SPRING | 08

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Ohio State is a Comprehensive Cancer Center designated by the National Cancer Institute

frontiers

TURNING CANCER DISCOVERIES INTO TREATMENTS

BUMPER CROP

Can tomatoes stop cancer? Steven K. Clinton, MD, PhD, is leading research into the science of functional foods.

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inside ▸▸ CANCER RATES IN YOUNG ADULTS | DARWIN IN A CANCER CELL ▸

BY JARON M. TERRY

How many colleges does it take to develop foods designed to improve the health of people around the world? Six—and all six colleges are part of The Ohio State University.

In 1995, a landmark study that followed nearly 50,000 men for 20 years reported that those who ate more tomatoes or tomato products experienced a lower risk of prostate cancer. The Health Professionals Follow-up Study concluded that eating eight to 10 servings a week of tomato products reduced prostate-cancer risk by 35 percent.

The tomato finding had intrigued Steven K. Clinton, MD, PhD, a medical oncologist and physician scientist who specializes in prostate-cancer treatment and prevention at The Ohio State University Comprehensive Cancer Center-James Cancer Hospital and Solove Research Institute. "I wanted to determine if this association was real or just coincidence, and, if so, how tomatoes may prevent cancer."

Today, Clinton believes more than ever that dietary modifications can delay prostate-cancer development. "If successful," he says, "our work will contribute to recommendations that lower the risk of cancer, reduce the need for medical care and improve overall quality of life."

But teasing out exactly how foods prevent cancer is difficult. Research on tomatoes, for example, has largely focused on lycopene, a substance that makes tomatoes red. But a series of studies starting in 2003, led by Clinton, showed that lycopene alone has a modest ability to prevent prostate cancer in an animal model, while tomato products provided greater protection.

"Those findings tell us that if we want the maximum health benefits of tomatoes, we should eat tomatoes

NUMBER OF SUBSTANCES IN HUMAN DIET: ABOUT **20,000.** OF THESE, ONLY **52** ARE ESSENTIAL NUTRIENTS.

THE RESEARCHERS

STEVEN J. SCHWARTZ, PhD
Professor of Food Science and Technology

STEVEN K. CLINTON, MD, PhD
Medical oncologist and physician scientist

YAEL VODOVOTZ, PhD
Physical chemist and food scientist in the Department of Food Science and Technology

or tomato products and not just lycopene," Clinton says. "Combinations of dozens of plant-derived dietary components, called phytochemicals, are more likely to prevent prostate carcinogenesis than any single phytochemical derived from a food."

Clinton and his collaborators also study the prevention potential of soy and cruciferous vegetables—broccoli, cauliflower, cabbage—vitamin D, calcium, omega-3 fatty acids, selenium and vitamin E.

He and other OSUCCC chemoprevention researchers are working closely with Ohio State researchers in horticulture and crop science, food science and human nutrition to develop functional foods—foods and food ingredients that may provide health benefits beyond those expected from their traditional nutrients.

"We are not looking for one compound to fight cancer," Clinton says, "we're building better tomatoes, and we're using them to develop new functional foods that we can use in human studies to demonstrate anticancer properties."

The broad collaborations needed for this research are facilitated by Ohio State's Center for Advanced Functional Foods Research and Entrepreneurship (see sidebar on page 15). The Center brings together 22 investigators in six Ohio State colleges: the College of Food, Agriculture and Environmental Science, which established the center; the College of Medicine; the College of Education and Human Ecology; the College of Public Health; and the College of Biological Sciences.

"This is the beauty of a land grant university," Clinton says. "Ohio State is one of very few universities in the nation to have an academic medical center, an NCI-designated Comprehensive Cancer Center, a College of Public Health, and specific departments such as Human Nutrition, Food Science and Technology, and Horticulture all located on a single campus. We are only beginning to see faculty cross-fertilize and develop novel collaborative projects that can establish an entirely new discipline focusing on health-promoting foods."

NOT QUITE A V8

Clinton is working with researchers in the Center for Advanced Functional Foods to develop a tomato-soy drink and a soy-almond bread that may help prevent prostate cancer. Other OSUCCC researchers are clinically testing lozenges and lollipops of concentrated black raspberries to reduce recurrence of oral cancer in patients treated for the disease.

This year, Clinton is initiating a dose-finding clinical trial in men with prostate cancer using the tomato-soy drink that will culminate a series of studies in food and nutrition research.

Developing the drink demanded collaborations across a wide range of disciplines. The goal was to produce a tomato-soy food that could be used in a future, large, prostate-cancer prevention trial.

He first organized a study to determine if men with active, asymptomatic prostate cancer would be able to eat a diet rich in tomato products and soy protein—enough to provide a range of phytochemicals and at least 25 mg of lycopene and 80 mg of soy isoflavones per day.

STEVEN K. CLINTON, MD, PhD ▸▸

"If we can develop a tomato product that, when consumed in modest amounts, reduces prostate-cancer risk by even 10 percent, we are talking about preventing 22,000 cases per year in the United States."

For eight weeks, 41 male volunteers chose their own tomato products, which included raw tomatoes, juice, sauce, catsup and other items. They were given powdered soy protein to mix with other foods.

Measurements of lycopene levels in the blood and of soy isoflavones in the urine showed that the men readily complied with the diet. The analyses were done by long-time Clinton collaborator Steven J. Schwartz, PhD, professor of Food Science and Technology and his laboratory.

The men overwhelmingly favored tomato juice as their product of choice. "It can accompany any meal and be taken almost anywhere," Clinton says. "It's almost as convenient as a pill for a long-term clinical trial."

The Ohio State team hypothesized that adding soy protein to the tomato juice would increase its anticancer activity and provide an easier way for men to consume soy. To develop a tomato-soy drink, Clinton and Schwartz collaborated with researchers in food science and technology, in crop science and in human nutrition.

They began with a phytochemical-rich tomato developed by David M. Francis, PhD, associate professor

IT TAKES OVER
TWO POUNDS
OF FRESH TOMATOES TO MAKE ABOUT A HALF POUND OF TOMATO SAUCE.

PHOTOGRAPH BY ROMAN SAPECKI

SECRET INGREDIENTS

Researchers are developing new functional foods to use in human studies to demonstrate anticancer properties.

Components that show anticancer activity

lycopene

+

soy isoflavones
lignans
protease inhibitors
saponins

=

Tomato-soy beverage, to be drunk twice daily. A dose-finding study for the tomato-soy drink is set to begin in 2008.

ACCORDING TO THE AMERICAN CANCER SOCIETY, 218,890 NEW CASES OF PROSTATE CANCER WERE EXPECTED IN THE U.S. IN 2007, AND MORE THAN 27,000 MEN WILL DIE OF THE DISEASE.

of Horticulture and Crop Science at Ohio State, and grown at Ohio State's North Central Agricultural Research Station. The tomatoes were processed into juice by the Department of Food Sciences and Technology in collaboration with a local company.

Evidence that soy reduces prostate-cancer risk comes from epidemiological, clinical, animal and cell-culture studies. The risk of prostate cancer is at least 10-fold lower in Asian countries where soy is a standard part of the diet compared with the United States, for example, and soy beans have many components that show anticancer activity, including isoflavones, lignans, protease inhibitors and saponins.

But adding the soy phytochemicals to tomato juice required experimentation. "We had to add the isoflavones without unduly increasing the drink's viscosity," says Yael Vodovotz, PhD, a physical chemist and food scientist in the Department of Food Science and Technology. "It had to remain a product that was pleasant to drink."

So instead of soy protein, Vodovotz tested soy germ and soy extracts, which are rich in isoflavones and would have little effect on viscosity and flavor.

Before coming to Ohio State seven years ago, Vodovotz worked at NASA's Johnson Space Center developing foods for the mission to Mars. There she began formulating a soy bread, a project she completed at Ohio State with help from Cory Ballard, an undergraduate student with considerable industry experience.

In the end, they developed an almond-soy bread that Vodovotz describes as "quite delicious, with a rather nutty flavor, dense texture and yellowish color."

The almonds improved the bread's flavor, but more importantly, they contain an enzyme called beta-glucosidase, which converts soy isoflavones into a form more easily absorbed by the body. Clinical trials will soon be conducted to see if the isoflavone profile in the soy-almond bread can modulate biomarkers of prostate-cancer patients differently than those in the original soy bread.

Adding ingredients to improve absorption of phytochemicals is an important direction of functional food design. For the tomato-soy drink project, Schwartz's laboratory analyzes the levels of lycopene, as well as other carotenoids and phytochemicals, in blood and prostate tissues.

"Our recent studies demonstrated that adding a little olive oil as a source of lipid to tomato products enhances the absorption of many phytochemicals," Schwartz says.

The absorption of soy isoflavones and polyphenols is measured in cells by the laboratory of Mark L. Failla, PhD, chair of the Department of Human Nutrition. Failla is also a specialist in manipulating the composition of meals to improve absorption.

Last, the investigators chose to package the drink in small six-ounce cans for their convenience and familiarity.

Clinton and his colleagues have already tested the tomato-soy drink in 20 healthy volunteers. "We wanted to be sure that people would drink it twice a day and have no unpleasant experiences or medical side-effects," Clinton says. "Products rich in phytochemicals can affect bowel function or have other effects that we must understand before proposing longer studies or studies in people with other illnesses."

A dose-finding study for the tomato-soy drink is set to begin in 2008. It will involve about 80 men scheduled to undergo prostatectomy at the James Cancer Hospital and Solove Research Institute. The men

will be divided into groups that will consume one, two or three cans of juice per day for several weeks prior to surgery.

After surgery, samples of the prostate glands and blood will be sent to Schwartz for analysis. This should reveal if the tomato and soy phytochemicals are taken up by the prostate in sufficient quantities to alter genes involved in prostate cancer. It will also identify the dose—the number of six-ounce cans—that men should drink daily during a possible future large prostate-cancer prevention study.

ENHANCING FROM THE GROUND UP

Research to improve the drink's potency is already under way. For example, tomatoes and tomato products contain mainly a form of the lycopene molecule called all-trans-lycopene. The body, however, absorbs forms called cis-lycopene, particularly tetra-cis-lycopene.

So Francis, a plant geneticist and crop science specialist, made use of natural variation in tomatoes to develop a variety of orange tomatoes that is high in tetra-cis-lycopene.

To learn if humans would absorb cis-lycopenes from the tomato, Schwartz, Francis, Clinton and their colleagues designed a study that gathered 12 volunteers who ate two meals that included sauce made from the tomatoes. The researchers took blood samples from each volunteer before the meal and at seven intervals afterward, the last at 9.5 hours.

"The results showed that specialty tomato varieties can be developed to increase the availability and absorption of cis-lycopene from tomato products," Francis says. Research led by Schwartz has shown that manipulating how tomatoes are processed can also increase cis-lycopene levels.

But before these other forms of lycopene are used in the drink, Clinton says, "we want to test them in the laboratory to learn if they have equal or better anticancer properties to the more common all-trans form we are using now."

Adding additional components is yet another way to increase the potency of the tomato-soy drink. In 2007, Clinton and collaborators at the University of Illinois published findings from an animal study showing that a diet of 10 percent tomato powder and 10 percent broccoli powder slowed prostate-tumor growth more than either tomato or broccoli alone. Thus, broccoli extract may eventually be added to the tomato-soy drink.

"Functional-food development requires continued evolution and improvement," Clinton says. "This research constantly moves back and forth from the plant and crop scientists to the food scientists to the bench scientists and our patients.

"If we can develop a tomato product that when consumed in modest amounts reduces prostate-cancer risk by even 10 percent, we are talking about preventing 22,000 cases per year in the United States. This effort will pave the way for future combinations of phytochemical-rich tomato products in combination with other effective dietary components and chemopreventive agents that together provide a safe and potent regimen for prostate-cancer prevention," Clinton says.

"That's what functional-food development is all about."

Collaborations among departments bring new functional-food products to consumers.

WORK FOR FOOD

The Ohio State University's Center for Advanced Functional Foods Research and Entrepreneurship was established in 2006 by the College of Food, Agriculture and Environmental Science.

"The Center facilitates the development of functional foods that have a demonstrated ability to fight cancer, heart disease and other conditions," says director Steven J. Schwartz, PhD, professor of Food Science and technology.

That mission requires a variety of research expertise. It includes basic scientists who test phytochemicals in foods for their cancer-prevention potential; horticulture and crop scientists who develop plant varieties with desired phytochemicals; food scientists who process fresh fruits and vegetables into flavorful food products; analytical chemists and nutrition scientists who measure the body's ability to absorb the desired phytochemicals; and Comprehensive Cancer Center researchers to test the activity of these products in the laboratory and in clinical trials.

In addition, agriculture and extension specialists will work with Ohio businesses to bring new functional-food products to consumers.