

# Study sheds light on diabetes drug for prostate cancer

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Alex Papachristodoulou. Credit: Columbia University Irving Medical Center

In the years since a 2005 study found that diabetes patients taking metformin had lower rates of cancer, oncologists have been excited by the prospect of using the inexpensive, safe, and widely used diabetes

drug to prevent or slow the development of many cancers.

But in studies of [prostate cancer](#), metformin performance has been mixed, with some studies reporting a lower incidence of [prostate cancer](#) among men using metformin and others finding no relationship.

Now [a study](#) published in *European Urology* from Columbia researchers suggests that metformin is indeed a promising drug that could prevent the progression of prostate cancer, but only for tumors with low levels of NKX3.1, which are more likely to develop into aggressive cancers.

"Until this study no one understood this essential aspect of metformin and which patients could benefit," says Columbia oncologist Mark Stein, MD, who is helping design a clinical trial to test the idea in newly diagnosed patients, but was not involved in the new study. "The new work reinvigorates the idea of using this safe and inexpensive drug in a way that could benefit [prostate cancer patients](#), potentially sparing them from additional treatment, and allows us to test the drug in a more focused way."

The researchers found that metformin restores cancer-fighting [mitochondrial activity](#) that is lost when NKX3.1 levels are low, prevents [prostate cancer progression](#) in mice, and is associated with better survival in patients with low-NKX3.1 tumors but not high-NKX3.1 tumors.

"Where we see metformin having the biggest impact is in patients who've just been diagnosed with prostate cancer," says Alex Papachristodoulou, Ph.D., associate research scientist, who conducted the research in the lab of Cory Abate-Shen, Ph.D., chair of the Department of Molecular Pharmacology & Therapeutics.

Most patients with new diagnoses of prostate cancer have low-grade

tumors that are not treated and are instead monitored by [active surveillance](#). But some of these tumors will become more aggressive and potentially life-threatening.

"Metformin could be given to patients under surveillance with high-risk tumors when there's still time to prevent progression to advanced disease," Abate-Shen says.

## **The mitochondria connection**

The idea to test metformin and its interaction with NKX3.1 developed from Papachristodoulou and Abate-Shen's previous study, which revealed how low levels of the protein promote prostate cancer.

Low levels of NKX3.1 have been linked with aggressive disease for years, but it was unclear why the deficiency drove cancer development. Papachristodoulou and Abate-Shen found that when prostate cells are under oxidative stress (as happens during prostate cancer development), NKX3.1 moves into the cells' mitochondria to reduce the stress and protect the cells. If NKX3.1 levels are low, less protection is available, and prostate cells are more likely to turn malignant.

"That's when we realized how metformin might be able help, since metformin is known to act on the mitochondria," Papachristodoulou says.

## **In mice and men, metformin slows prostate cancer**

To test metformin's effect on low-NKX3.1 prostate cancers, the researchers gave metformin to low-NKX3.1 mice that tend to develop prostate cancer.

"These mice mimic the progression from lower- to higher-grade prostate cancer, similar to the cancers found in men who are put on active surveillance," Papachristodoulou says, "but with metformin, we were able to stop further progression of the cancer."

The researchers then looked at human prostate cancer cells and tissues, confirming that metformin works on the same mitochondrial processes in people and prevents further cancerous changes.

"The work was very elegant," says Stein. "The models they have developed to understand the disease were key to answering the question. And to find a whole new mechanism of action for a drug that's so ubiquitous is very unusual."

Finally, with the help of long-standing clinical collaborators James McKiernan, Renu Virk, and Mitchell Benson at Columbia; Max Loda at Cornell; and others in Europe, the researchers retrospectively examined the effect of metformin in two groups of men who had been treated for prostate cancer. (Many men in both groups took metformin for their diabetes.)

After measuring NKX3.1 levels in [tissue samples](#) from the patients, researchers found that metformin only benefited patients with low NKX3.1 levels and mitochondrial impairment. Remarkably, among men with low NKX3.1 cancers under active surveillance, those taking metformin (three out of three) had their cancers downgraded during the surveillance period, while three out of four patients who did not take metformin had their cancers upgraded.

## **Potential to help reduce prostate cancer disparities**

Papachristodoulou and Abate-Shen are now working with Stein, McKiernan, Loda, and others to set up a clinical trial to test whether

[metformin](#) can prevent the progression of prostate cancer in men with newly diagnosed, low-NKX3.1 tumors who are under active surveillance.

NKX3.1 levels are not typically measured in men newly diagnosed with prostate cancer, but based on the two cohorts examined, about 50% to 60% of patients may have low-expressing NKX3.1 tumors.

Metformin could be particularly helpful for Black men, Papachristodoulou says, because they are more likely than white men to develop aggressive prostate cancer.

"Though some of the [health disparities](#) are due to socioeconomic and health care inequities, we think there are biological factors like differences in NKX3.1 levels and mitochondria that also contribute," Papachristodoulou says.

Along with studies to find additional biomarkers that identify patients with the greatest risk of developing aggressive prostate cancer, Papachristodoulou will continue to pursue disparities research in the Abate-Shen lab and his future independent career.

Mitochondria, he thinks, may provide some answers.

"The search for biomarkers that can predict prostate cancer development and progression has largely focused on the nuclear genome, overlooking the mitochondrial genome," he says, "but we know that alterations in mitochondrial genes are associated with lethal prostate cancer, particularly in Black men. I'm hoping that ... I'll be able to identify more mitochondrial-related biomarkers like NKX3.1 and we can ultimately improve survival."

**More information:** Alexandros Papachristodoulou et al, Metformin Overcomes the Consequences of NKX3.1 Loss to Suppress Prostate

Cancer Progression, *European Urology* (2023). DOI: [10.1016/j.eururo.2023.07.016](https://doi.org/10.1016/j.eururo.2023.07.016)

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