

# TAMOXIFEN AND HIGH RISK WOMEN TO PREVENT BREAST CANCER

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Recently a study was presented at the American Society of Clinical Oncology to outline the potential benefits of Tamoxifen use, a hormonal oral therapy, in an attempt to decrease the risk of development of breast cancer in women who are deemed high risk.

Currently, breast cancer is the number one malignancy in women and the second cause of cancer death in the United States in women.

There has been a variety of strategies over the years to decrease the death rate from breast cancer. These have included encouraging women to perform self-examination, having routine physician examination, undergoing mammography as well as addressing high-risk groups.

National surgical adjuvant breast project study produced the FDA to approve Tamoxifen to decrease the risk of breast cancer in high-risk women. Tamoxifen was first approved by the FDA in 1978. At that time it was used for women with advanced breast cancer.

Subsequently, its use was moved up to the adjuvant setting. Adjuvant means that there was no evidence of breast cancer but that the administration of the agent could diminish recurrence rates of breast cancer.

It was recommended for use in women with estrogen receptor cancer. Estrogen receptor are proteins on the cancer surface and can be detected by pathologists. Essentially, every woman with breast cancer will know whether their breast cancer is estrogen receptor positive or negative.

When studied in the adjuvant setting, Tamoxifen five years after diagnosis reduced breast cancer recurrence rates by 47% and decreased death rate by 26%. Statistical analysis was performed to show the importance of this.

There were other benefits of Tamoxifen observed in addition to reducing the recurrence rate of breast cancer. Tamoxifen also reduced the occurrence of contralateral breast cancers.

Contralateral breast cancers were reduced by 47% in women who took Tamoxifen for five years. Furthermore, this same National Surgical Group called the NSABP reported that Tamoxifen reduced the rate of invasive breast cancer by 45% in the same breast when it was used in addition to lumpectomy and radiation when ductal carcinoma in situ, a pre-invasive breast cancer was diagnosed.

To enter in the prophylactic study for Tamoxifen, women were either 60 years or older and had lobular carcinoma in situ or 35 years of age and had a five year predicted risk of breast cancer development of 1.66% or greater. This risk factor was based on Gail model. The Gail model includes age, number of first degree relatives with breast cancer, number of prior breast biopsies, presence of atypical hyperplasia in the breast, age of first live birth and age at menarche or onset of menstruation.

In this study 13,388 women were randomized to either receive Tamoxifen or placebo. Seventy eight of the people continued on the therapy in the study. At the conclusion of the study Tamoxifen reduced the rate of invasive breast cancer by 49%.

The rate of breast cancer development was 43.4 per thousand women in the placebo group compared to 22.0 per thousand women in the Tamoxifen group.

In the Tamoxifen group there was a 1.3% chance of breast cancer at five years compared to a 2.6% chance of breast cancer when placebo was given. Furthermore, diminishing breast cancer occurred in all age groups. In women 49 years or younger there was a 44% reduction. In women 50 to 59 there was a 51% reduction and women 60 years or older there was a 55% reduction in breast cancer. Non-invasive breast cancer such as ductal carcinoma in situ was also decreased in the Tamoxifen group by 50%.

For those with lobular carcinoma in situ by history there was a 56% reduction and those with atypical hyperplasia there was an 86% reduction in breast cancer.

That was an American study. There were also European studies including one from the United Kingdom and another from Italy. The English study was smaller and the Italian allowed the use of hormonal replacement therapy and had different risk groups and showed no benefit of Tamoxifen in preventing breast cancer.

For women with ductal carcinoma in situ there is a 3.3% risk of contralateral breast cancer at five years. Tamoxifen reduces this rate by 47% and overall the risk of all new breast cancers in women with diagnosed ductal carcinoma in situ was reduced from 13% to 8.8% when using Tamoxifen. This reduction is 44%.

Another issue is how late can Tamoxifen be safely and effectively implemented? A French study looked at 524 women with breast cancer who received no hormonal therapy yet had been diagnosed two years earlier. They were randomized to receive either Tamoxifen or not.

There was a 38% reduction in breast cancer when Tamoxifen was used. Another study looked at 140 breast cancer patients treated 2 months to ten years after diagnosis. There, there was a survival benefit for the group receiving Tamoxifen. This study undertaken by Chlebowski et al and published in the Journal of Clinical Oncology looked at a variety of other issues as well.

There was an increased rate of endometrial cancer in women not having a hysterectomy who received Tamoxifen. The relative risk was 2.53. It was mainly seen in women older than 50. Cancers developed were felt not to be more aggressive than usual.

Some suggest that using Tamoxifen for five years quadruples the rate of endometrial cancer creating an excess death from endometrial cancer of about one to two per hundred thousand post-menopausal women.

The authors noted that the increase in endometrial cancer was half as great as the decrease in contralateral breast cancer development and that, "endometrial cancer less commonly results in a fatal outcome."

The authors note that screening for endometrial cancer in women on Tamoxifen lack data proving effectiveness. Recommended are annual gynecologic evaluations including PAP smear and pelvic exams and thorough evaluation of any vaginal bleeding.

NSABP study evaluated coronary artery disease associated with Tamoxifen. There was no benefit seen to coronary artery disease for women taking Tamoxifen compared to placebo although Tamoxifen has been alleged to improve lipid profile. Other studies had shown beneficial effect by Tamoxifen on coronary artery disease.

The authors reported that in post-menopausal breast cancer, patients who take Tamoxifen as adjuvant therapy, bone mineral density preservation has been reported. In a negative vein, vascular events including stroke, pulmonary and leg blood clots were common in women taking Tamoxifen when compared to placebo. In this NSABP study there was 110 events in women on Tamoxifen compared to 77 in women on placebo.

The risks of Tamoxifen in vascular events was in the same category as women taking hormonal replacement therapy. There is a slight increase in cataract rates in women on Tamoxifen yet there was no adverse mental function or depression seen in women taking Tamoxifen therapy.

Hot flashes and vaginal discharges were seen more frequently in Tamoxifen takers than placebo. The authors concluded that the NSABP study, "supports a role for Tamoxifen therapy in reducing the risk in breast cancer."

Thus, a great amount of information is available for women who are at risk but yet do not have a diagnosis of breast cancer. It appears from American data that Tamoxifen can indeed lower the risk of breast cancer. It is generally considered a safe agent and in women who are at high risk should speak with their physicians and learn their risk on the Gail model for breast cancer.

Women properly informed can make the best decision.