

# Increased Risk of Breast Cancer Recurrence in Women Initiating Tamoxifen with CYP2D6 Inhibitors

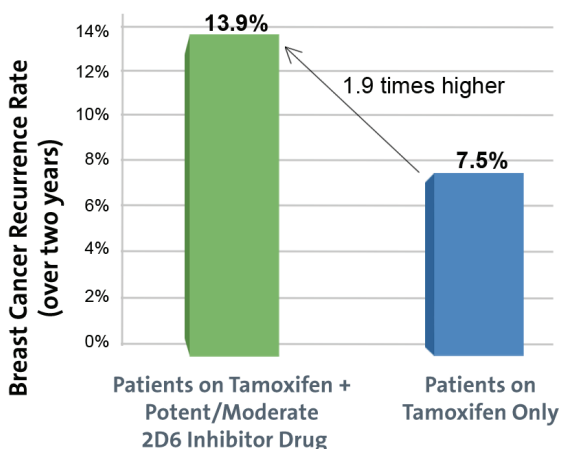
Based on a study by Medco Health Solutions, Inc. and the Indiana University School of Medicine; presented on May 30, 2009 at the 2009 American Society of Clinical Oncology (ASCO) Annual Meeting

## Background

Tamoxifen is one of the oldest and most widely used treatments for reducing the risk of breast cancer recurrence among women with estrogen-dependent tumors. Approximately a half-million women take tamoxifen in the United States, with 80,000 new patients starting the treatment each year. Tamoxifen works by blocking the estrogen receptors in breast cells and can reduce the risk of breast cancer recurrence by up to 50%. The drug is converted to its active form, known as endoxifen, by the liver enzyme cytochrome P450 2D6 (CYP2D6). A number of medications including some popular antidepressants that are frequently prescribed to treat depression and hot flashes, a common side effect of tamoxifen, can inhibit the functioning of this enzyme and reduce the effectiveness of the breast cancer drug. This effect is also naturally occurring in up to 10% of the population who have a genetic variation that decreases the functioning of CYP2D6. Our study examines the impact the use of CYP2D6 inhibitor medications has on the rate of breast cancer recurrence in women being treated with tamoxifen and specifically looks at the effects of different selective serotonin reuptake inhibitors (SSRIs).

## Data and Methods

Breast Cancer Recurrence in Patients Using Only Tamoxifen versus Patients Using Tamoxifen and a Potent/Moderate CYP2D6 Inhibitor



Using the National Medco Integrated Database System comprised of medical and pharmacy data claims for 10.7 million U.S. health plan members, we identified women with breast cancer who were newly prescribed tamoxifen therapy within a 30-month period from 2003 to 2005 and were on the medication for at least a two-year follow-up period, with the average being 2.7 years. All patients were persistent with their tamoxifen therapy and had to be at least 70% compliant; on average, patients were 90% compliant throughout the study. The sample, consisting of 1,298 women, was initially divided into two study groups; one cohort was made up of patients who, in addition to their tamoxifen treatment, were also taking a medication known to be a potent or moderate CYP2D6 inhibitor. Over the course of the study period, 27% (353) of these women took a potent/moderate CYP2D6 inhibitor in conjunction with tamoxifen. The average duration of concurrent use of tamoxifen and CYP2D6 inhibitors was 340 days. The other cohort consisted of 945 patients on tamoxifen therapy who were not using any CYP2D6 inhibitor medications during the study period.

A subsequent analysis was conducted based on findings that 60% of the women on a CYP2D6 inhibitor were using an SSRI. A subset consisting of women using any SSRI in addition to tamoxifen was examined. The group was split into two cohorts, one including 213 women who were taking a potent/moderate CYP2D6 inhibitor SSRI [Prozac® (fluoxetine), Paxil® (paroxetine) and Zoloft® (sertraline)], and one made up of 137 women on a weak CYP2D6 inhibitor SSRI [Celexa® (citalopram), Lexapro® (escitalopram) and Luvox® (fluvoxamine)].

The median age of the women in the group using a CYP2D6 inhibitor was 53 and for the tamoxifen-only cohort it was 52. The procedures the patients had undergone to treat their breast cancer included mastectomy, lumpectomy, lymph node dissection and radiation therapy.

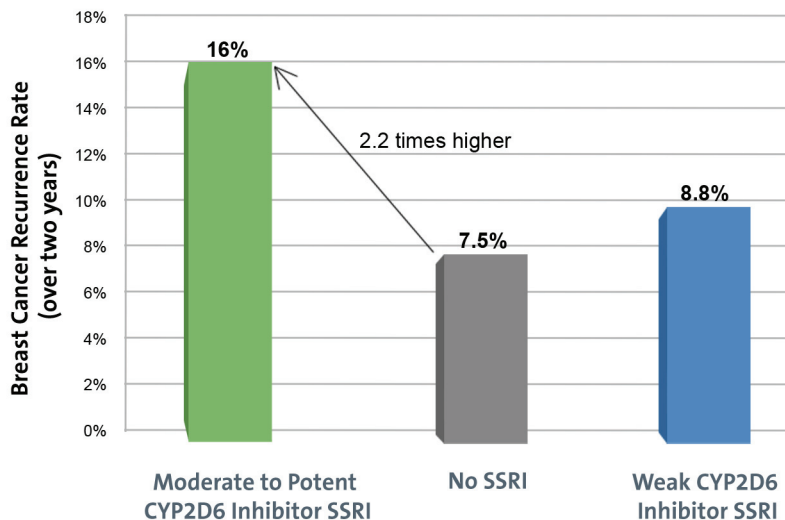
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## Results

Patients taking a potent/moderate CYP2D6 inhibitor while using tamoxifen had a two-year breast cancer recurrence rate of 13.9%, a statistically significant 1.9 times higher recurrence rate than those only using tamoxifen (7.5%). The subgroup of women on an SSRI that was a potent/moderate CYP2D6 inhibitor had an even higher rate of recurrence of 16.0%, while patients on an SSRI that was a weak inhibitor showed a breast cancer recurrence rate of 8.8%, which is not statistically different from the rate of recurrence of patients only taking tamoxifen. These findings support a clinically important drug interaction between tamoxifen and CYP2D6 inhibitors that results in nearly doubling the risk of a breast cancer recurrence for women taking any type of CYP2D6 inhibitor medication and showed a 2.2 times higher risk for women using fluoxetine, paroxetine and sertraline in conjunction with tamoxifen. The study also established that within the SSRI drug class, there are a number of drugs that have a weak inhibiting effect and do not pose any increased risk for breast cancer patients on tamoxifen.

### Breast Cancer Recurrence in Patients on Tamoxifen and SSRI



## Discussion

This is the largest study to date linking CYP2D6 inhibitors with a decrease in tamoxifen effectiveness and a substantial increase in the risk of recurrent breast cancer; it is also the first study to show the comparative impact of various antidepressants on breast cancer recurrence. Given the body of literature that now exists showing that certain SSRIs reduce the effectiveness of tamoxifen and increase breast cancer recurrence risks, as well as the availability of alternative medications, it is reasonable to conclude that potent/moderate CYP2D6 inhibitor SSRIs should be avoided in patients on tamoxifen.

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