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Chasing Hot Molecules

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Researchers continue to test supplement molecules that may prevent chronic disease, but do any of them work?

Headlines have called out red wine's resveratrol as a potential agent for extending both life and health. Carrots' beta carotene was thought to be a wonder antioxidant that could combat cancer. More recently people have started popping vitamin D pills at ever higher doses, hoping to ward off everything from stroke to diabetes. And the omega-3 fatty acids in fish oils have been heralded as heart and brain healthy.

Micronutrients—vitamins and minerals—are compounds that people need to ingest in small amounts to prevent disease and maintain health. Once-common nutrition-related diseases such as scurvy and rickets can largely be prevented through varied diets, supplements, and the fortification of foods. Those successes have fueled the notion that if enough of a micronutrient is good, more might be better.

Researchers have followed up on healthful hypotheses linking high doses of micronutrients—and other compounds found sparingly in foods—with chronic disease prevention. But in the randomized, controlled clinical trials needed to validate such connections, the results so far have shown mixed, contradictory findings or even unexpected harms. The boom and bust cycle confuses health-conscious consumers and has prompted some researchers to begin to question whether preventive supplements can ever stand up to the scientific scrutiny of clinical trials. The promise of a pill that would prevent cancer, heart disease, or any of a number of chronic diseases is an alluring goal, but the chemistry of preventing these diseases—and the complicated ways in which molecules and mixtures behave in the body—may put such prevention pills out of reach.

AN OUNCE OF PREVENTION

How does a particular compound get anointed as the new hope for preventing disease? To identify candidate molecules or supplements, researchers often begin by looking at the health status and behaviors of large groups of people. If these epidemiological studies reveal a link, say, between eating more carrots or drinking more red wine and lower disease rates, researchers might then look for a mechanism of action via biochemistry, cell culture studies, and animal models. These types of studies are critical for generating hypotheses, says JoAnn Manson of Brigham and Women's Hospital, in Boston.

With the terpenoid beta carotene, one of the earliest darlings of chemoprevention research, researchers hypothesized that the antioxidant properties of this micronutrient would counteract free radicals, preventing DNA damage and blocking inflammation. For resveratrol, a polyphenol, researchers have documented a variety of potential biochemical effects, including blocking inflammation, interfering with tumor blood vessel formation, stopping cancer cell proliferation, and modulating cell metabolism. Vitamin D's multiple forms are precursors of the steroid calcitriol, which has long been known to be critical for shuttling calcium into bone producing cells. More recently, mounting cellular and epidemiological evidence suggests that calcitriol also disrupts inflammatory pathways and could interfere with cell proliferation and blood vessel formation in ways that could protect against tumor growth.

Although these initial studies often get picked up by the media, they're just the first steps in understanding whether a supplement might improve health. With enough data from these initial studies, researchers begin randomized, placebo-controlled clinical trials in humans. "Randomized trials are really, really important in understanding whether there is a true cause and effect relationship", Manson says.

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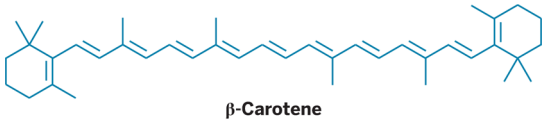
Despite the importance of trials, testing molecules like beta carotene or vitamin D in healthy individuals is substantially different from testing the latest cancer drug. For one thing, cancer drug trials target sick people who need treatment now; side effects from cancer drugs might be acceptable for a short-term treatment that could ultimately be lifesaving. In contrast, supplement trials in healthy individuals are often tracking diseases like diabetes, cancer, or heart disease that can take years to develop. Also, the differences in outcomes between those who take supplements and those who don't may be small, making them difficult to identify statistically and requiring potentially tens of thousands of subjects. As a result, such studies are enormously expensive—costing tens, sometimes hundreds, of millions of dollars—and take years.



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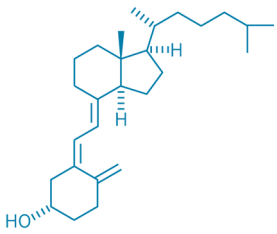

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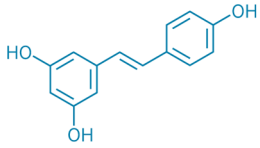

Resveratrol

TRIALS ON TRIAL

For the most part, the results of clinical trials have been disappointing. "Generally our experience after trials has been a bust cycle", says cancer epidemiologist Tim Byers of the University of Colorado in Denver. Either the agent, typically a supplement packaged in a pill, doesn't work or, even more commonly, the megadoses of these compounds that show effects in preliminary studies—often far above what's found in a typical diet—turn out to increase cancer risk, he adds.

Beta carotene is a prominent example of a supplement that failed to live up to hopes. Demetrius Albanes of the National Cancer Institute was a principal investigator of one such large trial of beta carotene. The Alpha-Tocopherol, Beta-Carotene (ATBC) Study, tested the effect of five to eight years of daily alpha tocopherol (vitamin E) and beta carotene supplements with a group of nearly 30,000 male smokers in Finland. To the team's surprise, instead of a lower disease risk, the men taking beta carotene had an 18% increased risk of developing lung cancer, Albanes says. Another large controlled clinical trial, the Physicians' Health Study run by Harvard Medical School and Brigham and Women's Hospital, showed no benefit and no harm from beta carotene. Further research to better understand the interplay between antioxidants and cancer suggests that reining in oxidative stress protects normal cells—and cancer cells.

The news for vitamin E was also equivocal. Taking alpha tocopherol did not affect lung cancer risk in the ATBC study. But the men taking vitamin E (50 IU) had a one-third lower incidence of prostate cancer, Albanes adds. Even so, a subsequent trial showed that vitamin E supplements (400 IU) actually increased prostate cancer risk by a third.

Though finding adverse outcomes hasn't been the primary purpose of these trials, Albanes adds, these studies also provide an important net for testing safety. At the same time, trial results showing no effect have limited implications, notes John Baron, an epidemiologist at the University of North Carolina, Chapel Hill. Changes in the dose, treatment length, or patient population could lead to different results.

HOPE FOR VITAMIN D

Vitamin D is today's star supplement. But despite the disappointments with other molecules, the large number of initial studies and the particularly strong correlations observed have fueled optimism that it may prove its worth in ongoing trials. The Vitamin D and Omega-3 Trial (VITAL) is one randomized controlled study looking at whether vitamin D supplements (2000 IU) and omega-3 fatty acids in the form of fish oil help to prevent heart disease and stroke. The team expects to release initial results by early 2018, says Manson, who is one of VITAL's principal investigators.

The basic science research and observational evidence with vitamin D is compelling, Manson notes, but clinical trials are critical. A trial looking at vitamin D presents a host of potential confounding factors. Individuals who take supplements often have other healthy lifestyle habits such as regular exercise. Active people also spend more time outdoors, and that additional sun exposure leads their bodies to make vitamin D, boosting their blood levels even without dietary changes. So some of the benefits observed in preliminary, nonrandomized studies among those who took vitamin D could be attributable to overall diet or regular exercise rather than the vitamin D pill.

Meanwhile Manson is also concerned that vitamin D has generated so much enthusiasm that clinicians are

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jumping the gun and potentially putting both their patients and the science at risk. Physicians are already prescribing megadoses of vitamin D to prevent cancer, cardiovascular disease, diabetes, and other diseases, she cautions, even against the backdrop of trials like the beta carotene one. In addition, individuals can easily buy vitamin D and other supplements over the counter, so they can easily take the pills on their own.

"It's very problematic", Manson says. Until it's clear that these supplements are warranted, it makes sense to err on the side of caution, she says. In addition, because the trial does not interfere with participants' regular, primary medical care, providers might recommend changes to participants' vitamin D use while studies like VITAL are in progress—which could compromise the results of these large trials. "It may in fact prevent a really conclusive test of hypothesis, and that would be to the detriment of public health", she cautions.

Limited regulatory oversight fuels the misconception that supplements are universally safe, Byers says. In the U.S., supplements are regulated as foods rather than as drugs. As a result, he cautions, supplement stores often sell pills that haven't been rigorously tested or those that have been shown in clinical trials to increase disease risks.

SHIFTING FUTURE

Unless a study like VITAL shows positive results, some researchers are pessimistic that many large-scale prevention trials like this one will move forward in the future because of trials' expense. And others note that limited research funding pushes the bar for such studies even higher.

Some cancer epidemiologists now think the search for a supplement that prevents cancer may be futile. Researchers continue to churn out hundreds of research papers each year reporting laboratory studies of the anticancer properties of various phytochemicals and other molecules, but Byers says, "I think it's highly unlikely—for general use anyway—that we will find compounds that are both effective and safe."

One problem in achieving definitive results may be in thinking of micronutrients like drugs, which are designed to act specifically and selectively, says Ole Vang of Roskilde University, in Denmark, who has studied resveratrol. A compound like resveratrol might target many different pathways and work in combination with other molecules in a mixture such as red wine, he says. Such subtle effects might be impossible to tease out definitively.

A more productive path for supplement research could be to look at benefits for patients who already have a significant risk factor for chronic disease, Byers says. In this case, participants might respond more quickly to the supplement, which could help researchers get clearer results. And for patients with a known risk factor for developing disease, the potential benefits of a supplement intervention could outweigh risks. For example, a large, randomized controlled trial showed that folic acid reduced the incidence of stroke in men in China with high blood pressure.

Byers expects that epidemiologists will continue to use observational studies to look at dietary factors. But he expects that future trials to look at lifestyle interventions for disease prevention will focus on other factors such as weight control and physical activity, Byers says.

Meanwhile, in the absence of clinical trial data showing that megadoses of polyphenols, vitamin E, vitamin D, or anything else prevents chronic disease, the best advice remains to eat a healthful diet of foods that carry these nutrients in moderation. Whether the individual micronutrients matter or not remains uncertain, but the fruits and vegetables that harbor these intriguing molecules are undeniably nutritious and delicious—and deserve a spot on the plate.

Sarah Webb is a freelance contributor to Chemical & Engineering News, the weekly newsmagazine of the American Chemical Society.

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