Newsweek e-commerce

Newsweek

January 17, 2005

Diet and Genes

It isn't just what you eat that can kill you, and it isn't just your DNA that can save you--it's how they interact.

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Edition: U.S. Edition
Section: Cover Story: Health For Life: Diet and Genes
Page: 40
Estimated printed pages: 7
Article Text:

Jose Ordovas has glimpsed the future of medicine, and there's good news for anyone who has just paid $4 for a pint of pomegranate juice. Ordovas, director of the Nutrition and Genomics Laboratory at Tufts University, believes the era of sweeping dietary recommendations for the whole population--also sometimes known as fads--may be coming to an end. Red wine may be better for your arteries than ice cream, but you can't create a diet that's optimal for everyone, Ordovas says--or, to put it another way, even Frenchmen get heart attacks sometimes. Within a decade, though, doctors will be able to take genetic profiles of their patients, identify specific diseases for which they are at risk and create customized nutrition plans accordingly. Some people will be advised to eat broccoli, while others will be told to eat... even more broccoli.

Maybe you have to be a nutritionist to appreciate the beauty of that scheme. The promise of nutritional genomics--a field that barely existed five years ago--is not to overturn a century's worth of dietary advice but to understand on the most basic level how health is determined by the interplay of nutrients and genes. The old paradigm was of a one-way process, in which "bad" foods gave you heart disease or cancer unless "good" genes intervened to protect you. New research suggests a continual interaction, in which certain foods enhance the action of protective (or harmful) genes, while others tend to suppress them. This supports what we know from observation, that some individuals are better adapted than others to survive a morning commute past a dozen doughnut shops. Pima Indians in the Southwest get type 2 diabetes at eight times the rate of white Americans. Individuals have widely varying responses to high- or low-fat diets, wine, salt, even exercise. Overwhelmingly, though, researchers expect that conventional dietary wisdom will hold for most people. So keep that vegetable steamer handy.

The model for nutritional genomics is the work that has already been done on drug-gene interactions. Researchers are starting to unravel the mystery of why a drug may be a lifesaver for one person while causing a fatal reaction in another and in a third has no effect at all. Why do a third of patients fail to respond to the antidepressants known as SSRIs, including Prozac, Paxil and Zoloft? The drugs are meant to increase levels of the neurotransmitter serotonin by blocking its "reuptake," or clearance from the brain.

Obviously, they can work only if serotonin is being produced in the first place. Last month researchers at Duke University discovered that some people have a variant gene which reduces the production of serotonin by 80 percent--making them both susceptible to major depression and resistant to treatment with SSRIs.

But food interactions are usually far more complicated. "Normally, you take one drug at a time and for a limited amount of time," says Dr. Muin Khoury, director of the Office of Genomics and Disease Prevention at the Centers for Disease Control and Prevention. "If you have a certain genetic variant, you stay away from a particular drug or take a different dose." But nutrients come in bulk, you consume them for a lifetime and you can get them without a prescription, even the Trucker's Pancake Special. Metabolism involves huge numbers of genes interacting in uncountable ways. There are at least 150 gene variants that can give rise to type 2 diabetes, 300 or more that are associated with obesity. Ordovas at Tufts compares the situation to an electrical panel: "We know about certain switches and how to turn them on and off. But in some people, you turn the switch but the light doesn't come on, because there are other switches upstream and downstream that we don't know about yet." It will be years before researchers have a good diagram of the circuit. That hasn't prevented the growth of a fledgling industry in personalized nutritional supplements to treat everything! from osteoporosis to obsessive-compulsive disorder. At least one comp any will even profile your genes to take the guesswork out of choosing makeup.

But pieces of the diagram are beginning to emerge. Green tea contains potent antioxidants known to help prevent heart disease and certain cancers, but only some women seem to show a reduction in breast cancer from drinking it. A study at the University of Southern California suggests that part of the reason lies in a gene that produces an enzyme called COMT that inactivates the cancer-suppressing compounds; women with the gene variant that produces a less active form of COMT showed the most benefit from tea.

One interaction that has been studied in detail involves two categories of enzymes known as phase 1 and phase 2. These work in sequence to eliminate certain toxins from the body, such as heterocyclic amines--potent carcinogens that form, infuriatingly, in the tasty crust on broiled meat. Actually, the amines are not inherently harmful; they are dangerous only after the phase 1 enzymes have begun metabolizing them, and before the phase 2s can finish the job. So, obviously, it is desirable to have a balance of the two enzymes. But some people have a variant gene that speeds up the phase 1 enzymes, so they form carcinogens faster than the phase 2s can get rid of them. This gene is found in 28 percent of white Americans, but roughly 40 percent of African-Americans and Hispanics and nearly 70 percent of Japanese-Americans (who, as it happens, have a high rate of stomach cancer). But there are ways to tweak the system: garlic contains nutrients that slow down the phase 1 enzymes, and a substance known as sulforaphane boosts levels of the phase 2s. And sulforaphane is easy to obtain. You get it from broccoli. "You can see where we're headed. We're starting to take the guesswork out of the things we eat," says Raymond Rodriguez, who heads the Center of Excellence in Nutritional Genomics at the University of California, Davis. One notable case is the gene for a

protein known as Apo E, which plays a major role in regulating cholesterol. It has three major variants (or "alleles"), designated E2, E3 and E4, of which E3 is the most common. People with one or two copies of the E2 allele generally have lower-than-average cholesterol, but the E4 variety--an estimated 15 to 30 percent of the population has at least one copy of the allele--is potentially lethal. It increases the risk of diabetes, it raises total cholesterol and it reverses the usual protective effects of moderate drinking. And it vastly increases the risks of smoking. "Smoking is bad for everybody," says Ordovas, "but in a person with E4 it's a total killer. We're not talking about probabilities. It's almost certain you'll get heart disease." But, he adds, E4 is extremely susceptible to environment. The increased diabetes risk is found only in people who are overweight. If you stop smoking, give up alcohol, exercise and eat a diet low in saturated fat, "you can remove all of the genetic predisposition for heart disease that comes with E4"--not just some, but all of it.

On the face of it, you could make a case for universal screening for the Apo E gene. But we don't do it, and the reasons shed light on the ethical complexities of the field. One reason is peculiar to the Apo E4 allele, which also doubles the risk of developing Alzheimer's. Since there's not much that can be done to prevent it, many doctors are reluctant to give patients this news, and many patients don't want to know it themselves. More generally, there is the danger that insurance companies will discriminate against people with risk factors in their genome. Ruth DeBusk, author of "Genetics: The Nutrition Connection," thinks this concern is overblown, because by and large the risks are spread across the population. "We all have some susceptibilities," she says. "It's not as if one group has all the bad genes and the rest of us are perfect." Susceptibilities, moreover, don't necessarily amount to destiny; perhaps we can figure out! what people with the E4 gene should eat to forestall dementia. But Jim Kaput, who founded a genomics-research company, wonders about people who get the correct nutritional advice for their genotype and then refuse to follow it. "Should the insurance company be obliged to pay for their health care, too?"

And--one might ask--what's the point of testing for something if the inevitable advice that comes out of it is to exercise and eat a healthy diet? Didn't we know that already? The answer lies in the "Churchill effect," people's natural inclination to believe that if Winston Churchill lived to 90 on a diet of marrow bones, champagne and cigars, why not them? "People always think the warnings don't apply to them," DeBusk says. "We hope if we can tell them 'Here's what you're at risk for,' it will hit home." Conversely, cardiologists now routinely put people on a low-salt diet to control high blood pressure, knowing it doesn't work for as much as half the population. Even if it doesn't work, it can't hurt, and the doctor, after all, isn't the one giving up hot dogs. But, as Dr. Victoria Herrera of Boston University says, telling patients to do something that doesn't work "makes liars out of doctors. We need to make a diagnosis based on genotype, so we can go beyond trial and error."

Not all research in the field is aimed at identifying alleles that differ among individuals. The broader purpose is to understand the interplay of nutrition and genetics. What protects Asians (at least the ones who still live in Asia and eat a traditional soy-based

diet) from hormone-sensitive breast and prostate tumors? The most common explanation is that soy contains compounds that bind to estrogen receptors on cells, making them unavailable to more potent hormones. But Rodriguez has identified a soy constituent called lunasin that increases, by his count, the activity of 123 different genes in prostate cells. Among them are genes that suppress tumor growth, initiate the repair of damaged DNA and promote apoptosis, the programmed "suicide" of damaged cells before they begin to multiply. H e hasn't been looking for different alleles of these genes, although it's likely they exist and may subtly affect how individuals respond to lunasin. The genetic factors predisposing men to prostate cancer can, in principle, eventually be identified and calculated for each individual. When all is said and done, though, the recommendation will probably stay the same: eat more soy. (And more fresh fruits and vegetables, and less saturated fat... and so on.)

Another compound getting a lot of study is curcumin, the yellow pigment in turmeric, an ingredient in curry spice. Curcumin reduces the action of a number of genes that promote inflammation, which is linked to heart disease, colon cancer and Alzheimer's. "It's probably no coincidence that India has the lowest incidence of Alzheimer's in the world," says Sally Frautschy, a professor of neurology at UCLA, who studies turmeric together with her husband and colleague, Greg Cole. "What I hear from the pharmaceutical indus! try," says Cole, "is 'What are you trying to do, ruin us?' "

There's not much chance of that, of course. More likely, nutritional genomics will create opportunities for drug companies to isolate, concentrate, synthesize and improve on the compounds in nature, which they've been doing for a hundred years. What Cole and his colleagues seek is to shed light on the mystery of how the human body has evolved the miraculous ability to overcome, once in a while, the threat posed by the consequences of its own appetites.

Caption:
Greens: Antioxidants on the menu at New York's Whole Foods market

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