Why does tamoxifen work better in some women?

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The anti-hormone therapy tamoxifen can reduce breast cancer recurrence by about half in women with hormone-sensitive breast cancer. But it works better in some women than others. Researchers are not sure why.

"We do know that some tumors are inherently resistant to tamoxifen because of tumor genetic changes," says Daniel L. Hertz, Pharm.D.,

Ph.D., an assistant professor in the University of Michigan College of Pharmacy and member of the U-M Comprehensive Cancer Center.

"These tumor have found pathways to overcome anti-estrogen treatment. But we also believe some patients may be less likely to benefit from tamoxifen or endocrine therapy because of their genetics," Hertz says.

One theory is that in some patients, tamoxifen is not activated to the more potent estrogen inhibitor endoxifen. Patients with low levels of endoxifen may have worse outcomes on tamoxifen.

A meta-analysis by the International Tamoxifen Pharmacogenetics Consortium points to genetic variants. Researchers found patients with certain variants on the gene CYP2D6 had worse survival. Later analyses of prospective clinical trials, however, did not find the same link.

New research presented by Hertz at the San Antonio Breast Cancer Symposium examined these prior studies to assess whether errors in genotyping - how they identify the genetic variants - could have accounted for the differing findings. Statistical deviations seen in the original meta-analysis had been attributed to genotyping error. But their secondary analysis revealed that statistical deviations were linked to enrolling patients from multiple institutions, not genotyping error.

Furthermore, advanced statistical modeling from Hertz and colleagues confirms that genotyping error would introduce negligible bias to the analyses of the prospective trials.

"Genotyping from the tumor in these prospective clinical trials is not the reason these analyses are negative," Hertz says. "Either there is some other reason that the later studies were negative or the initial study suggesting CYP2D6 as a marker was falsely positive."

This leaves more questions than answers about tamoxifen efficacy.

In another study presented in San Antonio, Hertz and colleagues found that variants in CYP2D6 and another gene, CYP2C9, contribute to endoxifen exposure. Hertz suggests that it may not be one single marker that predicts whether tamoxifen works.

"At this point we still have a hypothetical association between genotype and efficacy that has not been validated," he says. "For now, there is no clinical benefit to using CYP2D6 to inform tamoxifen treatment decisions. We need to validate these hypotheses."

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