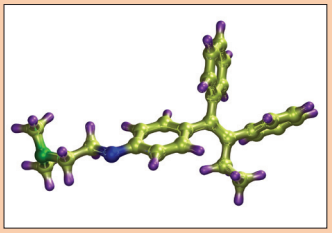
■ Journal Club Article

Tamoxifen Benefits and *CYP2D6* Testing in Women With Hormone Receptor–Positive Breast Cancer

Marcelle Kaplan, RN, MS, AOCN®, CBCN®, and Suzanne M. Mahon, RN, DNSc, AOCN®, APNG



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Cancer intervention strategies have been increasingly focused on developing therapies that are personalized and tailored to each individual's unique genetic profile. Evolving understanding of the metabolism and pharmacogenomics of tamoxifen, an early example of targeted therapy for women with hormone receptor–positive breast cancer, has created decision-making challenges for healthcare providers and their patients. This article reviews the pharmacology of tamoxifen, the genetics and physiology of the *CYP2D6* enzyme system that has important effects on tamoxifen metabolism, and subset data analyses from large controlled, clinical trials that cast new light on previously held beliefs about the utility of *CYP2D6* genotyping for predicting tamoxifen effectiveness and improved breast cancer outcomes in women with early-stage, hormone receptor–positive breast cancer.

Marcelle Kaplan, RN, MS, AOCN®, CBCN®, is a breast oncology consultant and an adjunct professor in the School of Nursing at Adelphi University in Long Island, NY, and Suzanne M. Mahon, RN, DNSc, AOCN®, APNG, is a professor in the Department of Internal Medicine and in the School of Nursing at Saint Louis University in Missouri. The authors take full responsibility for the content of the article. The authors did not receive honoraria for this work. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the authors, planners, independent peer reviewers, or editorial staff. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the *Clinical Journal of Oncology Nursing* or the Oncology Nursing Society. Kaplan can be reached at marcelle.kaplan@gmail.com, with copy to editor at CJONEditor@ons.org. (Submitted June 2012. Revision submitted September 2012. Accepted for publication September 16, 2012.)

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A strong focus has been placed in recent years on the development of cancer therapies that are personalized and tailored to each individual's unique genetic profile. Great strides have been made in the area of breast cancer. The use of estrogen- and progesterone-receptor profiling, which began in the 1970s (McGuire, Horowitz, Pearson, & Segaloff, 1977), represents one of the earliest applications of personalized medicine. Evolving understanding of the pharmacogenomics of tamoxifen, an early example of targeted therapy for women with hormone receptor–positive breast cancer, has created decision-making challenges for healthcare providers and their patients. This article will review the pharmacology of tamoxifen, the genetics and physiology of *CYP2D6*, and the clinical implications of both for women with hormone receptor–positive breast cancer.

Pharmacology of Tamoxifen

Adjuvant treatment with tamoxifen therapy over a period of five years has been shown to provide substantial benefit in hormone (estrogen and/or progesterone) receptor–positive breast cancer (stage not specified), reducing disease recurrence by about 50% and breast cancer mortality by about 33% after 15 years of follow-up (Rae et al., 2012). For premenopausal women with hormone-sensitive breast cancer, tamoxifen is the sole choice for adjuvant hormonal therapy (Hertz, McLeod, & Irvin, 2012). As an antiestrogenic agent, tamoxifen has a stronger binding affinity with the estrogen receptor (ER) than does estrogen. However, the tamoxifen compound itself is a relatively weak ER antagonist and is considered a prodrug; the antiestrogenic properties of tamoxifen are derived from its metabolites. The most clinically active metabolite is endoxifen, which has 30- to 100-fold greater affinity for the ER than tamoxifen (Regan et al., 2012; Snozek, O'Kane, & Algeciras-Schimnich, 2009).

The primary mediator in the conversion of tamoxifen to endoxifen is the cytochrome P450 2D6 (*CYP2D6*) enzyme system (Gaston & Kolesar, 2008; Kelly & Pritchard, 2012; Rae et al., 2012). *CYP2D6* activity is genetically coded by a specific gene, but inherited genetic alterations, called *CYP2D6* polymorphisms, can result in variations in enzymatic activity (Gaston & Kolesar, 2008). The *CYP2D6* system also is involved in the metabolism of many drug classes, including such common drugs as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), opioid analgesics, antipsychotic agents, antiarrhythmic agents, and antihistamines (Gaston & Kolesar, 2008).