prospective studies in the past. Hence, it remains to be clarified if vitamin D status is an unspecific marker for overall health or a causal factor affecting the risk of multiple non-skeletal diseases. The results of ongoing randomized controlled trials and large pooled Mendelian randomization studies, to which the results of the present study will contribute substantially, will enable a comprehensive, evidence-based appraisal of vitamin D in relation to CVD, cancer, and other non-skeletal health outcomes. The findings of the present work indicate that past statements about a possible prevention of cancer and CVD by improving vitamin D supply of the general population may have been premature.