

Vitamin D and Pancreatic Cancer Risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Cohort

□□ *Commentary on Stolzenberg-Solomon et al., p. 10213*

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In this issue, Stolzenberg-Solomon et al. report that higher circulating 25-hydroxy-vitamin D [25(OH)D] concentrations are associated with a higher risk of pancreatic cancer in the Alpha-Tocopherol Beta-Carotene (ATBC) cancer prevention cohort. Based on the large literature on vitamin D and cancer, this finding is most unexpected and should be interpreted with caution. These results are not necessarily generalizable to all populations, as the ATBC population is composed entirely of smokers who were selected because they were at high risk for lung cancer. Nevertheless, the results from this study are worth considering as they come from a well-designed study.

Understanding the etiology of pancreatic cancer has been a great challenge for several reasons, but the predominant one is the difficulties associated with studying a rapidly fatal disease. Pancreatic cancer survival rate at 5 years is <4%, and within 6 months of diagnosis, less than half the patients are alive. For this reason, epidemiologic research on pancreatic cancer has lagged behind other common cancers. Smoking is the only well-established risk factor for pancreatic cancer. More recently, however, accumulated evidence provides strong support for a causal role for type 2 diabetes, chronic pancreatitis, and obesity in pancreatic cancer etiology.

Inconsistent results in epidemiologic studies on pancreatic cancer are common, but explanations for these are not always simple. It has become clear that retrospective case-control studies, which have relied heavily on proxy interviews (not by choice, but as a result of high case fatality), have yielded inaccurate results and led us astray. The most notable example of this has been for obesity and pancreatic cancer. Over the past 10 years, a large number of prospective cohort studies, in which lifestyle and demographic characteristics were obtained before diagnosis, have reported a strong positive association for obesity and pancreatic cancer (e.g., 1–5). In contrast, earlier case-control studies (which relied more on proxy data) reported no association for obesity and pancreatic cancer risk. The influence of using proxy data on the association between obesity and pancreatic cancer was shown in a recent meta-analysis (6). The use of proxy data is just one example of the difficulties encountered when studying rapidly fatal cancers; others include the influence of selection bias, which for pancreatic cancer applies to both cases and controls. Therefore, evaluating study design is critical when interpreting the results of observational studies.

Although unexpected, the Stolzenberg-Solomon et al. results come from a prospective cohort study, which by design, inherently avoids many of the validity issues faced by retrospective case-

control studies. The study design is sound; vitamin D levels in circulation were measured before cancer diagnosis; cases and controls were matched on age and month of blood draw (to account for seasonal variation); the number of pancreatic cancer is large ($n = 200$); loss-to-follow-up is minimal (Finland has an excellent population-wide cancer registry). Retrospective studies with serum samples collected after disease diagnosis are always difficult to interpret given that disease can contribute to substantial changes in metabolites; but this is much less of an issue in this prospective study as the median follow-up time between the collection of the blood specimens and subsequent diagnosis of pancreatic cancer was 11.8 years. Are we then to believe, given these findings, that vitamin D may actually increase the risk of pancreatic cancer?

There is a large literature that shows that vitamin D has numerous anticarcinogenic properties and epidemiologic data are compatible with a protective role for vitamin D and total mortality (7). Ecologic data are not supportive of a strong positive association between vitamin D and pancreatic cancer as sunnier regions do not have higher rates of pancreatic cancer. In fact, the opposite is true, in the United States, relatively high pancreatic cancer rates are observed in states where UV exposure is low (8), and in Japan, an inverse correlation was noted between solar radiation and pancreatic cancer risk (9). Furthermore, in a recent, well-conducted prospective study among members of the Health Professionals Follow-up Study (HPFS) cohort by Giovannucci et al. (10), vitamin D exposure (based on multiple determinants of vitamin D status) was inversely associated with pancreatic cancer risk [relative risk, 0.49; 95% confidence interval, 0.28–0.86, for an increment of 25 nmol/L in predicted plasma 25(OH)D concentration]. The results for predicted vitamin D status and colorectal cancer in the study by Giovannucci et al. were consistent with previous prospective studies on colorectal cancer that had directly measured circulating 25(OH)D, confirming that the predictor score for vitamin D exposure accurately reflects plasma levels.

What may then account for the dramatically different results for vitamin D and pancreatic cancer between the ATBC and HPFS? There are several important differences between these two populations, including geographic location, education, occupation, and most importantly, smoking. At baseline, the ATBC study enrolled only current smokers, whereas the HPFS cohort study is a population of health professionals with a low smoking prevalence. The ATBC cohort consists of the same trial population, in which those randomized to the β -carotene supplement arm had an increased risk of lung cancer compared with the placebo arm (11). The β -carotene finding was borne out in a second trial among smokers (12). However, these trial findings were not replicated in a similar prevention trial of a population of physicians who were primarily nonsmokers (13).

It is conceivable that the association observed in the ATBC study is the result of confounding. Smoking is always a concern when studying the etiology of pancreatic cancer as it is a strong risk

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factor and is associated with numerous behavioral and lifestyle factors. In this cohort, all models included smoking intensity, duration, and cessation (during the trial period), and as there are only smokers, confounding by smoking is unlikely to have been substantial (and account for the findings). Confounding in this study, however, may have occurred as a result of an unknown risk factor. For example, given that vitamin D levels are largely a reflection of sun exposure, the association observed with vitamin D in the ATBC study could be due to a harmful effect from sun exposure, such as immune suppression (14). Alternatively, fish intake, which is consumed in large quantities in Finland and is a major source of dietary vitamin D in this study, may be a confounder if a pancreatic carcinogen is present in fish.

Ultimately, however, we cannot rule out the possibility that the association observed in this study is causal, despite the evidence

against it. If this is true, it is likely that the association will only apply to smokers and, perhaps, more specifically to those who have a generally low vitamin status. Progress is finally being made in uncovering the etiology of pancreatic cancer. This is mainly due to the increasing number of prospective studies that are large enough and/or have sufficient follow-up to contribute a large number of cases. Despite this, unexpected results are bound to occur and should be examined carefully. Stolzenberg-Solomon et al. should be commended for having conducted a well-designed study. However, most will probably agree that the final verdict on the role of vitamin D in pancreatic carcinogenesis is still out.

Acknowledgments

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