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Metformin Might Prevent Colorectal, Lung Cancers

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September 3, 2010 — The chance observation that diabetes patients taking metformin have a 40% reduced risk for cancer triggered intense research interest in this old off-patent drug.

Data from a small clinical trial and from an animal study reported in the September issue of *Cancer Prevention Research* suggest that metformin might suppress the development of precancerous colorectal lesions in humans and prevent tobacco-induced lung cancers in mice. The drug appears to alter cellular energy metabolism in a way that is particularly bad for cancers and precancerous cells. It is also attractive because it is relatively nontoxic.

During a press briefing organized by the American Association for Cancer Research to discuss the metformin data, Michael Pollak, MD, from McGill University in Montreal, Quebec, said that the new studies are important because they indicate the usefulness of metformin as a preventive agent. Dr. Pollak wrote a review of metformin and other biguanides in oncology that appears in the same issue of *Cancer Prevention Research*.

"Unlike chemotherapy or radiotherapy, which are intended to kill cancer cells in a directly toxic manner, metformin appears to target the cancer in a more subtle way, which involves cancer energetics. It also may act in some patients, especially diabetic cancer patients, by reducing levels of hormones that can stimulate cell growth, including insulin itself," Dr. Pollak said.

In the first human trial of metformin as a cancer preventive, Kunihiro Hosono, MD, and colleagues from the Yokohama City University School of Medicine in Japan report that nondiabetic patients randomized to 1 month of low-dose of metformin (250 mg/day) had a significant decrease in the mean number of rectal aberrant crypt foci (ACF), an endoscopic surrogate marker of colorectal cancer.

The researchers randomized 12 nondiabetic patients with ACF to treatment with metformin and 14 to no treatment. After 1 month, the metformin patients not only had fewer ACFs, they also had significant decreases in the proliferating cell nuclear antigen index.

Dr. Hosono and colleagues write that "this first reported trial of metformin for inhibiting colorectal carcinogenesis in humans provides preliminary evidence that metformin suppresses colonic epithelial proliferation and rectal ACF formation in humans, suggesting its promise for the chemoprevention of colorectal cancer."

Low-dose metformin did not cause any adverse effects, such as lactic acidosis, hypoglycemia, or diarrhea in this study.

In related work, a research team led by Phillip A. Dennis, MD, and Regan M. Memmott, MD, from the National Cancer Institute (NCI) Medical Oncology Branch in Bethesda, Maryland, studied metformin for prevention in a mouse model of smoking-related lung cancer. They exposed mice to the tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and then treated the mice with metformin in drinking water.

The researchers expected that a specific target (the rapamycin or mTOR pathway, an early event in tobacco-induced lung cancer) would be inhibited by metformin.

"After about 10% of the mouse lifespan — about 12 weeks — with the highest dose in the drinking water, we found a 33% reduction in tumor multiplicity and a 34% reduction in tumor size in the mice. In mice that did not get metformin, 100% got tobacco carcinogen-induced lung tumors," Dr. Dennis said at the press briefing. Overall, metformin reduced lung tumor burden by up to 53% at steady-state plasma concentrations that can be achieved in humans.

Despite this, mTOR was only modestly inhibited, so the researchers moved to intraperitoneal administration to achieve higher dose levels. This showed that metformin activated 5'-AMP-activated protein kinase in liver tissue (but not lung tissue), where it inhibited phosphorylation of the insulin-like growth factor (IGF)-1/insulin receptor. Mice injected with metformin daily for 12 weeks had a 72% reduction in tumor burden.

"We think that metformin was able to inhibit lung tumorigenesis caused by a tobacco carcinogen — when given in drinking water to achieve levels that could be attained in humans and when given by injection — and that the

mechanism involves hormone release from the liver. We are planning to move forward to study metformin as a chemopreventive agent in clinical trials," Dr. Dennis said.

Lewis Cantley, MD, from Beth Israel Deaconess Medical Center in Boston, Massachusetts, suggested at the press briefing that metformin might prevent tumors by reducing levels of insulin and IGF-1. He noted that 2 approaches to treating type 2 diabetes (insulin, which increases insulin levels, and metformin, which decreases them) appear to have opposite effects on cancer risk.

Dr. Pollak said that "metformin's effects in animals are similar to those of a brief period of fasting. On a normal diet, metformin fools the liver into thinking it is fasting."

It fell to Dr. Cantley to mention the elephant in the room: metformin is off patent and unlikely to attract pharmaceutical industry support for clinical trials to established the drug as a general cancer preventive. "This will have to have millions of dollars in either private or NCI support," he said.

Dr. Pollak reports consulting for Merck, Novo-Nordisk, Lilly, Pfizer, and Sanofi-Aventis. Dr. Hosono and Dr. Dennis have disclosed no relevant financial relationships. Dr. Cantley is founder of and a consultant for Agios.

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