



Cancer Prevention With a Diabetes Pill?

In 2005, Andrew Morris and his colleagues at the University of Dundee in the United Kingdom were following up on therapy for type 2 diabetes patients when they reported results that have since set the world of cancer research abuzz. They found that use of an insulin-lowering drug known as metformin was associated with a significant decrease in cancer incidence. Since then, half a dozen studies have confirmed it: Diabetics treated with metformin have from 25% to 40% less cancer than those who receive insulin as therapy or take sulfonylurea drugs that increase insulin secretion from the pancreas.

The idea that reducing insulin and insulin-like hormones in circulation may prevent tumors has become a bright hope for drug research. A host of insulin-suppressing drugs are in the pharmaceutical industry pipeline, says Lewis Cantley, director of the Cancer Center at Beth Israel Deaconess Medical Center, which is part of Harvard Medical School in Boston. But the companies may have been beaten to the punch: "Metformin may have already saved more people from cancer deaths than any drug in history," he says. It is one of the oldest and most commonly prescribed antidiabetic therapies in the world; some 120 million prescriptions are written for it yearly.

There is a caveat to the observational research linking metformin use to a decrease in cancer incidence, however: Studies of this kind are incapable of establishing a causal relationship. Maybe metformin prevents cancer in type 2 diabetics. Maybe insulin and the sulfonylurea drugs given instead of metformin promote cancer risk. Maybe something else entirely is going on.

Metformin activates an enzyme called AMPK in the liver, which then reduces the organ's synthesis and secretion of glucose, and thereby lowers blood glucose levels. But the drug also stimulates a tumor suppressor gene known as *LKB1*. Two University of Dundee biochemists, Dario Alessi and Grahame Hardie,

Dual use. Widely prescribed and cheap, metformin lowers insulin and, it appears, the risk of cancer.

worked out the AMPK-to-*LKB1* connection; Cantley and Reuben Shaw of the Salk Institute for Biological Studies in San Diego, California, did so independently. This connection was what prompted Morris to study cancer incidence in diabetics who are taking metformin.

As often happens in science, however, the physical mechanism may well be different from the hypothesized one. Instead of inhibiting cancer by activating AMPK and then *LKB1*, say Cantley and other researchers, metformin seems to work directly by lowering insulin and insulin-like growth factor (IGF) levels. "Metformin decreases glucose in the blood, and, as a secondary effect, decreases insulin levels," says Michael Pollak of McGill University in Montreal, Canada.

Evidence for that mechanism comes from animal studies. In September 2010, Phillip Dennis and his colleagues at the U.S. National Cancer Institute reported that metformin reduced lung cancer in mice that had been injected with potent tobacco-related carcinogens. But, as Dennis and his colleagues reported in the journal *Cancer Prevention Research*, they found no sign that metformin was activating AMPK in the lung tissue, as would be expected if that was the mechanism of action. In the liver, though, Dennis says, AMPK activation by metformin was "profound," and both insulin and IGF levels in the circulation were suppressed. The results, Cantley says, "support the hypothesis that anything that lowers insulin and IGF levels will inhibit tumor growth."

The results also "provide a strong rationale," as Dennis and his colleagues put it, for a clinical prevention trial. They hope to give metformin to patients who have had early stage lung cancer surgically removed and are at high risk of cancer recurrence. They intend to test the drug for safety, look for effects on insulin and IGF, and see whether it can prevent cancer in humans as it did for mice.

Other trials are beginning. One of the largest is being run by oncologist Pam Goodwin of the University of Toronto in Canada, who has been studying insulin and breast cancer since the mid-1990s. Goodwin says her interest was sparked after she realized that insulin may mediate the effects of obesity on breast cancer outcome. Fasting insulin levels in nondiabetic women are "predictive of breast cancer outcomes," she observes: Obese women have high insulin levels, and they "do badly."

Goodwin's group demonstrated 6 years ago that metformin lowers blood sugar and insulin levels by nearly one-quarter even in women who don't have diabetes. Now Goodwin and her colleagues are running a multinational clinical trial in which 3500 breast cancer patients will be randomized to receive either usual care plus a placebo or usual care plus metformin, to see if metformin helps improve survival and prevent recurrence of the disease. "We anticipate that it will take another 2 years to enroll everyone," she says, "and maybe 2 to 3 years after that before we have results."

Until then, as Goodwin emphasizes, the best they can say is that metformin *may* be beneficial for cancer. "All the preclinical and epidemiological evidence is pretty consistent and compelling, but all it's done is help us form a hypothesis. We need to proceed from here very, very carefully." **—G.T.**



Connecting the dots. Andrew Morris and colleagues showed that patients on metformin had 25% to 40% less cancer.