

FOOD

The omnivore's labyrinth

Finding the right food to help reduce our chances of cancer can be a maze. But ongoing studies and a little inventive cooking might point us in the right direction.

BY SARAH DEWEERDT

Twenty years ago, Paul Talalay was looking for new ways to prevent cancer, so he went grocery shopping. As a result of his trip to the supermarket, the Johns Hopkins pharmacologist and molecular scientist discovered sulforaphane, a compound contained in certain leafy vegetables. In a simple assay using mouse cells, Talalay and colleagues showed that sulforaphane dramatically boosts the activity of certain phase II enzymes, which form part of the body's cancer-fighting machinery¹. Later, they demonstrated sulforaphane's capacity to prevent tumour growth in rats exposed to a carcinogen².

The rest of us haven't been so fortunate with our anticancer shopping basket. Despite much research over the past 40 years, it's still not clear what to eat — or not eat — to help prevent cancer. Promising initial findings have often turned into statistical dead ends, leaving us culinarily confused.

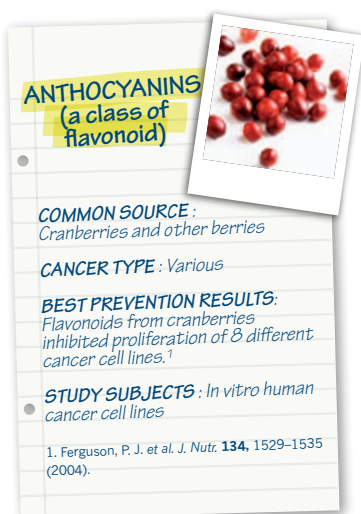
In the mid-1970s, epidemiological studies suggested that people who ate more fruits and vegetables were at lower risk of several

cancers³. Such findings led to public health efforts to get people to eat more fresh produce. In both the United States and the United Kingdom, for example, official dietary recommendations pushed for everyone to consume five portions of fruit and vegetables each day.

As epidemiologists began to use large-scale, prospective studies — a more powerful type of investigation — they frequently found weak, inconsistent or no links between fruit and vegetable consumption and cancer risk. Last year, University of Oxford epidemiologist Tim Key concluded from nearly three dozen large studies and meta-analyses from the last 20 years that “at least in relatively well-nourished Westernised populations, a general increase in total fruit and vegetable intake will not have a large impact on cancer rates” (ref. 4).

This is the story for many other aspects of diet. A high-fat diet was thought to lead to an increased risk of breast cancer, until it wasn't. Early studies of dietary fibre suggested that higher consumption could decrease chances of colon cancer, but that didn't pan out either.

And yet, as Talalay found, some foods do contain anticancer compounds. These so-called phytonutrients include resveratrol in grapes, curcumin in turmeric, and many others (see recipe cards). Some of these molecules, including sulforaphane and genistein (an isoflavone found in soybeans), are now on




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ISOTHIOCYANATES

- COMMON SOURCE:** Broccoli
- CANCER TYPE:** Breast
- BEST PREVENTION RESULTS:** Highest consumption (about 1 kg per month) had 60% of the risk of lowest consumption (< 350 g per month).¹
- STUDY SUBJECTS:** Human females

1. Ambrosone, C. B. et al. *J. Nutr.* **134**, 1134–1138 (2004).



their way to becoming pharmaceutical agents in cancer prevention (see First line of defence, page S5).

So why is figuring out the protective qualities of food so complicated? As scientists probe the complexities of diet and cancer, they are finding a host of reasons, from differences in types of vegetables to variations in human metabolism. At least seven factors underscore the difficulties.

1. *All vegetables are not created equal.* Phytonutrients are most often found in pungent vegetables (like onions and garlic), bitter ones (like mustard greens), or ones with acquired tastes (like mushrooms). There are also “a number of fruit and vegetables that are not major sources of phytonutrients,” says Johanna Lampe, an epidemiologist at the Fred Hutchinson Cancer Research Center in Seattle. And unfortunately, she says, these deficient foods include some of the most popular fruit and vegetables in the Western diet — apples and potatoes.

When Talalay analysed his trolley-load of fruit and vegetables from the supermarket for potential cancer-fighting activity, he found “a vast difference” between different types of produce, he recalls. The most potent were cruciferous vegetables (those in the cabbage family), specifically broccoli and its payload of glucoraphanin — the precursor of sulforaphane.

2. *All heads of broccoli are not created equal.* “So then we asked the question, is broccoli a good way to deliver sulforaphane?” says Talalay. “It turned out the answer was absolutely no” Different heads of broccoli varied 20-fold in their content of glucoraphanin. The specific variety, growing conditions, time of year, distance of transport and other factors all affect the concentration of phytonutrients.

Working with Johns Hopkins plant physiologist Jed Fahey, Talalay found that broccoli seeds were 10 to 100 times richer in glucoraphanin than adult plants, and certain varieties of seeds contained predictable amounts of the molecule. In fact, the most

consistent way to deliver glucoraphanin was to use three-day-old broccoli sprouts⁵.

Broccoli sprouts have become a powerful research tool for Talalay — and dozens of other scientists — to explore the role of sulforaphane in laboratory, animal and now human studies of cancer prevention. They also became a new food: Talalay likes to serve them at lab meetings with bagels and cream cheese.

3. *Human genomes vary.* Eating a known amount of phytonutrient doesn't guarantee that a predictable amount of the cancer-fighting molecule will enter the bloodstream. Differences here can be traced to variations in the genes involved in the digestive processes.

For example, the glutathione S-transferase M1 gene (*GSTM1*) influences the speed at which the body metabolizes sulforaphane and expels it in the urine. The faster it happens, the less beneficial the broccoli. Agricultural companies have developed several varieties of ‘super broccoli’ that are high in both glucoraphanin and related molecules to compensate for the effects of faster variants of the *GSTM1* gene.

GSTM1 is the best studied of the genes that influence phytonutrient metabolism, but it is just one of a rapidly growing list. For example, people who carry two copies of a particular variant of the *UGT1A1* gene make about 30% to 40% less than normal of a type of phase II enzyme. One study has shown that people with this genotype derive more cancer-protecting benefit from eating cabbage- and carrot-family vegetables — possibly because phytonutrients in these foods boost *UGT1A1* activity closer to normal⁶.

4. *Human microbiomes vary.* Some of the genes that determine the power of phytonutrients are not human. Gut bacteria heavily metabolize the phytonutrients from soy, turning one type of isoflavones into another. So depending on their intestinal bacteria, two people who eat the same amount of soy each day might receive not only different quantities of isoflavones, but also different end-products⁷. Between 30% and 50% of people harbour bacteria that produce equol, which some scientists believe is one of the more beneficial forms of isoflavone; around 80% to 90% of people have bacteria that produce O-desmethylangolensin, a less active molecule.

Gut microbiota reflect a complex interplay of diet and genetics. For example, vegetarians are more likely to produce equol than non-vegetarians, and Korean-American women are more likely to produce equol than white American women.

5. *Timing is everything.* Epidemiological studies of Asian populations show that higher consumption of soy foods — tofu, miso and the like — is associated with lower breast cancer risk. Yet, soy seems to provide

little protection to people who otherwise eat a typical Western diet⁸.

Equol may be part of that story, but there is also growing evidence that the age at which a person starts eating soy is critical to its effect. “In Asian women, soy seems to be more protective, but the reason for that is probably that the Asian women started eating soy early in life versus most Caucasian women starting to eat it later,” explains Gertraud Maskarinec, an epidemiologist at the University of Hawaii Cancer Center.

Much of the evidence for this hypothesis comes from animal studies: rats fed soy when they are young have fewer mammary tumours later in life, but rats fed soy only as adults do not get this benefit. There are a few suggestive clues in humans too. For example, women in Asia who grew up eating a traditional, soy-rich diet and then move to the West as adults do not seem to increase their risk of breast cancer⁹.

6. *Some phytonutrients are difficult to access.* Many are found in small quantities in bulky foodstuffs, or only in particular types of seasonal fruit and vegetables. This means it is impractical to eat enough to noticeably reduce cancer risk. For example, many berries are rich in a group of phytonutrients called anthocyanins, which are antioxidants and may have other cancer-fighting effects as well. “The problem with berries is that they are expensive and seasonal, so availability is a limiting factor for a lot of people,” says Cathie Martin, a plant biologist at the John Innes Centre in Norwich, United Kingdom.

Martin led a team that genetically engineered a tomato (which has few natural anthocyanins) to contain roughly the same concentration of anthocyanins as blueberries. In 2008, they showed that this deep purple tomato, known as Del/Ros1N, slowed tumour progression in a cancer-prone strain of mice. The mice fed Del/Ros1N lived longer than mice fed either ordinary red tomatoes or standard laboratory fare¹⁰.

Unlike berries, tomatoes are one of the

RESVERATROL

- COMMON SOURCE:** Red wine
- CANCER TYPE:** Glioma (brain)
- BEST PREVENTION RESULTS:** A daily dose of 40 mg/kg achieved long-term survival for 70% of subjects.¹
- STUDY SUBJECTS:** Rats harboring small subcutaneous gliomas

1. Tseng, S. H. et al. *Clin. Cancer Res.* **10**, 2190–2202 (2004).



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LYCOPENE

COMMON SOURCE:
Tomatoes

CANCER TYPE:
Prostate

BEST PREVENTION RESULTS:
Highest consumers reduced cancer risk by 10-20%.¹

STUDY SUBJECTS: Human males

1. Etrman, M. et al. *Cancer Epidemiol. Biomarkers Prev.* **13**, 340-345 (2004).



CURCUMIN

COMMON SOURCE:
Turmeric, curry

CANCER TYPE:
Colon

BEST PREVENTION RESULTS:
Reduced the number of precancerous tumors by up to 40%.¹
Reduced the number of precancerous tumors by an average of 60% and their size by an average of 50%.²

STUDY SUBJECTS: Mice, bred to be genetically susceptible to colon cancer¹
Humans who carry a genetic mutation of susceptibility to colon cancer.²

1. Perkins, S. et al. *Cancer Epidemiol. Biomarkers Prev.* **11**, 535-540 (2002).
2. Cruz-Correa, M. et al. *Clin. Gastroenterol. Hepatol.* **4**, 1035-1038 (2006).



GARLIC

COMMON SOURCE:
Many different dishes

CANCER TYPE:
Colorectal

BEST PREVENTION RESULTS:
High-consumers have 30% lower risk of cancer than the lowest consumers.¹

12-month consumption of garlic extract meant total size of polyps was one-third those of controls.²

STUDY SUBJECTS: Humans¹
Humans with precancerous colon polyps.²

1. Fleischauer, A. T. et al. *Am. J. Clin. Nutr.* **72**, 1047-1052 (2000).
2. Tanaka, S. et al. *J. Nutr.* **136**, 821S-826S (2006).



largest food crops in the world. Modern growing methods make them available all year round, and they're a popular and frequently consumed food. The anthocyanin-rich tomato could make potential anticancer foods much more readily available (though purple pizza sauce might take some getting used to).

Martin's team has also engineered a tomato strain that has a resveratrol concentration one thousand-times higher than in red wine. Resveratrol has anticancer activity in laboratory studies, but the quantities in red wine are so small that any benefit from the resveratrol would be far outweighed by the adverse effects of drinking excessive volumes of alcohol. "I'm not trying to take away anybody's red wine," Martin laughs — but she suggests that the tomato could be a more practical approach for resveratrol delivery.

7. *The whole (diet) is greater than the sum of its parts.* Sometimes, perhaps, it's not one food but the whole recipe that can be protective. That's what Thomas Kensler, an environmental health specialist, found when he began to study broccoli-sprout tea in Qidong, on the east coast of China. Kensler, based at Johns Hopkins University, expected the local people's gut bacteria to transform the tea's glucoraphanin into active sulforaphane. "There was tremendous interindividual variability," he says. "Some people were really good and some were really bad at this conversion reaction."

Talalay suggested to Kensler that adding a

bit of daikon radish to the tea might help eliminate these differences. Daikon radish contains an enzyme, myrosinase, that catalyses the glucoraphanin conversion. It was a neat trick — and one that demonstrates why it can be so difficult to isolate anticancer elements in a diet.

It is likely that these effects are not limited to experimental concoctions. Gut bacteria influence how phytonutrients are processed, but fibre intake and other aspects of the diet alter the gut ecosystem. Traditional Asian diets include not just large helpings of soy but also generous pours of green tea, which contains cancer-fighting epigallocatechins. Little is known about how diverse foods in a diet interact to affect cancer risk.

Specialized diets are far from the only way to decrease our chances of cancer, but they do add flexibility to cancer prevention strategies. Kensler began investigating sulforaphane after working for several years in China. One in ten people will develop liver cancer there during their lifetime so cancer prevention can make a real impact. Yet pharmaceuticals would be too expensive for many people to buy, and some people simply don't like taking pills. "I began to recognize that Western approaches aren't going to work around the world," Kensler recalls.

A broccoli-sprout tea was the perfect choice for this population. "Culturally it fits right in with their behavioural patterns and their own notions of how to preserve health," he says. Elsewhere, raw broccoli sprouts might be a more popular addition to diets. Some populations will be open to getting phytonutrients from a genetically engineered tomato, while other societies would recoil from designer foods. And in some cultures, purified phytonutrients in dietary supplement form might be the best approach. "Different delivery mechanisms are going to be appropriate for different

target populations," says Kensler.

But where does that leave the rest of us, as we ponder what foods to buy? For the time being we are stuck with familiar advice — eat more fruits and vegetables, and more whole grains. It can't hurt: after all, despite the healthy eating campaigns, fewer Americans today are getting their five-a-day than were a decade ago (yet another factor that makes interpreting studies of fruit-and-vegetable consumption and cancer rates more complicated).

Better guidance might be on the way. "A lot of the current recommendations are very generic — five 'helpings' of fruits and vegetables a day, but which ones are not specified," notes Martin. "I think we'll get closer to saying, 'eat the ones that are purple.'" Future dietary recommendations might also take genetics into account. We might learn how to tweak the composition of the gut microbiota, such as with probiotics, to maximize the cancer-fighting effects of foods. Plant breeders and farmers might pay more attention to phytonutrient content when they develop and sow vegetable varieties.

"Hopefully science can work together with the food industry to provide foods that are rich in components that are deemed healthy and safe," says Kensler. Perhaps then we will have clearer messages about how we can eat our way out of cancer danger. ■

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PURPLE TOMATOES: JOHN INNES CENTRE.