

August 6, 2002

Sunlight, a Cancer Protector in the Guise of a Villain?

By INGFEI CHEN

In contrast to the often repeated warnings about tanning and skin cancer, some scientists have been exploring an almost heretical notion: sunlight may actually protect against other cancers. The idea is not new; two epidemiologists proposed it 22 years ago. Their theory was that vitamin D, which the skin produces when exposed to sunshine, somehow prevents the growth of malignant cells.

People who live in less sunny, high-latitude regions do not make as much of the vitamin, and so they could be more vulnerable to tumors, the theory maintains.

At first, most scientists scoffed at the whole notion. Vitamin D, after all, was known to play a major role only in keeping bones strong. But two decades of research later, the possibility that the substance may wield some kind of anticancer power no longer seems so far-fetched.

While the hypothesis linking a lack of sun and vitamin D to cancer remains controversial, some researchers are looking into vitamin D as a possible remedy. Clinical trials in people are now under way, testing whether the vitamin or similar compounds can treat tumors or bolster chemotherapy.

Sunlight supplies the body with about 90 percent of its vitamin D. Ultraviolet rays prompt the skin to produce a biologically inert form of the substance, which is then converted into an active form, as a hormone called calcitriol.

In the early 1920's, scientists discovered that a deficiency of vitamin D from inadequate sunlight caused rickets, a childhood bone disease. For decades, experts believed that the vitamin mainly protected bones.

But in 1980, Dr. Cedric Garland and Dr. Frank Garland, epidemiologists and brothers, hypothesized that some cancers were brought on by a lack of sun and vitamin D.

They had noticed that National Cancer Institute maps revealed a striking geographic distribution of colon cancer deaths: the highest death rates were clustered in Northern states and were about three times as great as rates in the South.

Other scientists later suggested that low vitamin D levels also led to prostate cancer, noting that it was twice as common in blacks as in whites. Blacks are less prone to skin cancer because dark skin shields out sun rays, said Dr. Gary Schwartz, an epidemiologist at Wake Forest University. But the dark skin, he said, may explain the higher rates of prostate tumors.

"If you believe that sunlight causes one cancer, you can use the same evidence to argue that sunlight prevents another," Dr. Schwartz said. Men in Maine are 50 percent more likely to die of prostate cancer than are men in Florida, he added.

Studies by the Garlands, Dr. Schwartz and others have since shown that people in relatively sun-deprived regions, or with low vitamin D levels, appear at greater risk for a variety of cancers.

In April, researchers at the cancer institute reported that the chances of dying from breast, colon, ovarian and prostate cancer were reduced by about 10 to 27 percent for people in

the sunniest areas, compared with those to the north, based on death certificates in 24 states.

"The theory is increasingly being substantiated," said Dr. Cedric Garland, a medical professor at the University of California at San Diego. Dr. Garland believes that simply meeting the recommended dietary allowance for vitamin D, 400 international units a day for people over 50, may help ward off cancer. But 2,000 units a day can be toxic, he added.

Critics said the epidemiology reports did not prove that a deficiency of sunlight and vitamin D caused tumors.

"The evidence is provocative, but it's not ironclad," said Dr. Donald Trump, chairman of medicine at the Roswell Park Cancer Institute in Buffalo. The observational studies do not rule out other factors like genetics and diet.

"I think there's something to it," said Dr. John Milner, a nutrition researcher at the National Cancer Institute. But the data are not persuasive enough, he said.

Still, there is a body of laboratory evidence that vitamin D may have tumor-thwarting potential. Over the past 20 years research has found that calcitriol plays an important role in controlling cell growth and maturation — and that colon, prostate and breast cells even carry the protein receptor that binds to calcitriol.

Dr. Schwartz and his colleagues showed that prostate cells even make this hormone themselves. "It's enough to inhibit their own growth," he noted. Whereas androgens, or male hormones, are the gas pedal driving the prostate's growth, "the vitamin D is the brake."

In the petri dish, large doses of vitamin D or the hormone calcitriol can inhibit the proliferation of cancerous cells.

Some early experiments have also found that the vitamin D compounds convert tumor cells into normal cells, keep them from spreading, and even kill them in lab dishes. Studies suggest that the chemicals stymie tumors in rodents as well.

The research touched off hopes that calcitriol might prove a potent cancer therapy. But a major obstacle has been safety.

To achieve the high concentrations of vitamin D that produce anticancer benefits in the laboratory, researchers thought extraordinarily high daily doses would be needed, Dr. Trump said. Such amounts are toxic, driving up blood calcium levels, causing vomiting, weight loss, calcium deposits and even osteoporosis.

But Dr. Trump and his former associates at the University of Pittsburgh said they had solved the problem. In trials, they were able to give large amounts to cancer patients just three days a week, or even once a week.

Dr. Tomasz Beer, an oncologist at Oregon Health and Science University, has also been testing intermittent doses of calcitriol, alone or with other treatments, against prostate cancer. At a conference in May, he and colleagues presented the first clinical evidence that vitamin D might improve the effectiveness of chemotherapy.

In a continuing trial, 37 men with advanced prostate cancer received weekly doses of calcitriol and docetaxel, a chemotherapy drug, for six of every eight weeks. P.S.A., or prostate-specific antigen, levels were cut in half or greater in 81 percent of the patients. Among the group, the disease was held in check for a median period of about a year. In past studies of stand-alone docetaxel therapy, Dr. Beer said, 42 percent showed this kind of P.S.A. reduction, and tumors were controlled for a median time of about five months.

The benefits exceeded his expectations, he said, but they should be viewed with caution because the trial lacked a direct comparison group receiving just docetaxel. The next step is a major national clinical trial that is beginning to enroll patients. It will compare calcitriol plus docetaxel to the chemotherapy drug alone in 240 patients. Information on the trial can be found online at www.novacea.com/products/ascent.

"If that trial comes out negative, these early promising results will go into the dustbin of history," Dr. Beer said. But if the trial finds positive outcomes, "we'll have an exciting new, well-tolerated treatment for prostate cancer."

Meanwhile, labs worldwide have also been working to invent safer versions of calcitriol that eliminate its toxic effects. Scientists are now studying some of these vitamin D "look-alikes" in cancer patients.

Dr. Schwartz is conducting a trial of a drug called Zemplar in men with advanced prostate cancer. In Europe, a Copenhagen company called LEO Pharma is testing a compound, Seocalcitol, against a placebo in 1,100 liver cancer patients.

While vitamin D-based therapies look promising, Dr. Schwartz said, "The acid test is, Where is it going to be in 10 years?" In the next three to four years, researchers expect to start seeing some answers.