Breast Cancer Prevention: Concept to Reality

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Tamoxifen has been used clinically for more than 30 years (*1*). The compound is a nonsteroidal antiestrogen that has been extensively investigated in randomized clinical trials. Tamoxifen is now proven as the endocrine treatment of choice for all stages of estrogen receptor (ER) positive breast cancer (*2*) and it is calculated that 400,000 women are alive today because of tamoxifen treatment.

The success of tamoxifen in the treatment of breast cancer (*3*) focused all efforts on studying the long term safety and pharmacology of the drug as a potential chemopreventive in well women. The recognition in the laboratory that tamoxifen was not simply an antiestrogen at all sites, but a selective estrogen receptor modulator (SERM) allowed the consideration of tamoxifen use in well women to prevent breast cancer (*4*). Selective estrogen receptor modulation in post-menopausal women is demonstration by an estrogen-like effect on bones (*5*) and an estrogen-like action to lower circulating cholesterol (*6*), but an antiestrogenic effect on the growth of hormone dependent breast cancer (*2*). These data permitted the chemopreventive trial by the NSABP to go ahead in 1993. The results now show that tamoxifen reduces the incidence of breast cancer in high-risk women by 50% (*7*). However, in post-menopausal women, there is a modest increase in endometrial from 1 per 1000 to 4 per 1000 women. No deaths occurred from endometrial cancer in tamoxifen-treated women (*7*). After

extensive review, tamoxifen is the first drug to be available in the United States for the prevention of breast cancer and, indeed, any cancer.

In the search for improvements, we suggested a new chemoprevention strategy in 1990 (*3*). *Is this the end of the possible applications for antiestrogens? Certainly not. We have obtained valuable clinical information about this group of drugs that can be applied in other disease states. Research does not travel in straight lines and observations in one field of science often become major discoveries in another. Important clues have been garnered about the effects of tamoxifen on bone and lipids so it is possible that derivatives could find targeted applications to retard osteoporosis or atherosclerosis. The ubiquitous application of novel compounds to prevent diseases associated with the progressive changes after menopause may, as a side effect, significantly retard the development of breast cancer. The target population would be postmenopausal women in general, thereby avoiding the requirement to select a high-risk group to prevent breast cancer* (*3*)

Raloxifene is the result, and it has been shown to be effective at maintaining bone density and preventing fractures (*8,9*). Raloxifene is the second SERM to be used in general medicine (tamoxifen is the first). Most importantly, osteoporotic patients treated with raloxifene have a significant decrease in breast cancer incidence (*10*). Endometrial cancer is not significantly increased above placebo treated control (*10*). These data have advanced the testing of raloxifene as a breast cancer preventive in post-menopausal

women. At present, the study of tamoxifen and raloxifene is recruiting 22,000 high-risk women in the United States and Canada. Results should be available in 2005.

The question is why is raloxifene different than tamoxifen? The molecular mechanism of action of these two SERMs has been elucidated at the ER (*11,12*) and distinct differences in the estrogen-like properties of the complexes can be defined by structure function relationship studies. These data are important to design the next generation of SERMs (*11*) and to identify new targets for therapeutic intervention.

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