Study: Metformin for breast cancer less effective at higher glucose concentrations

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A University of Colorado Cancer Center study published online this month in the journal *Cell Cycle* shows that breast cancer cell growth, motility and aggression is promoted by excess glucose, as experienced by patients with diabetes and metabolic syndrome. The study also showed that patients with high glucose may require higher doses of the drug metformin to achieve the same anti-cancer activity as patients with normal glucose levels.

Metformin, the most common first-line drug in the treatment of type-2 diabetes, has been shown in previous studies to reduce breast cancer risk, improve survival, and increase the effectiveness of chemotherapy. Numerous Phase III clinical trials are currently evaluating the benefits

and best uses of metformin in breast cancer patients.

"We show that metformin works differently in high- compared to low-glucose conditions. Not only does it require a higher concentration of metformin to be active in high-glucose conditions, but we report that the drug regulates different genes within cancer cells at high as compared to normal glucose levels," says Ann Thor, MD, CU Cancer Center investigator, Todd Professor of Pathology at the University of Colorado School of Medicine, and the study's principal investigator.

The study evaluated the effects of metformin on 17 breast cancer cell lines representing each of the molecular subtypes of the disease, at varying glucose levels.

"Commonly, lab studies of metformin are performed with very high glucose concentrations – about 17 millimols of glucose per liter. But the average glucose level in healthy humans is only about one third of that dose – about 5 millimols per liter. And individuals with diabetes may have glucose at 10 millimols per liter. We wanted to study metformin activity under these conditions," Thor says.

So the question was this: how would metformin perform in breast cancer cells grown at more realistic, human levels of glucose?

"Results show that when you drop glucose down to human levels, metformin has an even bigger effect at standard doses. When glucose is high you need more metformin to achieve the same results," Thor says.

Thor also points out that skeptics of metformin treatment for cancer in general or breast cancer in particular frequently point to the high concentrations of metformin needed to create results in the laboratory.

"Our data helps to explain why higher doses of metformin are required

to obtain anti-cancer effects when cancer cells are grown in the lab, as compared to its use in humans," Thor says.

Interestingly, "it wasn't simply that the metformin effectiveness went up as glucose came down, but that entirely new mechanisms of action were present at lower glucose levels," Thor says.

Specifically, Thor and colleagues used RNA expression arrays to discover which genes were affected by metformin at high and low glucose concentrations. At high glucose concentrations, metformin primarily affected genes involved in metabolic processes and cell proliferation; at low glucose concentrations, metformin affected genes controlling cellular process and programmed cell death.

In addition to affecting the growth of breast cancer cells, Thor and colleagues show the drug decreases the ability of breast cancer cells to move within the body – a task necessary for the spread of the disease to other sites.

"An extension of this data implies that in breast cancer patients with diabetes or metabolic syndrome, metformin may less effective at the standard dose. To be effective, doctors may have to first explore glucose control or may have to use a higher dose of metformin," Thor says.

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