Power Foods

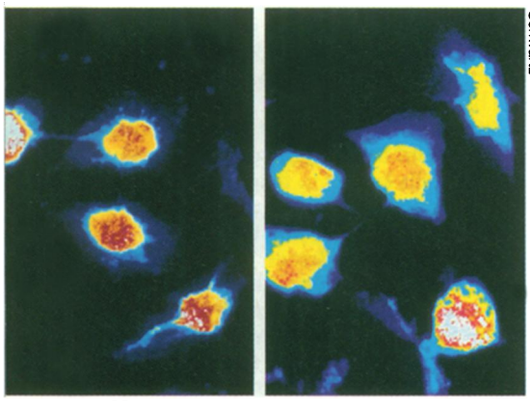
Looking at how nutrients may fight cancer

By TINA ADLER

Joel L. Schwartz and some other scientists are one up on the world's grandmothers. While grannies always seemed to know that vegetables keep us healthy, Schwartz and company know why.

The head chefs in many households have long preached the virtues of spinach, carrots, and other assorted garden goods. More recently, epidemiological studies have suggested that a diet rich in fruits and vegetables lowers the risk of various diseases — including cancer.

As a result, health-conscious consumers and researchers have taken a big interest in these comestibles' cancer-fighting properties. Many people, including cancer specialists, now take supplements of antioxidants common in fruits and vegetables. And some physicians give them to patients in hopes of preventing or curing cancer. Physicians are also using retinoids, vitamin A analogs found in dairy products, to fight cancer. However, only recently have scientists begun to understand how these nutrients combat cancer cells.



Schwartz

Human oral carcinoma cells — untreated (left), and treated with beta-carotene (right). The color signifies the concentration in the cell of a protein associated with the mutant p53 gene, believed to promote the growth of cancer cells. From high to low concentrations: white, red, orange, yellow, blue.

Research indicates that some of the key cancer-fighting ingredients in fruits and vegetables include the antioxidants beta-carotene, glutathione, and vitamins E and C. Antioxidants fight cancer, at least in part, by neutralizing DNA-damaging free radicals, the by-products of many of the body's normal metabolic functions.

Researchers are discovering a variety of ways in which nutrients help — and perhaps hinder — the body's fight against cancer. They are showing how beta-carotene and similar substances both thwart tumor growth and wiggle their way into the hearts of cancer cells, eventually knocking many of them out.

But antioxidants and retinoids seem unable to kill every cancer cell in a tumor, even in experimental animals, and that concerns researchers. Furthermore, large doses of nutrients may endanger some healthy people who take them as preventives.

Retinoids have many side effects and, taken in quantity, can cause kidney disease and birth defects, researchers acknowledge. Beta-carotene, which converts to vitamin A, may lower the concentration of vitamin E in people's blood (SN: 5/14/94, p.310).

Nevertheless, some physicians are giving their patients antioxidants and other vitamins. They use retinoids more often than vitamin E or beta-carotene, which appear less effective, says Raymond P. Warrell Jr. of the Memorial Sloan-Kettering Cancer Center in New York.

Doses of the vitamin A derivative all-*trans* retinoic acid put virtually all patients with acute promyelocytic leukemia (APL) into remission, he says. However, they still require chemotherapy to help prevent them from relapsing, and many patients develop a resistance to retinoic acid.

People with this uncommon disease have a mutation in the DNA of a retinoic acid receptor. This probably explains why supplements of retinoic acid have such a dramatic effect, Warrell asserts.

Fifteen months ago, his group began testing two new retinoic acids on 43 patients with advanced APL, lymphoma, various solid tumors, or lung cancer, he reported at the annual meeting of the American Association for Cancer Research in March.

The patients take either a natural or a synthetic retinoid and no other cancer drug. The study's single APL patient not previously treated with retinoic acid has gone into complete remission, and the two lung cancer patients have stabilized, Warrell says.

Other scientists are testing a combination of retinoids and the protein interferon on patients with advanced cases of kidney or cervical cancer or squamous carcinoma. Patients have had some "pretty impressive regressions and long, complete remissions" on this combination, Warrell says.

In most cases, antioxidants and other nutrients aren't strong enough to do the job alone. But large doses of nutrients combined with traditional cancer drugs appear to work synergistically in animal studies, say Schwartz, of the National Institute of Dental Research in Bethesda, Md., and others. Most of the research on how antioxidants and retinoids work takes place in the laboratory and uses hamsters, human tissue samples, and cell cultures.

A mixture of nutrients boosts the ability of four cancer drugs — interferon, tamoxifen, cisplatin, and decarbazine — to inhibit the growth of human melanoma cells in a laboratory culture, Kedar N. Prasad and his colleagues at the University of Colorado Health Sciences Center in Denver report in the November 1994 NUTRITION AND CANCER.

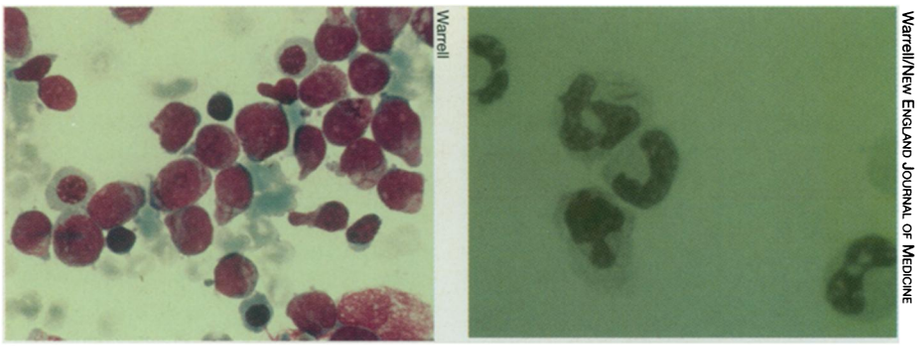
And others have found that a combination of vitamins C and E, beta-carotene, and retinoic acid, used without cancer drugs, stops cancer cells more effectively than any of the substances by itself.

Why such combinations work better remains unclear, Prasad says. However, a mixture of nutrients and cancer drugs has more opportunities to disrupt the cell, Schwartz notes. Also, the combination of nutrients may work better because it more closely resembles what the body gets naturally from foods, he adds.

Key to the cancer-fighting success of retinoids and antioxidants, researchers say, is their ability to influence the growth and development of cells. Malignant tumor cells take longer to die than healthy cells and generally repair damage to their DNA more quickly and thoroughly. Retinoids and antioxidants, however, can disrupt this protected life of cancer cells.

When Schwartz and his coworkers try to induce oral cancer in hamsters whose diets include extra beta-carotene, the hamsters develop fewer precancerous cells and fewer and smaller tumors than hamsters that don't receive the nutrient.

Moreover, the hamsters on the beta-carotene have fewer epidermal growth factor receptors in their precancerous tissue, he reported at the American Association for Dental Research annual meeting in March. This suggests that beta-carotene slows cancer development by limiting the entry of growth factors into precancerous cells, he says.



Leukemia cells from bone marrow before (left) and after (right) treatment with all-trans retinoic acid. Retinoic acid forces the immature cells to mature and die.

In addition, beta-carotene may trigger genes that normally cause cells to mature and die, Schwartz says. The tissues of animals treated with beta-carotene have higher concentrations of a protein associated with the so-called wild type p53 gene, which inhibits the growth of cancer cells, he notes. The treated animals also have less of a protein associated with a mutant p53 gene believed to promote cancerous growth (SN: 12/24&31/94, p.422).

Antioxidants generally destroy malignant cells but not healthy ones. "In simplistic terms, cancer cells appear to have a leaky cell membrane, whereas normal ones have an intact one," explains Gerald Shklar of the Harvard School of Dental Medicine in Boston.

Also, beta-carotene and other nutrients don't always act as antioxidants in tumor cells, because of tumor cells' unique metabolic activity, Schwartz says. When beta-carotene enters malignant cells, the nutrient functions as a reactive oxygen molecule and releases electrons that damage the cells' DNA.

Tumor cells may not break down beta-carotene and other carotenoids the way normal cells do, ongoing studies by Norman I. Krinsky of Tufts University School of Medicine in Boston and his colleagues suggest.

When normal tissue metabolizes carotenoids, either vitamin A or retinoic acid and five or six other breakdown products form. Cancerous tissue appears to turn beta-carotene into both vitamin A and retinoic acid. Retinoic acid has more influence than vitamin A in regulating proteins that control cell death, Krinsky says.

He and his colleagues are investigating how precancerous cells break down beta-carotene. Once a tumor becomes malignant, carotenoids can't help much, he contends. But precancerous tissue might be amenable to outside regulation, possibly by beta-carotene. He and his coworkers also plan to study the effects of other carotenoid breakdown products on cancerous tissue.

Tumor growth depends in part on angiogenesis, the formation of new blood vessels. Two antioxidants, glutathione and vitamin E, inhibit oral cancer in hamsters, in part by putting the brakes on angiogenesis, say Shklar and Diane Shklar of Tufts University School of Dental Medicine in Boston. The two nutrients, they reported at the dental research meeting, inhibit angiogenesis equally well. The Shklars are now investigating whether a combination of the two might work better.

The Shklars and their coworkers also argue that antioxidants thwart cancer growth by boosting the body's immune response. "Immune cells can actually find and destroy tumors and . . . are enhanced by antioxidants," Gerald Shklar says. Beta-carotene and vitamin E stimulate macrophages and lymphocytes to secrete more of certain cytokines, substances toxic to tumor cells, he reported at the International Society for Nutrition and Cancer last September.

Cells release cytokines right at the tumor, he says. "They don't produce enough to do any damage to the rest of the body."

Nevertheless, antioxidants and other vitamins have their dark side, researchers warn. John E. Biaglow at the University of Pennsylvania in Philadelphia and his colleagues find that antioxidants interfere with the ability of radiation to kill cancer cells. He recommends that patients stop taking antioxidant supplements for a few days prior to their radiation treatments.

"We are trying to improve the kill rate of radicals produced by radiation or drugs," he says.

Many epidemiological studies have found benefits to eating a diet rich in antioxidants. But two recent cancer prevention trials, conducted among heavy smokers in Finland and in U.S. patients with precancerous polyps, found antioxidant supplements had either no benefit or harmful effects (SN: 7/23/94, p.54).

Some scientists, however, argue that the studies were poorly conceived and that the patients received insufficient quantities of antioxidants. In the Finnish study, participants took "less than I'm taking every morning," Gerald Shklar says.

Without more insight into how these agents function and interact with each other, physicians "can give [antioxidants] from here to doomsday and you'll get all kinds of responses — good, bad, and indifferent," Schwartz adds.

However, he expresses concern about the effects of antioxidants and retinoids, starting with his observation that antioxidants don't eliminate or prevent all tumors. If hardier cancer cells survive, "you could eventually produce bigger and better tumors," he says.

Because they may enhance the body's normal immune response, large doses of antioxidants can worsen canker sores and could theoretically enhance or exacerbate the onset of other autoimmune diseases, such as juvenile diabetes, Schwartz contends.

Moreover, researchers do not know how well the findings in animals will apply to people, he adds.

It remains unclear whether the experience of the APL patients or that of the heavy smokers in Finland better foreshadows the future of antioxidants in the fight against cancer. But scientists hope to ensure that the story of nutrient supplements and cancer ends well, by learning exactly how the drugs work.

Then physicians will know how to use the supplements in the proper dosages and combinations, on the right diseases, and at the right time. And only then will antioxidants and other vitamins have a real chance of success. Meanwhile, listen to your grandmother and eat your fruits and vegetables, scientists say. □

Supplements of the scientists

At a recent conference, one presenter asked the audience of about 2,000 scientists to raise their hands if they took vitamin supplements. About 2,000 hands went up, says Pennsylvania's John E. Biaglow, a supplement user himself.

Harvard's Gerald Shklar takes 15 milligrams of beta-carotene, 400 units of vitamin E, and 500 milligrams of vitamin C. The dental research institute's Joel L. Schwartz swallows a similar dose but takes twice as much beta-carotene.

Do these scientists care whether the vitamins are synthetic or natural? "They are all the same," both say.

Colorado's Kedar N. Prasad disagrees, arguing that studies show that naturally derived vitamin E inhibits tumor cells better than synthetic versions.

He also warns against taking certain multivitamins. Most come loaded with iron, copper, and manganese, which generate enormous amounts of free radicals when they interact with vitamin C, he asserts. — *T. Adler*