# New Research Sheds Light on Why Tamoxifen May Lead to Higher Risk of Uterine Cancer

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Since its introduction in the 1970s, tamoxifen has significantly improved survival rates for millions of patients with estrogen receptor–positive breast cancer. However, alongside its life-saving benefits, tamoxifen has also been linked—though rarely—to an elevated risk of uterine cancer. Until now, the precise molecular cause of this effect has remained unclear.

A new study published August 22 in Nature Genetics led by researchers at Dana Farber Cancer Institute, Mass General Brigham, the Broad Institute of MIT and Harvard, and Berlin Institute of Health (BIH) at Charité sheds light on the mechanism underlying this link and how blocking a specific molecular pathway may offer a way to prevent uterine cancers from occurring in patients taking tamoxifen.

"Our findings suggest that tamoxifen activates a cell growth signaling pathway in cells in the uterus," said co-corresponding author Gad Getz, PhD, Director of Bioinformatics at the Mass General Cancer Center and an Institute Member at Broad.

Researchers performed whole-exome sequencing of 21 uterine cancers that were associated with previous tamoxifen use and compared their genetic makeup with those of non-tamoxifen-associated uterine cancers in published databases. Results found only 14% of post-tamoxifen uterine cancers harbored cancer-related PIK3CA mutations, compared to 48% of uterine cancers diagnosed in women who hadn't taken tamoxifen. This finding of lower rates of PIK3CA mutations, a key component of the PI3K pathway, in tamoxifen-exposed patients was validated in three independent cohorts.

To see how tamoxifen might induce cancer without inducing genetic changes, the researchers exposed mice to estrogen, tamoxifen, or no treatment. Compared to the other groups, mice exposed to tamoxifen had greater activity in the P13K-AKT pathway, which regulates uterine cell growth, in part through insulin-like growth factor 1 (IGF1), a hormone that encourages cell growth.

Researchers then exposed mice to both tamoxifen and alpelisib, a drug that blocks the P13K pathway and is also used in the treatment of breast cancer. The addition of alpelisib significantly decreased PI3K-AKT signaling, IGF1 receptor activation, and cell proliferation.

The study suggests that blocking the PIK3 pathway could reduce the low but concerning risk of tamoxifen-associated uterine cancer.

“Future clinical research can confirm whether combining non-mutant selective PI3K inhibitors with tamoxifen reduces the risk of uterine cancer and ultimately saves lives,” said co-corresponding author Rinath Jeselsohn, MD Director for ER+ Translational Discovery Research at Dana-Farber Cancer Institute and an Associate Member of the Broad Institute. “From a clinical perspective, it is also important to emphasize that tamoxifen does not cause mutagenesis in the uterus and this mechanism of tumor genesis is consistent with the fact that the risk of uterine cancer occurs during and shortly after tamoxifen and is not a lifetime risk.”

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