

Metformin and vitamin D3 show impressive promise in preventing colorectal cancer

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The concept was simple: If two compounds each individually show promise in preventing colon cancer, surely it's worth trying the two together to see if even greater impact is possible.

In this instance, Case Western Reserve cancer researcher Li Li, MD, PhD, could not have been more prescient.

Not only did the combination of the two improve outcomes in animal studies, but the dual-compound effect was dramatically better than either option alone. Even better, these impressive results required only modest amounts of metformin and Vitamin D3, making concerns about side effects from mega-dosing entirely moot. Their piece served as the cover feature February's edition of *Cancer Prevention Research*.

The results are so promising, in fact, that Li, the Case Comprehensive Cancer Center's associate director for prevention research, already has three options in mind for clinical trials—outright primary prevention, prevention of colon adenoma recurrence, and enhancement of chances for survival for those who have colorectal cancers. In addition, compounds already are commercially available, which means they have proceeded successfully through several rounds of safety testing. As a result, the path to tests on humans will be somewhat smoother.

"In the two animal models, we showed that metformin and vitamin D3 did indeed work together," Li said. "Clearly, if we put the two together, they are much more potent in preventing colon neoplasia than by taking

just either one of them alone. The medium dose also tells us that it is not necessary to take huge doses of the drugs to have a cancer-prevention effect. If the results in the animal models translate to humans, that will be a highly significant finding in colorectal cancer prevention."

Vitamin D3 is synthesized in the skin through diet or ultra violet irradiation. Among other things, the nutrient regulates cell proliferation, differentiation and apoptosis, all key components in preventing runaway cell growth characteristic of cancer. Importantly, vitamin D3 inhibits activation of the Wnt/ β -catenin pathway, which triggers the genes responsible for proliferation of [colon cancer cells](#).

Metformin inhibits abnormal cell growth by stimulating the AMP-activated protein kinase (AMPK) pathway. AMPK leads to weakened mTOR signaling and protein synthesis necessary for cancer cells to grow. Metformin has also been shown to suppress proliferation of colon epithelial cells and aberrant crypt foci (ACF). ACF are clusters of abnormal tube-like glands in the colon and rectum that lead to the development of colorectal polyps, often the precursors to colorectal cancer.

The metformin-vitamin D3 research in the mice and rats grew out of a collaboration formed between Case Western Reserve and researchers in China as part of what had been the Case Western Reserve Center of Transdisciplinary Research on Energetics and Cancer (TREC) program led by Nathan A. Berger, MD, (2005-2011) and the Case-China Health Initiative that Li directs. The National Institutes of Health-funded Case TREC targeted research toward reducing cancer linked with obesity, poor diet and low levels of physical activity. Li was principal investigator in one of the three main projects in the TREC program and has since engaged in active collaboration with investigators in China. Therefore, it was a natural for him to turn to colleagues in China to collaborate in the metformin-vitamin D3 research in lab animals. Essentially, Li conceived

the hypothesis and participated in the study's design, while Lanzhou University scientists performed the extensive study in 110 rats and 125 mice.

For the investigation in China, the rats were induced chemically for a predisposition to develop neoplasia (precancerous cells) of the colon. The mice were induced chemically to develop colitis, an inflammation of the colon that often leads to neoplasia. In both the rats and the mice, some groups of the animals received varying doses of both vitamin D3 and metformin, and other groups received either vitamin D3 alone or metformin alone. The control groups either received no drug or Celebrex (celecoxib), a powerful non-steroidal anti-inflammatory drug as a positive control. The rats received treatment for 18 weeks and the mice for 20 weeks.

"Few colon neoplasias developed in the animals receiving moderate doses of metformin-vitamin D combination," said Li, also director of Swetland Center for Environmental Health and Mary Ann Swetland Professor of Environmental Health Sciences and professor of Family Medicine at Case Western Reserve University School of Medicine. "On average, there was also a 40 percent decrease in the development of polyps in all animals receiving both drugs in combination compared to the control groups."

Overall, rats treated with metformin and vitamin D3 or with each compound singly experienced decreased numbers of tumors compared to the control groups, but the moderate dose metformin-vitamin D3 combo resulted in the most significant tumor-inhibiting effect. Tumor numbers in the colons of the rats were substantially less in the moderate-dose combo group. As for the mice, numbers of colorectal tumors were significantly fewer in the metformin-vitamin D3 combo group and noticeably fewer in mice treated with vitamin D3 alone.

Clinical trial options in humans include:

- Testing dual metformin-vitamin D3 as an ongoing therapy for individuals who have had colorectal cancer as neo-adjuvant therapy. The goal would be increasing their chances for survival. Data has shown that vitamin D levels alone have been associated with better survival for people diagnosed with the illness;
- Testing the metformin-vitamin D3 combination as a prevention measure in individuals with familial adenomatous polyposis (FAP). FAP causes affected individuals to acquire thousands of colon polyps when they are in their 20s, and by the time they are age 30 or 40, they are diagnosed with colon cancer;
- Administering both compounds in individuals diagnosed with colon cancer one to four weeks before their surgery. The idea would be to compare their initial cancer biopsy tissue with the removed colon cancer tumor for changes in gene expression levels. The findings would reveal mechanisms for the progression of the disease, and then therapeutics could be developed to interrupt those.

"Persons with a 10 millimeter or larger adenoma polyp or high-grade neoplasia have a 50 percent chance for recurrence within four years," Li said. "We can screen them for colon cancer with colonoscopy every few years, but we don't have much to offer them in terms of prevention. This metformin-vitamin D3 combo may provide an opportunity to prevent recurrence."

The incidence of colon cancer is unlikely to recede any time soon. The illness is linked to obesity, metabolic syndrome, insulin resistance and diabetes, and these conditions are on the rise in the Western world and encroaching on Asia, particularly China. If proven effective, the metformin-vitamin D3 combo could eventually be prescribed in individuals with a strong family history of [colon cancer](#) and with leading

risk factors.

"There is a lot of talk now about drug repurposing today where one drug developed for one condition can be used for an entirely different one," Li said. "Here we have two well-proven medicines that if you put them together, they appear prevent cancer, and they are safe."

Also weighing on this latest research by Li and fellow investigators was Stanton Gerson, MD, Asa & Patricia Shiverick and Jane Shiverick (Tripp) Professor of Hematological Oncology, and Director of the Case Comprehensive Cancer Center at Case Western Reserve University.

"Millions of individuals with diabetes, even those who are pregnant, are taking metformin, and individuals with vitamin D deficiency are taking vitamin D3 medications," he said. "So metformin and vitamin D3 may already be providing a [colorectal cancer](#) prevention benefit to a significant number of people."

Provided by Case Western Reserve University

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