

# Doctors Seek To Prevent Breast Cancer Recurrence by Lowering Insulin Levels

By Karyn Hede

Even in this era of targeted molecular therapies, an old drug can sometimes provide a surprising new benefit. A case in point, the diabetes drug metformin is emerging as a potential treatment for breast cancer on the basis of evidence that cancer patients with lower insulin levels have better outcomes. But using a diabetes drug to lower insulin levels in patients who are not diabetic has caused concern among some researchers, who say that doctors first need to know more about how metformin works in the oncology setting.

First isolated as an active ingredient in the medieval herbal remedy goat's rue, metformin has been used to treat type II diabetes for more than 50 years. The U.S. Food and Drug Administration approved its use in the United States in 1995, and it is now the most prescribed drug for type II diabetes, the adult-onset form of the disease that accounts for 90%–95% of all diabetes cases.

After several epidemiological studies linked metformin use to lower cancer rates and reduced risk of cancer death, some physicians proposed adding metformin to cancer treatment regimens. Among the first to advocate its use was Pamela Goodwin, M.D., a medical oncologist at Mount Sinai Hospital in Toronto. In a recent editorial in the *Journal of Clinical Oncology*, Goodwin laid out a rationale for adding metformin to adjuvant breast cancer treatment, citing evidence that elevated insulin levels, often associated with obesity, may be a biological link connecting obesity with lower survival.

"If you look at the effect of insulin, the women in the highest quartile of insulin levels in the studies that have been done all

yield the same result: They have a triple risk of death," Goodwin said. "If we could lower those insulin levels by 25%, we might see a 5%–6% absolute improvement in outcome, and that's huge."

Goodwin bases her optimism on several published studies, including a prospective cohort study of 512 nondiabetic women with early-stage breast cancer that she published in 2002. The study showed that women with the highest fasting insulin levels had three times the risk of recurrence

and death compared with women with the lowest insulin levels. Other large studies have replicated this finding. The NCI-sponsored Health, Eating, Activity, and Lifestyle (HEAL) study confirmed that higher body mass index and lower physical activity levels are associated with higher insulin levels

in breast cancer survivors and that women with invasive disease and the highest insulin levels have three times the risk of death of women with the lowest insulin levels. Melinda Irwin, Ph.D., an epidemiologist at the Yale School of Public Health in New Haven, Conn., presented those data at the American Association for Cancer Research's prevention meeting last year.

"The high-insulin effect is large," said Michael Pollak, M.D., professor of oncology at McGill University in Montreal. "The adverse effect of high insulin on outcome of postmenopausal breast cancer is in the same order of magnitude as the beneficial effect of adjuvant chemotherapy. This is nothing subtle."

Pollak, who studies the association of high insulin levels with breast and colorectal

cancer incidence, agrees with Goodwin that therapies to reduce high insulin levels in cancer patients could dramatically reduce cancer-related deaths. "In postmenopausal women, where obesity is associated with a bad [breast cancer] outcome, it's a very reasonable hypothesis that the bad outcome is because obesity is associated with high insulin," he said.

Two other large studies, using data from Canadian and British diabetes registries, have shown that people taking metformin, and thereby lowering their insulin levels, had unexpectedly lower overall cancer rates than



Michael Pollak, M.D.

patients taking diabetes medications such as sulfonylureas. These drugs work by raising insulin levels to force blood glucose levels down.

"Previously the endocrinologists who used metformin to treat diabetes called it an insulin-sensitizing agent because when type II diabetic patients were given metformin, their insulin levels fell. So the endocrinologists thought the drug was making the insulin work better," said Pollak. But if metformin actually worked by making cells more sensitive to insulin, he said, it would probably increase tumor growth because insulin stimulates breast cancer cell growth.

Pollak found that the opposite was true. When he studied the effect of metformin in both estrogen receptor-positive and estrogen receptor-negative breast cancer cells in culture, the drug reduced breast cancer cell growth.

## AMP Kinase Pathway

Pollak also showed that metformin protected breast cancer cells from the growth-stimulating effects of insulin by activating the AMP kinase metabolic pathway, which

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reduces cell growth and division. That study, published in the November 1, 2006, issue of *Cancer Research*, fueled the idea that metformin may actually work directly on cancer cells to inhibit growth, in addition to its indirect insulin-lowering effect.

A recent experiment testing metformin's effect in colon cancer supports Pollak's finding that the AMP kinase pathway is involved. Craig Thompson, M.D., director of the Abramson Cancer Center at the University of Pennsylvania in Philadelphia, led a study, published last July in *Cancer Research*, showing that metformin slowed the growth of colon cancer cells that lacked the master tumor suppressor p53. The researchers injected human colon cancer cells that had normal p53 function into one side of mice and injected colon cancer cells lacking p53 into the other side. After 4 weeks of treatment with metformin at doses comparable to the human therapeutic dose, the p53-deficient tumors were half the size of the p53-deficient tumors in mice that had not received metformin. There was no difference in the size of tumors with normal p53 expression.

Thompson concluded that the tumors grew more slowly because when metformin turns on AMP kinase, it forces a switch to a metabolic pathway that requires active p53. Without p53, metformin stymies tumor growth.

#### Cautionary Note

These recent laboratory results have swelled interest in metformin's antiproliferative effect on cancer cells. But other scientists are sounding a cautionary note about proceeding with human trials.

Kevin Claffey, Ph.D., and his colleagues at the University of Connecticut's Center for Vascular Biology in Farmington studied the effect of metformin in a tumor xenograft model that used four cell lines: two with estrogen receptors and two without. In all animals, Claffey showed that metformin induced AMP kinase and reduced cell growth. However, in one of the estrogen receptor-negative cell lines, called MDA-MB-435, systemic metformin also induced production of vascular endothelial growth factor, which promotes the growth of blood vessels that feed tumors. Metformin appeared to trigger a twofold increase in blood vessel growth

compared with control animals, and the researchers observed tumor progression after 40 days of metformin administration.

"We saw selective activation of this secondary [vascular endothelial growth factor] pathway for survival and angiogenic response," said Claffey. "The concern is that we just don't know enough about either the specific tumor types that you would want to treat [with metformin] or whether this is a more global concern that you might promote an angiogenic response. One of the clear points that we see is that the phenotypic diversity of breast tumor cells could determine very distinct responses, both positive and negative, from metformin treatment."

Pollak and Goodwin acknowledged that Claffey's study could raise concerns but countered that one small animal study using one cell line should not negate the existing evidence of metformin's safety and potential for reducing cancer deaths. Goodwin pointed out that the concentration of metformin given to the animals was 40 times higher than human therapeutic doses. Claffey said that the dose, although high, was necessary because rodent metabolism differs from that of humans; also, the

physiological response, as measured by reduced insulin-like growth factor 1 levels, was equivalent to the human response to therapeutic doses.

“I believe that the bulk of the evidence still supports the rationale for clinical studies for metformin,” Pollak said. “But we do have to exercise some caution because this model gave an unexpected result.”

Goodwin just completed a prospective phase II clinical trial of 32 nondiabetic breast cancer patients that showed that metformin reduced fasting insulin level by 22%. She is now planning a multicenter phase III randomized, double-blind, placebo-controlled trial of metformin in early-stage breast cancer patients.

But some physicians who have looked at the metformin data say that the evidence supporting the launch of large trials is shaky. Jeffrey Johnson, Ph.D., a diabetes specialist at the University of Alberta, led the study showing that diabetes patients who took metformin had an unexpectedly better outcome than those taking sulfonylureas.

“We should start some smaller trials and get an understanding in a controlled clinical environment, but at the same time I think we need to build up further epidemiological evidence,” Johnson said. “If the initial small-scale trials are supportive, then we can go on to larger trials.”

Another approach is to study the effects of exercise, which can reduce levels of not only insulin but also estrogen and leptin, as well as promote weight loss—all of which are associated with better outcomes. Yale’s Irwin recently completed a study of 75 overweight, inactive, postmenopausal breast cancer survivors. After a 6-month aerobic exercise program, the exercise group had reduced their insulin level by 6%, whereas the control group increased their insulin level by 36%.

Irwin said that isolating one factor, such as insulin level, helps researchers measure effects but that the overall benefits of exercise for breast cancer patients could make it the preferred intervention. Although metformin is a potential intervention to prevent

breast cancer recurrence, she said, exercise is well tolerated and has few side effects.

“Currently, I don’t think enough oncologists or surgeons are recommending physical activity for their cancer patients,” she said.

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