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Pharmacogenomic Variation of *CYP2D6* and the Choice of Optimal Adjuvant Endocrine Therapy for Postmenopausal Breast Cancer: A Modeling Analysis

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Abstract

Background—Adjuvant endocrine treatment with aromatase inhibitors improves disease-free survival compared with tamoxifen in postmenopausal women with estrogen receptor–positive breast cancer. This difference could be due to differences in tamoxifen metabolism because levels of endoxifen, the active tamoxifen metabolite, vary with the number of mutant alleles, including the *4 allele, of the gene encoding cytochrome P450 2D6 (*CYP2D6*).

Methods—We created a Markov model to determine whether tamoxifen or aromatase inhibitor monotherapy maximized 5-year disease-free survival for patients with the wild-type *CYP2D6* genotype (wt/wt). Annual risks of recurrence with aromatase inhibitors and tamoxifen in breast cancer patients who were not selected by *CYP2D6* genotype were derived from the Breast International Group 1–98 trial. Genotype frequencies and the hazard ratio for cancer recurrence on tamoxifen among patients with the *4/*4 genotype relative to the wt/wt or wt/*4 genotypes ($HR_{*4/*4} = 1.86$) were based on data from an analysis of the North Central Cancer Treatment Group trial of adjuvant tamoxifen. We explored the impact of *CYP2D6* (*4) heterozygosity on disease-free survival for wt/wt patients by studying a range of effect (ie, recurrence on tamoxifen) estimates, from no effect of the single mutation ($Eff_{wt/*4} = 0$, recurrence rate in wt/*4 patients same as that in wt/wt patients) to complete effect ($Eff_{wt/*4} = 1$, recurrence rate in wt/*4 patients same as that in *4/*4 patients).

Results—With $HR_{*4/*4} = 1.86$ and $Eff_{wt/*4} = 0.5$, the 5-year disease-free survival of tamoxifen-treated patients with no mutations (wt/wt) was 83.9%, that is, essentially the same as that (84.0%) for genotypically unselected patients who were treated with aromatase inhibitors. With greater $HR_{*4/*4}$ estimates, disease-free survival with tamoxifen exceeded that with aromatase inhibitors in wt/wt patients, even at lower assumed $Eff_{wt/*4}$ ratios.

Conclusions—Modeling suggests that among patients who are wild type for *CYP2D6*, 5-year disease-free survival out-comes are similar to or perhaps even superior with tamoxifen than with aromatase inhibitors. Endocrine therapy tailored to *CYP2D6* genotype could be considered for women who are newly diagnosed with breast cancer, particularly those who have with concerns about either the relative toxicity or the increased cost of aromatase inhibitors.

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Adjuvant endocrine therapy reduces the risk of recurrence and improves survival among women with hormone receptor–positive breast cancer (1). Because most breast cancers, especially those among postmenopausal women, are hormone receptor positive, hundreds of thousands of women worldwide initiate adjuvant endocrine treatment each year. Historically, the standard recommendation for such patients has been 5 years of therapy with the selective estrogen receptor modulator tamoxifen (1).

Two large randomized clinical trials—the Breast International Group Trial 1–98 (BIG 1–98) (2) and the Arimidex, Tamoxifen Alone or in Combination trial (3)—have shown that initial adjuvant endocrine treatment with aromatase inhibitors yields improved disease-free survival compared with tamoxifen in postmenopausal women with estrogen receptor–positive breast cancer. These findings have led many oncologists to adopt aromatase inhibitors as their preferred initial adjuvant therapy for postmenopausal women with hormone receptor–positive breast cancer (4). However, interpretation of these trial results is complicated by new pharmacogenomic data that suggest that the clinical benefit of tamoxifen may vary according to the cytochrome P450 (CYP) 2D6 genotype of the patient (5–7).

CYP2D6 is the cytochrome P450 isoform that is mainly responsible for catalyzing the conversion of tamoxifen to endoxifen (8), the tamoxifen metabolite that is thought to be the primary mediator of estrogen-dependent suppression of cell proliferation (9). The *CYP2D6* gene has multiple allelic variants, some of which, including the *4 allele, result in the loss of CYP2D6 enzyme function. Population genetic studies (10–12) have revealed that variations in the *CYP2D6* gene sequence correspond to pharmacogenomic variations in endoxifen levels among women taking tamoxifen. For example, in a study of 80 newly diagnosed breast cancer patients who were beginning tamoxifen treatment, Jin et al. (10) found that those who carried either the homozygous (*4/*4) or the heterozygous (wt/*4) variant genotype of *CYP2D6* had statistically significantly lower mean plasma endoxifen levels (20.0 and 43.1 nM, respectively) than those who carried the homozygous wild-type (wt/wt) genotype (78.0 nM). Additional studies have also supported the finding of a *CYP2D6* gene dose effect on plasma concentrations of endoxifen (11,12). These data prompted a Food and Drug Administration advisory panel to recommend in October 2006 that a warning label be added to tamoxifen; the panel cited the new pharmacogenomic studies (5,12) indicating that the drug is less effective in women who carry a mutation in one of the enzymes used to metabolize tamoxifen than in those who do not.

Both of the landmark clinical studies (2,3) that revealed improved disease-free survival outcomes for up-front adjuvant treatment with aromatase inhibitors vs tamoxifen accrued patients irrespective of their *CYP2D6* gene mutation status. Given the link between *CYP2D6* mutation status and compromised clinical outcomes among mutation carriers on tamoxifen, it is likely that aromatase inhibitors would be the preferred treatment for a woman with deficiencies in tamoxifen metabolism, such as those heterozygous (wt/*4) or homozygous (*4/*4) for the *4 mutation of *CYP2D6*. However, for women who do not carry a *CYP2D6* gene mutation that affects tamoxifen metabolism, the decision about which type of adjuvant endocrine therapy to undergo is not as clear. To date, no genotype analysis of patients who participated in the randomized trials comparing adjuvant tamoxifen with aromatase inhibitors has been performed. However, it is reasonable to infer that if these trials had been restricted to women with wild-type tamoxifen metabolism, the women in the tamoxifen arms would have had better outcomes than those that were reported. To study the magnitude of difference between reported outcomes on tamoxifen and the estimated efficacy of tamoxifen in patients with-out *CYP2D6* gene mutations, we constructed a decision-analytic model using data from *CYP2D6* pharmacogenomic studies and used the model to evaluate whether an aromatase inhibitor or tamoxifen is the optimal initial treatment choice for the large

majority of postmenopausal women who do not carry a mutation that affects the function of the *CYP2D6* enzyme.

Methods

Model Design

We developed a Markov decision model (13) to simulate the clinical histories of hypothetical cohorts of postmenopausal women with hormone receptor–positive invasive breast cancer. The model simulated the transition between two health states—from being well with no evidence of cancer recurrence to having recurrent local or regional disease or being diagnosed with a new primary breast cancer—for women who are newly treated for breast cancer. In these simulations, women newly treated for breast cancer start in the “well” or “without disease” state and each month face a probability of experiencing a recurrence. The model was run 60 times using monthly cycles to calculate the 5-year disease-free survival probability. The model was designed and analyzed using TreeAge Pro 2005 software (TreeAge Software, Williamstown, MA).

Data Sources and Assumptions

Model estimates for recurrence probabilities by initial treatment—aromatase inhibitor or tamoxifen—were derived from the annual hazard rates from the BIG 1–98 (2) (Table 1 ; R. Gelber PhD, November, 2006, BIG 1–98 Steering Committee: personal communication). These estimates apply to all breast cancer patients in the study population regardless of *CYP2D6* genotype. We assumed that the recurrence probabilities during a given year were constant.

We then used the model to estimate recurrence probabilities for each *CYP2D6* (*4) genotype, that is, wild-type (wt/wt), heterozygous mutant (wt/*4), and homozygous mutant (*4/*4). Base case values for genotype-specific hazard ratios for recurrence were derived from a study by Goetz et al. (5), who analyzed the geno-types of postmenopausal women who were enrolled on the tamoxifen-only arm of a randomized North Central Cancer Treatment Group (NCCTG) trial (NCCTG 89-30-52). Of the 256 eligible patients who were assigned to this arm, 223 were genotyped (213 via paraffin-embedded tumor blocks and 10 via blocks of normal [ie, buccal] tissue). Clinical outcomes by *CYP2D6* (*4) mutation status were assessed for the 190 patients for whom the *CYP2D6* (*4) allele was successfully amplified. We assigned a hazard ratio for recurrence on tamoxifen among *4/*4 mutation carriers relative to the wild-type (wt/wt) and heterozygous (wt/*4) carriers ($HR_{*4/*4}$) of 1.86, that is, the hazard ratio with adjustment for clinical factors that was reported by Goetz et al. (5). In addition, we used the *CYP2D6* (*4) genotype frequency values reported by Goetz et al. (5) for the breast cancer patients in their study population: 72.1% for wt/wt, 21.1% for wt/*4, and 6.8% for *4/*4 (Table 1). We assumed that neither the hazard rate for recurrence on aromatase inhibitors nor the tumor stage varied by *CYP2D6* genotype.

We designed the model so that when the recurrence probabilities for each genotype were adjusted using the weight of their genotypic frequency and then combined, they produced a recurrence probability that was consistent with that of the genotypically unselected population on tamoxifen. The model was also calibrated to account for slight changes in genotypic frequencies within the disease-free patient population that occur over time as the relatively greater percentage of mutation carriers experience a recurrence and their representation among the “well” population declines. We then examined which of the two treatment strategies—tamoxifen or aromatase inhibitor monotherapy—optimized 5-year disease-free survival in the wild-type subgroup.

We defined the *effect* of having a single chromosome affected by the *CYP2D6* mutation in heterozygous patients as $Eff_{wt/*4}$. The increased hazard ratio of recurrence among heterozygous patients was defined by the following formula:

$$Eff_{wt/*4} \times (HR_{*4/*4}) + (1 - Eff_{wt/*4}) \times (\text{hazard ratio of recurrence in wt/wt patients}).$$

Data suggest an intermediate clinical phenotype for heterozygous (wt/*4) patients taking tamoxifen (6,7)—that is, outcomes for heterozygotes were between those for wild-type (wt/wt) and double mutant (*4/*4) patients—but small numbers have precluded precise estimates for the hazard ratio in heterozygous patients. Therefore, we varied the effect of a single *CYP2D6* (*4) mutation from 0 (ie, no effect of carrying a single mutation, where the hazard rate for wt/*4 equals that of wt/wt) to 1 (ie, complete effect, where the hazard rate for wt/*4 equals that of *4/*4 mutation carriers). In the base case analysis, we assumed that $Eff_{wt/*4} = 0.5$, which corresponds to a hazard ratio for recurrence among wt/*4 patients that is midway between that in patients who carried the *4/*4 mutation and that in wt/wt patients. Note that the formula for the recurrence rate in heterozygotes is dependent on $HR_{*4/*4}$ when $Eff_{wt/*4}$ is not equal to zero; because $HR_{*4/*4}$ is defined as a hazard ratio for recurrence on tamoxifen among *4/*4 mutation carriers relative to both the wild-type (wt/wt) and heterozygous (wt/*4) carriers, the calculation of $HR_{*4/*4}$ was determined by a formula that solved for both equations as well as adjusting for the change in genotype frequency over time.

Sensitivity Analyses

We performed a two-way sensitivity analysis to test the robustness of the results to variations in model parameters. We simultaneously varied $HR_{*4/*4}$ (the increased hazard ratio for recurrence on tamoxifen among *4/*4 patients relative to wt/wt and wt/*4 patients) from 1.0 (ie, no increased recurrence) to 3.0 and $Eff_{wt/*4}$ (the increased hazard ratio for recurrence on tamoxifen among wt/*4 patients relative to wt/wt patients) from 0 (ie, no increased recurrence) to 1.0 (ie, recurrence rate equals that of *4/*4 patients). This sensitivity analysis compared 5-year disease-free survival in wt/wt patients by treatment strategy for all possible combinations of $HR_{*4/*4}$ and $Eff_{wt/*4}$.

We also reran the model using data from a more recent analysis of the Goetz et al. cohort (7) that included information about the use of selective serotonin reuptake inhibitors (SSRIs)—agents that inhibit the function of the *CYP2D6* enzyme—so that patients who had received SSRIs could be excluded to allow for a more accurate assessment of the true effect of *CYP2D6* mutation on outcomes. With these patients excluded, NCCTG trial data revealed a hazard ratio for recurrence on tamoxifen for homozygous mutation carriers relative to both wild-type and heterozygous patients ($HR_{*4/*4}$) of 2.6 (95% confidence interval [CI] = 1.34 to 5.07) and for homozygous mutation carriers relative to wild-type patients alone of 2.9 (95% CI = 1.47 to 5.73); the hazard ratio for recurrence among heterozygous patients relative to wild-type patients was 1.60 (95% CI = 0.94 to 2.71) (M. Goetz MD, V. Suman PhD, June, 2007: personal communication). We examined the effect of using these estimates on outcomes for wild-type patients treated with tamoxifen in the two-way sensitivity analysis as described above.

CONTEXT AND CAVEATS

Prior knowledge

In two clinical trials, adjuvant endocrine treatment with aromatase inhibitors yielded improved disease-free survival compared with tamoxifen in postmenopausal women with

estrogen receptor–positive breast cancer. Recent pharmacogenomic data suggest that the clinical benefit of tamoxifen may vary with the number of mutant alleles the patient carries in the gene that encodes *CYP2D6*, the cytochrome P450 isoform that is mainly responsible for catalyzing the conversion of tamoxifen to its functional metabolite endoxifen.

Study design

A decision-analytic model was constructed using data from *CYP2D6* pharmacogenomic studies and used to evaluate whether an aromatase inhibitor or tamoxifen is the optimal initial treatment choice for postmenopausal women who do not carry a mutation that affects tamoxifen metabolism.

Contribution

Modeling suggests that among patients who are wild type for *CYP2D6*, adjuvant treatment with tamoxifen appears to provide 5-year disease-free survival outcomes that are similar or perhaps even superior to those achieved with aromatase inhibitors.

Implications

Endocrine therapy tailored to *CYP2D6* genotype could be considered for women who are newly diagnosed with breast cancer.

Limitations

The model relies on the assumptions and estimates used. The model cannot be used to study the question of whether or how to sequence therapy. The findings apply to only postmenopausal women.

Results

Our model, which was designed to reproduce the recurrence rates among patients in the BIG 1–98 trial (who were not selected by genotype), yielded a 5-year disease-free survival of 84.0% for those receiving aromatase inhibitors and 81.3% for those receiving tamoxifen. We used this model to examine disease-free survival by *CYP2D6* genotype. In the base case analysis, we assumed an increased hazard ratio for recurrence on tamoxifen for homozygous mutation carriers (*4/*4; 6.8% of patients) of 1.86 relative to wt/wt and wt/*4 patients. In the base case analysis, we also assigned heterozygous patients (wt/*4; 21.1% of patients) a hazard ratio of recurrence on tamoxifen halfway between that of the homozygous mutation carriers and wild-type patients ($\text{Eff}_{\text{wt}/*4} = 0.5$). With these parameters, the 5-year disease-free survival of tamoxifen-treated patients with no mutations (wt/wt) was 83.9%, that is, essentially the same as that for genotypically unselected patients who were treated with aromatase inhibitors. Figure 1 displays the disease-free survival curves for patients treated with aromatase inhibitors and tamoxifen in the genotypically unselected population as well as those for patients in each genotype subgroup (wt/wt, wt/*4, and *4/*4), as modeled using the basic assumptions of $\text{HR}_{*4/*4} = 1.86$ and $\text{Eff}_{\text{wt}/*4} = 0.5$.

To examine the robustness of our findings across a range of assumptions for the impact of heterozygosity at the *CYP2D6* locus and hazard ratios for recurrence among homozygous mutation carriers, we conducted a two-way sensitivity analysis that simultaneously varied $\text{HR}_{*4/*4}$ and $\text{Eff}_{\text{wt}/*4}$ (Table 2 and Figure 2). The highest value of $\text{HR}_{*4/*4}$ tested in the sensitivity analysis—3.0—was the one at which 5-year disease-free survival estimate for homozygous mutation carriers approximated that for patients not receiving any hormonal therapy (1).

The data shown in Table 2 and Figure 2 are for wild-type patients only. Although the $HR_{*4/*4}$ and $Eff_{wt/*4}$ parameters directly influence the recurrence rates in mutation carriers only, outcomes among wild-type patients are also an indirect function of these parameters because the weighted sum of the genotype-specific curves is a fixed value. Increases in the $HR_{*4/*4}$ and $Eff_{wt/*4}$ values (ie, moving to the right and down, respectively, in Table 2) resulted in a higher recurrence rate among mutation carriers and thereby increased the 5-year disease-free survival probability for wild-type patients.

Figure 2 displays results of the two-way sensitivity analysis in graphical form. Each point on this figure can be described by an (x,y) coordinate. The x-axis plots $HR_{*4/*4}$, and the y-axis plots $Eff_{wt/*4}$. Each (x,y) point represents a unique $HR_{*4/*4}$ and $Eff_{wt/*4}$ combination. The shading of an (x,y) point corresponds to the treatment strategy that maximizes 5-year disease-free survival in wt/wt patients—gray for upfront treatment with an aromatase inhibitor, white for upfront treatment with tamoxifen—for that particular combination of $HR_{*4/*4}$ and $Eff_{wt/*4}$. The white “zone” therefore depicts the combinations of $HR_{*4/*4}$ and $Eff_{wt/*4}$ parameters for which tamoxifen optimizes 5-year disease-free survival in the wt/wt subgroup, whereas the gray zone depicts those for which aromatase inhibitors optimize 5-year disease-free survival in this subgroup.

This sensitivity analysis allows for the rapid interpretation of results when further relevant data become available. For example, by using the updated but unadjusted estimates from the NCCTG trial data ($HR_{*4/*4} = 2.6$ and hazard ratio for recurrence for wt/*4 patients relative to wt/wt of 1.60; M. Goetz MD, V. Suman PhD, June, 2007; personal communication), we calculated an $Eff_{wt/*4}$ of 0.316. We then used our two-way sensitivity analysis to examine the optimal treatment strategy among wt/wt patients with these updated estimates and found that with an $HR_{*4/*4}$ of 2.6 and a calculated $Eff_{wt/*4}$ of 0.316 wt/wt patients who receive upfront treatment with tamoxifen should have better 5-year disease-free survival than those who receive upfront treatment with aromatase inhibitors (asterisk in Figure 2).

Likewise, our base case analysis used a hazard ratio of recurrence on tamoxifen for heterozygous patients that was halfway between that for the homozygous mutation carriers and that for wild-type patients ($Eff_{wt/*4} = 0.5$). However, Table 2 reveals that with an $HR_{*4/*4}$ of 2.0, even with a smaller difference between the effect of tamoxifen in heterozygous and wild-type patients, wild-type patients treated with tamoxifen would have disease-free survival that was similar to that of patients treated with an aromatase inhibitor (eg, 83.2% vs 84.0% at $HR_{*4/*4} = 2.0$ and $Eff_{wt/*4} = 0.25$).

Discussion

The effect of genotypic variation in *CYP2D6* on tamoxifen metabolism is one of the best characterized and most clinically important examples of pharmacogenomics in cancer. We used decision-analytic modeling of the available data to explore how *CYP2D6* variation might influence adjuvant therapy recommendations for postmenopausal women with breast cancer. We found that among patients who are homozygous wild type for *CYP2D6*, adjuvant treatment with tamoxifen appears to provide 5-year disease-free survival outcomes that are similar or perhaps even superior to those achieved with aromatase inhibitors. This finding differs from the results of clinical trials in unselected populations, in which aromatase inhibitors have demonstrated statistically significant improvements in disease-free survival over tamoxifen (2,3).

A limitation inherent to all modeling studies, including ours, is the reliance of the model on the assumptions and estimates used. The validity of our findings therefore rests on the soundness of the estimated hazard ratios for recurrence for tamoxifen-treated patients with

homozygous or heterozygous mutations at the *CYP2D6* locus used in the model. Our base case model assumed an $HR_{*4/*4}$ of 1.86, which was derived from the adjusted hazard ratio for recurrence on tamoxifen among *CYP2D6* $*4/*4$ mutation carriers that was seen in NCCTG trial (5). Emerging data from other groups support this hazard ratio estimate. For example, a German study (6) estimated a hazard ratio for event-free survival of 1.89 (95% CI = 1.10 to 3.25) among a pooled sample of women homozygous or heterozygous for either the $*4$ mutation or the much less frequent *CYP2D6* $*5$ mutation. A revised analysis of the NCCTG trial that defined patients on SSRIs as well as those who were homozygous mutation carriers as “poor metabolizers” found an adjusted hazard ratio for disease-free survival on tamoxifen of 2.2 ($P = .02$) (14). As shown by our two-way sensitivity analysis (Figure 2), with this hazard ratio for homozygous mutation carriers, as long as the $Eff_{wt/*4}$ (proportion of $HR_{*4/*4}$ attributed to $wt/*4$) is as little as 0.34, tamoxifen would be the preferred treatment choice for wt/wt patients. If we used the hazard ratios estimated after excluding SSRI-treated patients ($HR_{*4/*4}$ of 2.6 and a calculated $Eff_{wt/*4}$ of 0.316), wild-type patients who receive initial treatment with tamoxifen would have better 5-year disease-free survival than those who receive initial treatment with aromatase inhibitors. However, the size of the cohort after exclusion of the SSRI-treated patients was too small to allow the investigators to generate hazard ratio estimates adjusted for potential confounding factors. We chose to use the adjusted estimates from their full cohort in our base case analysis, thus introducing an intentional conservative bias.

In addition, our model results are heavily dependent on the estimates we used for the efficacy of tamoxifen in heterozygous patients. Our base case analysis used a hazard ratio of recurrence on tamoxifen for heterozygous patients that was halfway between that for the homozygous mutation carriers and that for wild-type patients ($Eff_{wt/*4} = 0.5$). Although some clinical data support an intermediate phenotype, or gene-dose effect, for heterozygous patients on tamoxifen (6,7), we do not currently have precise estimates for the hazard ratio of recurrence in this subgroup. We therefore studied the range of tamoxifen effects in heterozygotes, including the assumptions that an intermediate level of endoxifen is completely inactive (ie, $Eff_{wt/*4} = 1$) and that it is maximally active ($Eff_{wt/*4} = 0$). However, even when we assumed a much smaller difference between the effect of tamoxifen in heterozygous and wild-type patients than halfway between that for $*4/*4$ and wt/wt patients (ie, $Eff_{wt/*4} = 0.5$), disease-free survival for wild-type patients on tamoxifen appeared to be similar to that of patients treated with an aromatase inhibitor (eg, 83.2% vs 84.0% at $HR_{*4/*4} = 2.0$ and $Eff_{wt/*4} = 0.25$; Table 2).

Other key assumptions of our model were that cancer type, cancer stage, and the efficacy of treatment with aromatase inhibitors do not vary by *CYP2D6* genotype. A growing body of literature supports these assumptions. For example, genotype analysis revealed no statistically significant association between *CYP2D6* mutation status and tumor size, nodal status, or histologic grade in women who were or were not treated with tamoxifen (6). The same study found no differences in clinical outcome by *CYP2D6* genotype among women who did not receive tamoxifen (6). Finally, aromatase inhibitors do not undergo conversion to active metabolites (15), and there are no in vitro data to suggest the metabolism of these agents by the *CYP2D6* enzyme. Nevertheless, it is possible that unknown factors may contribute directly to the worse clinical outcomes experienced by *CYP2D6* mutation carriers.

Our model was designed to examine the initial use of either tamoxifen or aromatase inhibitors. However, postmenopausal breast cancer patients may receive sequential therapy with tamoxifen followed by an aromatase inhibitor (16). There is the possibility that sequential tamoxifen followed by aromatase inhibitor treatment might improve disease-free survival more than aromatase inhibitor therapy alone, as suggested by meta-analyses of

clinical trials (17) and by our previous modeling efforts (18,19). Because the hazard ratios for recurrence on aromatase inhibitors after tamoxifen therapy are not currently available for *CYP2D6* genotype subgroups, we could not use this model to study the question of whether or how to sequence therapy. In addition, because the data informing our model estimates were derived from trials in postmenopausal women and because aromatase inhibitors are not effective in premenopausal women (20), our findings apply to only postmenopausal women.

What are the implications of our findings for tailored therapy based on *CYP2D6* genotype? Currently, there is no widespread testing for *CYP2D6* gene mutations in breast cancer patients, and the role for such testing to guide endocrine therapy decisions is not well established. Although our findings were based on a model with embedded assumptions and estimates, the model itself was simple and incorporated values for genotype frequencies and only two parameters ($HR_{*4/*4}$ and $Eff_{wt/*4}$) along with the results of a large randomized clinical trial that compared treatment with adjuvant tamoxifen vs aromatase inhibitors. Our model had no embedded assumptions regarding the natural history of breast cancer; instead, it used the direct patient outcome data provided by a randomized trial. Confirmatory pharmacogenomic analyses of *CYP2D6* genotype and clinical outcomes (6,7) suggest that any bias in the estimates used in our base case model would have caused us to underestimate rather than overestimate the effectiveness of tamoxifen in wild-type patients. Nevertheless, our model is still only a model that used estimates for key parameters that were based on analyses of small numbers of women. The most direct method of establishing these parameters would be through genotype analysis of women who are enrolled in the large randomized trials of tamoxifen vs aromatase inhibitors. In the absence of such information, we cannot make any definite recommendations regarding whether or which patients should undergo genetic testing.

However, while we await direct comparisons of outcomes by genotype, decisions about adjuvant endocrine treatment are being made for thousands of postmenopausal women who are newly diagnosed with breast cancer. Our model raises the possibility that tailored therapy based on pharmacogenomics could be considered for such women. In particular, women who are concerned about the relative toxicity or cost of an aromatase inhibitor as initial treatment might consider *CYP2D6* genetic testing and pursue treatment with tamoxifen if found to be wild type at *CYP2D6*. To obtain definitive recommendations about genetic testing, studies that explore associations among *CYP2D6* genotype, endoxifen levels, and efficacy of tamoxifen vs aromatase inhibitors are of tremendous interest and importance. Because the vast majority of breast cancers in postmenopausal women are estrogen receptor positive and the majority of women who are diagnosed with breast cancer do not carry a *CYP2D6* gene mutation, results of such studies could have important implications for the treatment of breast cancer.

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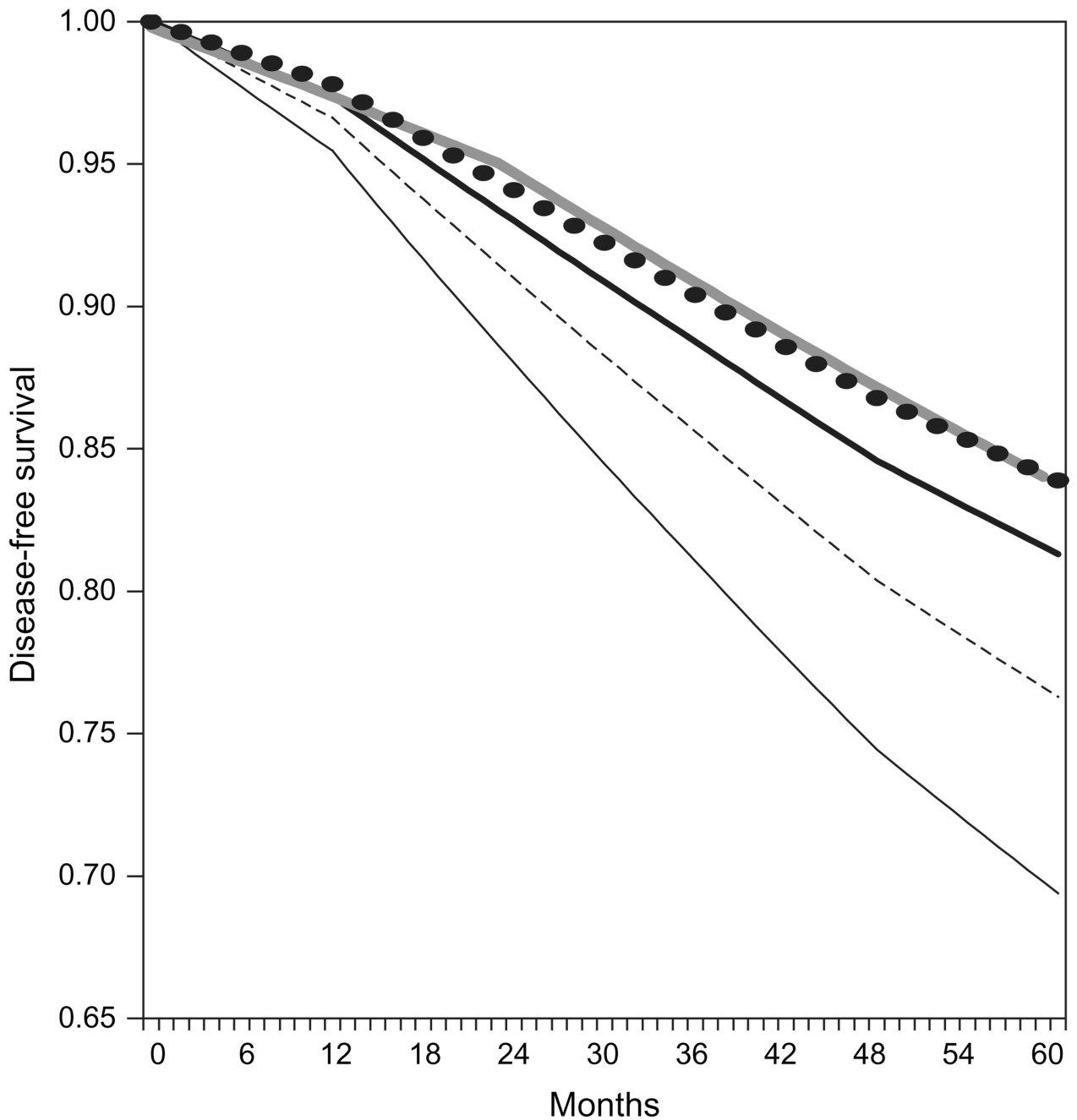


Figure 1.

Model results for disease-free survival in the unselected population and in each genotypic subgroup. For these analyses, we assumed a hazard ratio of recurrence in homozygous mutation carriers ($*4/*4$) of 1.86 ($HR_{*4/*4} = 1.86$) and that the increased hazard ratio in heterozygotes ($wt/*4$) was half that in $*4/*4$ homozygotes. The **thick gray line** represents the aromatase inhibitor strategy in the unselected population. The **thick black line** represents in the tamoxifen strategy in the unselected population. The tamoxifen strategy in the wild-type (wt/wt) subgroup is shown as **black circles**, in the $wt/*4$ subgroup as a **thin dashed black line**, and in the $*4/*4$ subgroup as a **thin solid black line**.

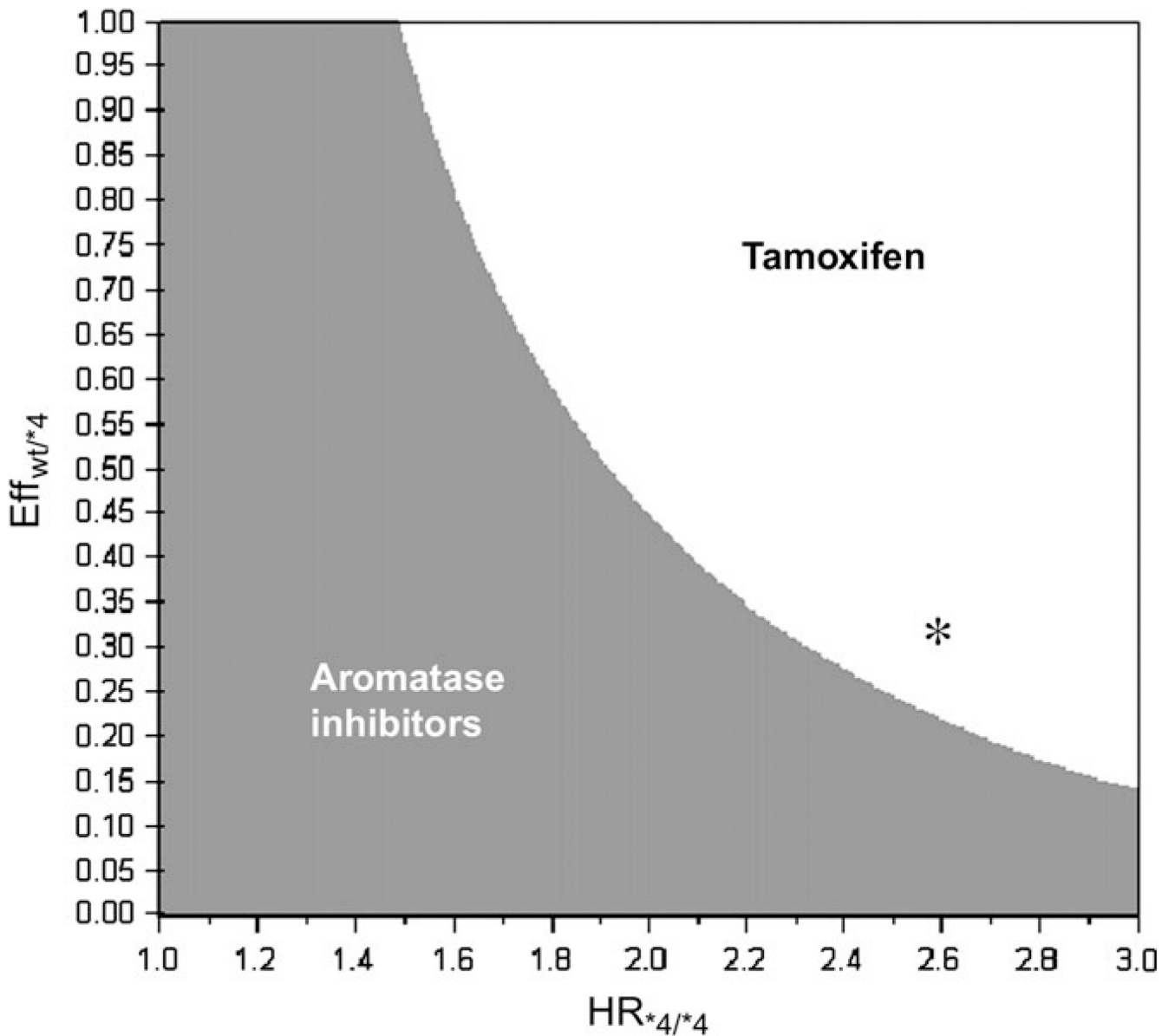


Figure 2.

Two-way sensitivity analysis for the wild-type (wt/wt) subgroup. The hazard ratio of recurrence among the homozygous mutation carriers ($HR_{*4/*4}$) is plotted on the x-axis, and proportion of $HR_{*4/*4}$ attributed to heterozygotes ($Eff_{wt/*4}$) is plotted on the y-axis. The **gray zone** represents the combinations of $Eff_{wt/*4}$ and $HR_{*4/*4}$ for which aromatase inhibitors optimize 5-year disease-free survival for wt/wt patients. The **white zone** represents the combinations of $Eff_{wt/*4}$ and $HR_{*4/*4}$ for which tamoxifen optimizes 5-year disease-free survival for these patients. The **asterisk** marks the combination of $HR_{*4/*4}$ and calculated $Eff_{wt/*4}$ —2.6 and 0.316, respectively—that corresponds to updated but unadjusted estimates from the North Central Cancer Treatment Group trial data.

Table 1

Model parameters*

Variable	Value	Source (reference)
Annual hazard rate of recurrence with aromatase inhibitors		
Year 0–1	0.0243	
Year 1–2	0.0268	
Year 2–3	0.0415	BIG 1–98 (2)
Year 3–4	0.0414	
Year 4–5	0.0401	
Annual hazard rate of recurrence with tamoxifen		
Year 0–1	0.0264	
Year 1–2	0.0460	
Year 2–3	0.0469	BIG 1–98 (2)
Year 3–4	0.0481	
Year 4–5	0.0397	
<i>CYP2D6</i> (*4) genotype frequencies (%)		
Wild type (wt/wt)	72.1	
Heterozygous (wt/*4)	21.1	Goetz et al. (5)
Homozygous mutant (*4/*4)	6.8	
Hazard ratio for disease-free survival in *4/*4 patients		
Adjusted	1.86	Goetz et al. (5)

* BIG 1–98 = Breast International Group Trial 1–98.

Table 2

Five-year disease-free survival for homozygous wild-type patients receiving tamoxifen obtained by varying the hazard ratio of recurrence among the homozygous mutation carriers ($HR_{wt/*4}$) and the proportion of the $HR_{/*4/*4}$ that was applicable to heterozygotes ($Eff_{wt/*4}$)*

$Eff_{wt/*4}$	$HR_{/*4/*4}$				
	1.0	1.5	2.0	2.5	3.0
0.0	81.3	81.8	82.3	82.7	83.1
0.25	81.3	82.3	83.2	84.1	84.8
0.50	81.3	82.9	84.3	85.6	86.7
0.75	81.3	83.5	85.4	87.1	88.7
1.0	81.3	84.1	86.6	88.7	90.6

* Five-year disease-free survival is expressed as a percentage. Combinations of $HR_{/*4/*4}$ and $Eff_{wt/*4}$ for which 5-year disease-free survival for wt/wt patients on tamoxifen is greater than that for wt/wt patients on aromatase inhibitors (ie, >84%) are shown in bold.