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## The power of produce

Whether it fights cancer depends on which you eat, how you eat it -- and your genes.

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NO dessert until you finish your vegetables! Health experts probably wish they could use that line on the recalcitrant American public.

Fruits and vegetables are packed with vitamins, minerals, antioxidants, fiber and scores of phytochemicals that scientists are just beginning to understand, and studies have shown that people who eat more fruits and vegetables have a lower risk of heart disease, stroke, diabetes -- and some kinds of cancer.

Since its inception in 1991, the 5 A Day campaign, led by the National Cancer Institute and Produce for Better Health Foundation, has upped its daily recommendation to as many as 13 servings under a new campaign name.

And in bestselling health books and the popular press, the talk of fruits and vegetables is sometimes breathless. Pomegranate juice is a "miracle medicine"! Blueberries are "the super berry"! Kale can keep you alive! Tomatoes for life everlasting!

Eat or drink this produce, we are told, and the powerful clout of super-antioxidants and tumor-fighting chemicals they contain will bash that cancer before it gets going.

In fact, the anti-cancer clout of fruits and vegetables is nuanced and complex, and a story still evolving in labs across the country. At times the science has proven to be murky. Small studies that rely on what people remember of their diets from years past often find a strong preventive effect of eating lots of fresh produce.

But recently, some large population studies -- which follow tens of thousands or hundreds of thousands of people for years -- have reported weak or nonexistent connections between produce and cancer. Scientists are still trying to understand these seeming contradictions.

This much seems to be true: When it comes to fighting cancer, the power of produce will depend on who -- genetically -- you are, the variety of vegetables or fruits you select and even whether you cook them or not.

You also have to eat the whole thing. Sorry, no shortcuts with pills containing lycopene, beta carotene or vitamin C.

Not all fruit and vegetables, it seems, are equal when it comes to their cancer-fighting capacity. Some of the strongest evidence is for cruciferous vegetables, such as broccoli, cauliflower and kale. Dark, leafy greens such as spinach and chard, cooked tomatoes, apples, pears and citrus all show cancer-protective effects in some large studies.

And preliminary clinical trials are finding that various berries -- black raspberries, blueberries and even pomegranates -- may be cancer-fighters, shrinking tumors and even staving off cancer recurrence in some patients.

Much of the research on fruits, vegetables and cancer is founded on the "antioxidant hypothesis." Antioxidants, including vitamins A, C and E, and carotenoid pigments including lycopene (the red in tomatoes) and beta carotene (the orange in carrots), act to mop up or neutralize free radicals that can cause DNA damage. Accumulation of such damage can cause normal cells to turn cancerous. So foods high in antioxidants should -- in theory -- help prevent cancer from initiating.

Handfuls of studies involving a few hundred people tested this idea in the 1980s and early 1990s by comparing the diet history of subjects diagnosed with cancer to those of similar people without cancer.

The consistency of these studies led the World Cancer Research Fund, a nonprofit based in the United Kingdom that funds and promotes research on cancer and lifestyle, to conclude in a massive 1997 report that there was "convincing or probable" evidence that fruits and vegetables have a preventive effect against cancers of the mouth, pharynx, esophagus, lung, stomach, colon, rectum, larynx, pancreas, breast and bladder.

The report even suggested that 20% of cancers worldwide could be prevented if everyone just ate 14 to 28 ounces of varied fruits and vegetables every day.

The catch, however, is that this type of research, which relies on people remembering their diet from many years past, is open to bias. People diagnosed with disease are especially likely to misjudge what they used to eat, partly because they're looking for a reason for their illness.

What's more, recent larger and better-designed studies have appeared to be washouts.

In 2004, for example, researchers at the Harvard School of Public Health found that among a total of more than 109,000 men and women tracked from 1984 to 1998 in two long-term studies, there were zero cancer protective effects of eating five-a-day.

And another large survey of more than 521,000 people from 10 countries in Europe found no relationship between overall fruit and vegetable consumption and lymphoma, breast, prostate cancer or gastric cancer.

Unlike the previous studies, which were open to the bias of a tainted memory, such long-term studies enroll and track populations before they get sick, giving a better picture of the relationship between diet and health.

Why such gold-standard epidemiology studies find such weak interactions is hard to say, says Dr. Walter Willett, professor of epidemiology and nutrition at the Harvard School of Public Health and leader of the Harvard research.

One possibility, he says, is that the critical window for fruit and vegetable intake is early in life, in the decades before cancer appears, when the original DNA damage starts. Fruit and vegetable intake 30 years ago might be protective against cancer today, and "the trials that go on five or 10 years may just be too short to see these benefits," he says.

Another flaw could be that measures of total fruits and vegetables don't capture the importance of variety -- or the right kinds of fruits and vegetables, says Karen Collins, nutrition advisor to the nonprofit American Institute of Cancer Research, which supports diet-cancer research.

"If you have someone who eats a lot of potatoes and iceberg lettuce, they would come out on a survey as eating a large amount," she says. "But they are certainly not consuming the wide array of nutrients and phytochemicals that we would be hoping to get."

In the U.S., survey data from the Department of Agriculture have shown that 52% of our overall vegetable consumption comes from iceberg lettuce, potatoes and canned tomatoes.

Indeed, it may matter very much which array of produce people choose to eat. "The evidence has gotten even more substantial that fruits and vegetables as a group do not seem to be strongly related to cancer in general. It . . . looks like we have to get down to specific fruits and vegetables," Willett says.

The effects of fruits and vegetables on cancer risk are also influenced by cooking methods. Take, for example, the tomato, which rose to the top of the super-food list in the 1990s when the Harvard group found that men who ate more tomatoes -- and more of the potent antioxidant lycopene -- had a lower rate of prostate cancer. Lycopene is fat-soluble and most easily enters the blood when cooked or eaten with fat, as in tomato sauce. The team reconfirmed its results in 2002 for 47,365 men followed for 12 years. Men who ate two sauce servings a week, versus less than once a month, showed a 23% reduced prostate cancer risk.

Cooking may also alter the effects of cruciferous vegetables -- broccoli, cauliflower, kale and many others. These are among the few vegetables that show significant protection, even in large population studies, against several cancers, including of the bladder, lung and prostate.

Just this month, researchers analyzing a large trial called the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial found that among nearly 30,000 men followed for a little more than four years, those eating broccoli more than once a week had a 45% reduced prostate cancer risk, compared with men who ate it less than once a month. "For this family of vegetables, the evidence really does seem to be mounting that it is protective for a variety of cancers," says Vicki Kirsh, lead author of the study and a scientist at Cancer Care Ontario in Toronto.

Cruciferous vegetables are rich sources of glucosinolates, the compounds that give these vegetables their pungent, spicy or bitter aroma. When chewed and digested, the breakdown products of glucosinolates, including anti-carcinogens chemicals called isothiocyanates, act to promote detoxifying enzymes.

Unlike with tomatoes, cooking broccoli to within an inch of its life is not good. These compounds are water soluble and can be lost when cooked. A study from 2003 found that boiling cruciferous vegetables for 8 to 15 minutes resulted in an 18% to 59% decrease in glucosinolates.

Genes matter too. There are inherited differences among people, it turns out, that affect the speed with which broccoli's helpful compounds are metabolized. People who produce less of an enzyme that breaks down isothiocyanates keep the anti-cancer chemicals around longer. Studies of people with colon and lung cancer confirm that such people seem to get much more protection from eating cruciferous vegetables than others.

Genetic differences may also matter for tomatoes. In the PLCO trial, researchers found that blood levels of lycopene and tomato product intake were only associated with a reduced prostate cancer risk in men with a family history of the cancer.

Other fruits and vegetables are also showing up as cancer-protective in powerful epidemiological studies. The PLCO study this year showed that spinach, a rich source of the antioxidants folate and lutein, might help ward off prostate cancer. And a few weeks ago, another big study, of nearly 500,000 men and women, found citrus fruits seemed protective against esophageal cancer, as were spinach and tree fruits such as apples and pears.

Apples, a rich source of the antioxidant and anti-cancer compound quercetin, also showed a protective effect against lung cancer.

But even as researchers begin to isolate the individual compounds that give some fruits and vegetables anti-cancer effects, it's becoming clear that they don't work alone. Trials of pure supplements (be it vitamins A, C or E, beta carotene and lycopene) often yield small benefits.

For example, a 2003 rat study found that only whole tomatoes (given as powder) improved prostate cancer survival. Lycopene didn't. And a 2004 analysis of 170,000 subjects from 14 trials found no overall effect of vitamin supplements on several cancers.

In fact, high doses of antioxidants might be harmful in some cases, possibly promoting tumor growth in already-established cancers. The best-known example is a trial of nearly 30,000 male smokers in Finland who were given beta carotene and vitamin E. The trial was stopped prematurely when it emerged that lung cancer risk was increasing, not decreasing, for those on large doses of beta carotene.

"There is not one active ingredient that you put in a tablet and there you go -- bam," says Navindra Seeram, assistant director of the Center for Human Nutrition at UCLA. "When you start to isolate individual compounds and put them alone . . . the action is going to be totally different and you might even have toxicity."

Seeram, like many food researchers, has shown in cell culture that important compounds in fruits and vegetables, be they lycopene, vitamin C or quercetin, have increased anti-cancer powers when combined with the seemingly trivial chemicals found with them in the fruit.

That doesn't necessarily mean you have to crunch into an intact apple or broccoli chunk.

These days, researchers are studying whole food extracts or juice to find new cancer fighters. Studies of cells in dishes show promise for foods such as mushrooms, avocados and garlic.

One up-and-coming group is the dark red-purple fruits, including raspberries, blueberries, cherries, grapes (and wine) and pomegranates. The deep pigments of these fruits are polyphenols called flavonoids. Studies with human cells have shown that they act as powerful antioxidants, anti-inflammatory agents, inhibitors of tumor growth and promoters of an orderly kind of cell suicide that cancer cells can no longer do.

Seeram and his UCLA colleagues have been working with pomegranate extract. In 2006 they published the results of a small, phase-two clinical trial on 46 men treated for prostate cancer. Subjects each drank eight ounces of juice daily, and their prostate specific antigen (PSA) counts, an indicator of cancer progression, were monitored for nearly three years.

The results showed a dramatic decrease in how long it took for the PSA counts to double. Before treatment, the doubling time was 15 months, and by the end of the trial it was 54.

Gary Stoner, professor of internal medicine at Ohio State University, has been working with black raspberries for 15 years after finding they contained the highest concentration of the polyphenol ellagic acid.

In a study published in 2001, his group found that rodents fed powdered black raspberries as 5% to 10% of their total diet developed as much as 47% fewer esophageal tumors than animals that weren't fed the extract.

Stoner and colleagues now have preliminary results from some small clinical trials. In one, they gave 50 people recovering from colon cancer surgery 60 grams of powdered berries every day. Eighteen weeks after treatment, the patients showed a 50% reduction rate in colon polyp size and number. In another trial, daily treatment with the powder reduced lesion size in patients with oral cancer.

But when the team tried a similar treatment for 20 patients with Barrett's esophagus, an early-stage cancer, it found no change in lesion size after 26 weeks.

Although there is more research to be done, Stoner recommends a daily serving of berries for people with certain risk factors -- those who smoke or have precancerous lesions of the mouth, colon polyps, or a genetic history of cancer. Fresh berries are good, but he suggests that the higher concentration of chemicals in freeze-dried berries might be more beneficial.

Fruits and vegetables are just part of the recipe for a cancer-free life.

In June, researchers published an analysis a trial that followed 1,490 women for nearly nine years after they were found to have breast cancer (the Women's Health Living and Eating, or WHEL, trial). Breast cancer survivors who ate five servings of fruits and vegetables a day but didn't exercise didn't reduce their risk of cancer recurrence. Nor did women who exercised but didn't eat produce.

But women who exercised -- the equivalent of 30 minutes of walking, six days a week -- and had high fruit and vegetable intake cut cancer recurrence by 44%.

This same trial also makes the point that just because some is good doesn't mean more will be better. In July, researchers published an analysis of the other 1,537 women in the WHEL trial. This group averaged about nine to 13 daily servings over the course of the study but showed no additional benefit for breast cancer recurrence or mortality compared with those who were told to eat five servings daily.

Collins of the American Institute of Cancer research said that the WHEL women on a high fruit and vegetable diet didn't manage to lose any weight, despite reporting lower calories. "Weight control and physical activity has a huge impact on post-menopausal breast cancer risk," she says. "Fruits and vegetables . . . are very important, but they cannot carry the ball alone."

Harvard's Willett also stresses the importance of physical exercise and maintaining a healthy body weight. Excess weight is a major factor for cancer,, he says. "It really is a close No. 2, after cigarette smoke, for an avoidable cause of cancer."

And just as fruit and vegetables alone can't cure cancer, just as supplements don't provide the benefit of whole foods, there is no single magic cancer food either, says UCLA's Seeram.

"Someone is always going to ask: 'Is the blueberry the best?' 'Is the pomegranate the best?' But the compounds from the different foods act in different ways -- they complement each other," he says.

"You really need this totality of diverse fruits and vegetables on your plate to attack all the different mechanisms that cancer works through. Because cancer is such a complex disease."