The article by Afzal et al. in this issue of *Clinical Chemistry* (1) presents data showing an association of low concentrations of vitamin D with risk of tobacco-related cancers. The authors found that vitamin D was not associated with other types of cancer, that the effect was stronger among smokers, and that it appeared to be independent of levels of tobacco consumption among smokers. Although these data suggest that increasing concentrations of plasma 25-hydroxyvitamin D [25(OH)D], especially among smokers, may lead to cancer protection, the data remain suggestive rather than conclusive.

Science is ripe with examples of promising hypotheses based on observational data that did not hold up under more rigorous randomized controlled trials. An early panacea was β-carotene, which was hypothesized to reduce cancer incidence (2). At the time, it was the exciting new theory and garnered much attention. When tested in randomized controlled trials, however, the promising hypothesis failed to hold up. The Physicians’ Health Study, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) trial, the Beta-Carotene and Retinol Efficacy Trial (CARET), and other trials found no overall effect of β-carotene on cancer (3). Whereas observational analyses can carefully control for many confounders, residual confounding cannot be ruled out. There is a persistent and consistent association of consumption of fruits and vegetables with reduced cancer among smokers, and that it appeared to be independent with other types of cancer, that the effect was stronger including cancer, was inconsistent and inconclusive. Several observational studies have now been conducted on vitamin D, the nutrient with the current most widespread appeal, that have suggested a possible protective effect for both cancer and cardiovascular disease. An effect on cancer has biologic plausibility on the basis of animal studies and studies of effects on cells. Residual confounding may still occur, however, since concentrations of 25(OH)D are related to factors such as obesity, physical activity, and diet (7). Reverse causation must also be considered when evaluating dietary exposures.

Data from trials of vitamin D so far have been limited. An early trial suggested a protective effect of a combination of vitamin D and calcium on total cancer (8) but was based on a relatively small number of events. There was also little difference between the combination of vitamin D and calcium and the calcium-only arms. There have been few trials to date directly testing vitamin D alone, and results were null for 3 trials that did compare vitamin D interventions and total cancer in secondary analyses (7).

In 2011, the Institute of Medicine released a new report on dietary reference intakes for vitamin D (9). The panel concluded that although vitamin D plays a role in bone health, evidence for other outcomes, including cancer, was inconsistent and inconclusive. Several observational studies found an association between 25(OH)D concentrations and cancer risk, but these also were inconsistent and could not prove causality. Several new trials of vitamin D are now ongoing, however. One is the Vitamin D and Omega-3 Trial (VITAL) (10), which will include >20 000 men and women across the US. VITAL will test the effects of 2000 IU/day of vitamin D3 (cholecalciferol) over a 5-year follow-up period. Although this level has generally been recognized as safe, there must be careful monitoring for any adverse effects, especially among individuals with high baseline values of vitamin D.

Of course, not all questions can be answered with randomized trials. Trials are generally restrictive in their eligibility requirements and test a single dose or a
limited set of doses. They can provide unbiased answers to specific questions, but these may not generalize well to a clinical population. For example, several observational studies have shown a reduced risk of cardiovascular disease with hormone therapy. Short-term trials of lipids supported this, showing a reduction in LDL cholesterol concentrations with hormone therapy. The Women’s Health Initiative, however, found no preventive effect, and even found an increase in cardiovascular disease among women assigned to the active hormone therapy intervention (11). Controversy exists, however, about the timing of the intervention relative to the natural changes in hormone concentrations due to menopause. Although raising hormone concentrations many years postmenopause may not be beneficial, it remains possible that sustaining hormone concentrations from menopause onward may provide some benefit (12). Trials are currently underway that are designed to test this specific hypothesis.

Trials may also have low power to detect effects on rare outcomes, such as site-specific cancers. Because a single trial may have few cases of rare cancer types, meta-analyses may ultimately be required to find a definitive result. Effects on cancer may also have a long latent period, requiring follow-up of long duration, which may not be feasible in randomized trials. While evidence from trials is accruing, observational studies such as that by Afzal et al. (1) can be useful in examining effects on rarer events over long periods of time in a cost-efficient manner, and in defining hypotheses to be tested later in trials. In the Copenhagen City Heart Study, the authors found an increased risk of tobacco-related cancers among those with low baseline concentrations of vitamin D, but no increase in other cancers. The tobacco-related cancers included lung, head and neck, bladder, pancreatic, stomach, kidney, and liver cancer. Other studies, however, have found inconsistent results for some of these, including in the Vitamin D Pooling Project of Rarer Cancers (13), which found no protective association with esophageal, gastric, kidney, or pancreatic cancers, and which even found an increase in pancreatic cancer at very high vitamin D concentrations. Data from the Copenhagen Study can add to the burgeoning pool of evidence related to these rare cancers.

The inability to test a wide range of doses in randomized trials for rare outcomes is another limitation of trials, and observational studies may provide important insight into these issues. Such observational data can examine a range of doses and suggest optimal concentrations with regard to disease risk. The study by Afzal et al. (1) attempts to provide just such insight. They found a dose–response relationship of tobacco-related cancers with concentrations of 25(OH)D, with increased risk in categories at lower values and a continuous reduction on the log scale. Such information is difficult to acquire in trials at fixed dose, particularly for rare-cancer outcomes. The baseline concentration of the nutrient can have a pronounced impact on effect size and must be considered in addition to the dose of any supplement intervention (14).

The authors go on to suggest that vitamin D may be a mediator of the relation between smoking and tobacco-related cancer, for example by modifying the carcinogenicity of chemicals in tobacco smoke, and provide a simple assessment of mediation. This concept needs to be explored more thoroughly, however. The authors do not report the overall effect of smoking and whether this changes with the addition of vitamin D to the model. In fact, the amount smoked still had a sizeable effect on tobacco-related cancers within groups defined by baseline plasma 25(OH)D. A more sophisticated causal analysis could try to elucidate the direct and indirect effects of smoking vs vitamin D, taking into account confounders in various pathways as well as potential interactions and nonlinearity (15). Ideally, data for changes in both of these exposures would be used to attempt to evaluate the causal relationships.

Trials may also help us here. Examining effects within subgroups may help determine whether there is a difference by smoking status. Randomized comparisons can show how much vitamin D concentrations are increased in both smokers and nonsmokers and whether this translates into reductions in tobacco-related and other cancers in both groups. Carefully controlled observational analyses of trial data may more clearly show whether the effects of tobacco smoke are linked to vitamin D concentrations.

Thus, the article offers additional information regarding the effects of vitamin D, including in an established cohort with limited sun exposure over a long period of time, but it cannot be definitive. Although the article offers an intriguing hypothesis regarding vitamin D and tobacco smoke, it is just another piece in the puzzle. Observational epidemiology can be valuable in suggesting associations, however, even when results cannot be considered fully causal. Fortunately, unlike many other exposures, questions on the benefits of micronutrients can often be followed up with further testing in randomized trials. Such data are necessary before supplements or other additives can be considered to be clinically recommended.

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