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Editorial

Anticancer Vitamins du Jour—The ABCED's So Far

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It started 30 years ago with vitamin A: the idea that some cancers might be caused by vitamin deficiencies. Animal experimental models led us to the notion that cancer risk might be ''materially'' reduced by supplementation with beta-carotene, a retinol precursor (1). Although that idea was seductive, we were all disappointed when 2 large randomized controlled trials that began in 1985 in Finland and the United States reported an 18% increased risk of lung cancer caused by high-dose beta-carotene supplementation and a 28% increased lung cancer risk caused by a combination of beta-carotene and retinol (2, 3). The vitamin A era was over.

Next came the B vitamins. Again, based on animal experimental evidence and supported by epidemiologic evidence of connections between diets low in B vitamins and increased cancer risk, a large randomized controlled trial was begun in 1985 in central China, where micronutrient deficiency was common and where rates of cancers of the stomach and esophagus were extraordinarily high. Nonetheless, several years of supplementation with a combination of riboflavin (vitamin B_2) and niacin (vitamin B_3) had no effect on incidence of upper gastrointestinal cancers (4). Interest in folic acid (vitamin B_9) persisted, though, in part because of its striking effect on neural tube birth defects, coupled with speculation about possible benefits of food fortification for diseases such as colorectal cancer that were inversely associated with diets rich in folate-containing foods and supplements. However, a 7-year randomized controlled trial found that high-dose folic acid supplements actually increased risk of colorectal adenomas (5). The vitamin B era was over.

Next came vitamin C, a popular charge led by none other than Linus Pauling, the brilliant and charismatic 2-time Nobel laureate. Of all the cancers thought to be related to vitamin C deficiency, gastric cancer led the way, and of all the places on Earth where a vitamin C deficiency correction trial might yield benefits for gastric cancer, Linxian, China, would be the best. Indeed, vitamin C was tested in the Linxian trial, but just as for the B vitamins, vitamin C produced no change in gastric cancer rates (6).

Next, slightly out of alphabetical order, came vitamin E. In 1993, we launched headlong into a love affair with vitamin E fueled by compelling observations that those who chose to take vitamin E supplements were at lower risk of heart disease (7, 8). Vitamin E supplementation became the rage as several large, randomized controlled trials were mounted. When those results finally came in, the findings were again disappointing: vitamin E supplementation offered no benefit for heart disease, and it slightly increased overall mortality (9, 10). In the meantime, though, because of a secondary observation that prostate cancer incidence was lower in the vitamin E arm of the same Finnish trial that tested beta-carotene (vitamin E had also been included as a factor) (11), a large factorial trial of vitamin E (and selenium) was carried out for reducing prostate cancer incidence. Disappointment again: there was no effect of either selenium or vitamin E on incidence of prostate cancer (12). The vitamin E era ended in a whimper.

Over 2 decades of searching for an anticancer vitamin, we had seemed to skip over vitamin D in its proper alphabetical sequence. In my role as a member of the World Cancer Research Fund Expert Panel that considered the evidence from commissioned meta-analyses of the world's literature on nutritional epidemiology, I remember feeling concern as we finished our work that we might have underestimated the importance of vitamin D because the bulk of the evidence available at that time was derived from ecologic studies (13). Subsequently, the International Agency for Research on Cancer conducted a comprehensive review of the evidence for vitamin D and cancer prevention, concluding that vitamin D may play a protective role in colorectal cancer, but not for prostate cancer, and that the evidence is weak for breast cancer (14). The conclusion by the International Agency for Research on Cancer about the weakness of the evidence for breast cancer has been a source of controversy among vitamin D protagonists (15, 16), but subsequent nested cohort studies have found no relation between breast cancer risk and circulating levels of vitamin D (17, 18).

Nonetheless, vitamin D remains the cancer-preventing vitamin du jour. Just search the phrase ''vitamin D and cancer'' on the Internet to see what sorts of information and products are now being marketed to the public. Vitamin D is the new vitamin A, the new folic acid, the new vitamin C, the new vitamin E.

An outstanding set of papers in this issue of the *American Journal of Epidemiology* reports on findings about the relation between circulating levels of vitamin D and subsequent cancer risk in a set of pooled cohort studies conducted in the United States, Europe, and Asia. These studies found

no suggestion of an inverse association between vitamin D levels in the circulation and later incidence of 6 types of cancers (upper gastrointestinal, ovary, endometrial, pancreatic, kidney, and non-Hodgkin lymphoma). Although these cancers are characterized as ''rarer,'' this set of sites collectively accounts for about a quarter of all deaths from cancer in the United States. These studies offer compelling evidence against the hypothesis that circulating levels of vitamin D are relevant to risk of these cancers. This new information is important because an International Agency for Research on Cancer review had decided that evidence was previously insufficient to draw conclusions about these 6 cancer sites (14).

Whenever null findings are found, it is important to consider the usual suspect reasons, and the authors of these papers have done an outstanding job of that. The size of this pooled analysis is large enough to discount concerns about low statistical power; there is a good level of internal consistency in the previously documented associations between vitamin D levels and factors such as seasonality, race, gender, diet, physical activity, and body mass index; there was substantial interindividual variation in these cohorts; and there did not seem to be confusion between confounding factors or factors potentially in the causal pathway. The question as to whether the time interval studied was the correct one remains unanswered, however. If the geographic ecologic associations between sun exposure and cancer risk are, in fact, due to long-term cumulative effects of lifelong vitamin D exposures, then cohort studies in adulthood will not be fully informative. However, it is important to note that this longer-term ecologic possibility is not consistent with the other ecologic observation of seasonal variation in cancer incidence that is often also attributed to vitamin D levels in the circulation (19).

The only association observed in this set of 6 analyses was a troubling one: that risk of pancreatic cancer was doubled for those in the highest quintile of circulating vitamin D levels. This observation is disconcerting both because pancreatic cancer is now the fourth leading cause of cancer death in the United States and because the proponents of the vitamin D hypothesis are now arguing that substantially elevating circulating blood concentrations into that range should be a nutritional policy objective for the general population (15, 16). As pointed out by Dr. Helzlsouer (20) in this issue of the *Journal*, many ongoing randomized controlled trials are now using quite high doses of vitamin D. As we await clearer evidence of benefits from those trials, we will also need to be prepared to be vigilant about their individual and collective power to assess any potential harms (21, 22).

It is timely for us to now reflect on the history of the past 25 years of our alphabetical approach to studying single vitamin deficiency states as causal factors for cancer. We have learned some hard lessons along the alphabetical way. We now know that supernutritional levels of vitamins taken as supplements do not emulate the apparent benefits of diets high in foods that contain those vitamins (13), and we now know that taking vitamins in supernutritional doses can cause serious harm. In short, we have found that the reality of human biology is far more complex than is suggested by our simple ideas.

Finally, it is important to recognize the efforts of the many Vitamin D Pooling Project of Rarer Cancers collaborators who carried out such a remarkable set of studies. As pointed out by the Institute of Medicine, we are now in an era of ''big science,'' in which definitive answers to big questions will increasingly require massive efforts and large-scale collaborations (23). Carrying out these types of collaborations requires foresight, skill, and patience. Large-scale collaborations are critically important, though, for our improved understanding of the true nature of the determinants of human health. The dual problems of type 1 and type 2 errors have best been exemplified in genetic epidemiology, but false discovery has been a problem in nutritional epidemiology as well. Even though there was consistency in the overall null observations across most of the cohorts in this pooled analysis, there was some variation. It is easy to imagine that, without this collaborative analysis, we might have been led down several blind alleys derived from analyses of various subgroups and interactions. We all should be grateful to the Vitamin D Pooling Project of Rarer Cancers investigators for having saved us from years of false leads, as well as for their vision and skill in carrying out this outstanding collaborative project.

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Tim Byers (e-mail: tim.byers@ucdenver.edu)
Colorado School of Public Health, University of Colorado Cancer Center, Aurora, CO 80045

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