Breast Cancer Risk in Primary Care
Implications for Chemoprevention

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Background: Some women may benefit from taking tamoxifen citrate for breast cancer prevention if the probability of benefit outweighs that of adverse events. We determined the proportion of women aged 40 to 69 years attending general internal medicine practices who were potentially eligible for tamoxifen chemoprevention and calculated the maximum proportion of breast cancers that could be prevented.

Methods: Six hundred five women aged 40 to 69 completed self-administered questionnaires in the waiting rooms of 10 general internal medicine practices in North Carolina in 2001.

Results: Among white women, 9.0% (95% confidence interval [CI], 5.1%-15.2%) in their 40s, 24.0% (95% CI, 18.2%-31.0%) in their 50s, and 53.4% (95% CI, 46.1%-61.3%) in their 60s had a 5-year Gail model estimated breast cancer risk of 1.66% or greater. Among black women, 2.9% (95% CI, 0%-15.0%) in their 40s, 7.1% (95% CI, 1.1%-24.4%) in their 50s, and 13.0% (95% CI, 3.1%-34.3%) in their 60s had a similar risk. When adverse events were considered in white women, 10% or fewer in all age groups were potentially eligible for chemoprevention. The maximum proportion of breast cancers prevented in eligible women was 6.0% to 8.3%.

Conclusions: Small numbers of women in primary care practices are eligible for discussions about chemoprevention; the maximum proportion of breast cancers prevented if eligible women take tamoxifen is also small. Challenges lie in targeting discussions to the most appropriate women and in finding new chemoprevention strategies that have less risk of harms.

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For the past 30 years, clinicians have used screening with mammography and breast examination as the primary approach for control of breast cancer. Despite the important role of screening, randomized trials document its modest effect on breast cancer mortality.¹² New evidence suggests consideration of another approach: chemoprevention of breast cancer with selective estrogen receptor modulators.

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Results of the National Surgical Adjuvant Breast and Bowel Project's Breast Cancer Prevention Trial (BCPT) showed a 49% reduction in the incidence of breast cancer (175 cases of invasive breast cancer among 6599 women in the placebo arm vs 89 cases among 6576 women in the tamoxifen citrate arm) among high-risk women 35 years and older who were randomized to tamoxifen, a selective estrogen receptor modulator, compared with placebo.³ The BCPT also found that tamoxifen increased the risk of serious adverse outcomes, such as endometrial cancer and thromboembolic events (eg, pulmonary embolism, deep venous thrombosis, stroke). Although not FDA-approved for breast cancer prevention, raloxifene hydrochloride, another selective estrogen receptor modulator, has been shown to reduce the incidence of breast cancer by a similar amount.⁴ Raloxifene also increases the incidence of deep venous thrombosis and pulmonary embolism, but not endometrial cancer or stroke.⁵ Expert groups suggest that clinicians discuss tamoxifen chemoprevention with women who could realize a net health benefit.⁶⁷ This includes women with a high potential of benefit and a low potential of harm from taking tamoxifen.

The relative risk reduction in breast cancer incidence in the BCPT was the same for all risk groups; women with a higher
METHODS

This study was a part of the Making Prevention Work study funded by the National Cancer Institute. For this study, we recruited 10 community general internal medicine practices in the 4 cities included in the larger study; all agreed to participate. We excluded solo practices to maximize the efficiency of recruitment at each study site; we excluded academic practices because we were focused on community practices. The Institutional Review Board of the School of Public Health at The University of North Carolina at Chapel Hill approved the study.

Trained research assistants consecutively approached women aged 40 to 69 in the waiting rooms of the participating practices from January 15, 2000, to May 30, 2000, requesting that they complete a 5- to 10-minute anonymous self-administered written questionnaire. Women were recruited on Tuesdays, Wednesdays, and Thursdays in each practice for 2 consecutive weeks. The questions asked about breast cancer risk factors used in the Gail model calculations, about factors that affect the risk for harms with the use of tamoxifen (history of thromboembolic conditions, diabetes mellitus, hypertension, and hysterectomy), and about worry regarding breast cancer. Women with a history of breast cancer or colon cancer were excluded.

The Gail model estimates breast cancer risk based on information about 7 risk factors: age, ethnic group, number of first-degree relatives with breast cancer, age at menarche, age at first live birth, number of breast biopsies, and presence of atypical hyperplasia in the biopsy specimen. The Gail model was developed using data from a group of mostly white women; modifications to the model were later made to allow for race-specific determinations of breast cancer risk. The analysis in this article was limited to women who identified themselves as white or black because few women of other ethnic groups were surveyed (<5% of the larger study).

The Gail model also requires information about the presence of atypical hyperplasia on breast biopsy samples. Because most women do not know this information, 2 approximations were used. One involved asking a proxy question, “Have you ever had an abnormal biopsy?” Response options were “yes,” “no,” and “unknown.” Of the 145 women who had had at least 1 biopsy, 13 (9.0%) responded affirmatively. In other studies, 2% to 17% of breast biopsy specimens showed atypical hyperplasia. Only “yes” responses were included in the calculation for atypical hyperplasia. As another approach, all women with biopsies were coded as “unknown” for atypical hyperplasia. Both approaches gave nearly identical results; the first approach is reported herein.

Because age is an important risk factor for breast cancer and for harms from tamoxifen, all analyses were stratified by decade of age (40-49, 50-59, and 60-69 years). The frequencies of demographic information and breast cancer risk factors for the Gail model were examined separately for white and black women. Five-year breast cancer risk estimates were computed for each individual using FORTRAN code for the Gail model obtained from the National Cancer Institute (D. Pee, PhD, written communication, June 4, 2000). Exact binomial confidence intervals were calculated.

To determine potential risk factors for harms from tamoxifen for breast cancer prevention, women were asked questions about their medical history. Women responded yes or no to questions about whether a physician had ever told them that they had high blood pressure, diabetes mellitus, blood clots in the legs, or blood clots in the lungs. Although hypertension and diabetes mellitus are not specific contraindications to the use of tamoxifen, they were included as risk factors because these conditions also increase the risk of stroke. An intact uterus was included as a risk factor for tamoxifen for women older than 50 years.

Women with an estimated 5-year breast cancer risk of at least 1.66% were defined as having increased breast cancer risk. Women were defined as having a low risk for adverse events from tamoxifen if they were aged 40 to 49 without a history of thromboembolic events (deep venous thrombosis or pulmonary embolism), hypertension, or diabetes mellitus. Women aged 50 to 69 were required also to have had a hysterectomy. Discussion with women about tamoxifen was considered to be appropriate if they had an increased risk of breast cancer and a low risk for adverse events from tamoxifen. Because the small number of black women in our study limited the ability to reliably estimate the percentage of black women meeting both of these criteria, this analysis was restricted to white women.

To determine women’s worry about breast cancer, we asked “How worried are you about getting breast cancer?” Responses offered were “very worried,” “somewhat worried,” and “not worried.” Women were classified as worried if they responded that they were very or somewhat worried.
Efficient approaches to identifying women with high breast cancer risk were also examined. Age, family history, and history of previous biopsies are weighted most heavily in estimating breast cancer risk in the Gail model. Positive responses to family history and previous biopsy within age categories were compared with full Gail model risk calculations. In accord with the BCPT, increased 5-year breast cancer risk was defined as a 1.66% or higher 5-year probability of developing breast cancer.3

Using the distribution of individual Gail model risk estimates for women in the sample, we calculated the expected total number of breast cancers for 10000 similar white women in each age group (40-49, 50-59, and 60-69 years) during the next 5 years (10000 \( / \sum \text{probabilities of breast cancer} / \text{total number in the sample} \) = the number of cancers expected). In a similar manner, we calculated the expected number of breast cancers for the subgroup of women with increased breast cancer risk and low risk of harms from tamoxifen. Assuming that complete adherence to 5 years of tamoxifen use would reduce these cancers by 49%,3 the maximum percentage of breast cancers in each group that would be prevented by tamoxifen was estimated. These last 2 analyses were limited to white women because the number of black women in the sample was too small for stable calculations.

To confirm the estimates for breast cancer risk levels in women aged 40 to 49, information collected from similar surveys of women in the same 10 internal medicine practices from July 15, 1997, to February 28, 1998, (\( n = 1452 \), 85.0% response rate) was also analyzed. The questions for the Gail model risk factors and data analysis procedures were identical to those already described.

### RESULTS

#### PARTICIPANTS

Six hundred five women (84.9% of women we approached) agreed to complete the questionnaire. The most common reasons for nonparticipation were short waiting times before the office visit and feeling too ill. Nonrespondents and respondents had the same mean age. Other details about nonrespondents were not available for comparison.

Participants were predominately white (79%-89% of each group by decade). Almost all had finished high school and had health insurance (Table 1). The proportion of women who reported that they had ever had a breast biopsy ranged from 8.6% in younger black women to 32.1% in older white women; the proportion of white women reporting a biopsy was higher than that for black women in each age group. The proportion of women reporting a family history of breast cancer in a first-degree relative ranged from 2.9% to 21.4% by decade and racial group.

#### FIVE-YEAR BREAST CANCER RISK

The proportion of women with an estimated 5-year risk of breast cancer of 1.66% or higher as calculated by the Gail model increased with age. Estimated risks for white women were higher in each age group compared with

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*Table 1. Demographic Characteristics and Breast Cancer Risk Factors for All Women in Study*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>White</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 134)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insured</td>
<td>129 (96.3)</td>
<td>183 (95.3)</td>
<td>177 (91.7)</td>
</tr>
<tr>
<td>(n = 35)</td>
<td>34 (97.1)</td>
<td>27 (96.4)</td>
<td>22 (96.0)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ High school</td>
<td>2 (1.5)</td>
<td>1 (0.5)</td>
<td>24 (13.1)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>70 (53.4)</td>
<td>119 (63.6)</td>
<td>111 (60.7)</td>
</tr>
<tr>
<td>College graduate</td>
<td>59 (45.0)</td>
<td>67 (35.6)</td>
<td>48 (26.2)</td>
</tr>
<tr>
<td>Age at menarche, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 11</td>
<td>25 (18.8)</td>
<td>46 (24.2)</td>
<td>41 (21.5)</td>
</tr>
<tr>
<td>12-13</td>
<td>84 (63.2)</td>
<td>10 (57.9)</td>
<td>111 (58.1)</td>
</tr>
<tr>
<td>≥ 14</td>
<td>24 (18.0)</td>
<td>34 (17.9)</td>
<td>39 (20.4)</td>
</tr>
<tr>
<td>Age at birth of first child, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No children</td>
<td>32 (24.2)</td>
<td>33 (17.3)</td>
<td>14 (7.4)</td>
</tr>
<tr>
<td>≥ 19</td>
<td>18 (13.6)</td>
<td>36 (18.8)</td>
<td>46 (24.3)</td>
</tr>
<tr>
<td>20-24</td>
<td>29 (22.0)</td>
<td>73 (39.3)</td>
<td>86 (45.5)</td>
</tr>
<tr>
<td>25-29</td>
<td>27 (20.5)</td>
<td>34 (17.8)</td>
<td>30 (15.9)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>26 (19.7)</td>
<td>13 (6.8)</td>
<td>13 (6.9)</td>
</tr>
<tr>
<td>Breast biopsies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>109 (81.3)</td>
<td>145 (75.5)</td>
<td>131 (67.9)</td>
</tr>
<tr>
<td>1</td>
<td>18 (13.4)</td>
<td>30 (15.6)</td>
<td>44 (22.8)</td>
</tr>
<tr>
<td>≥ 2</td>
<td>7 (5.2)</td>
<td>17 (8.9)</td>
<td>18 (9.3)</td>
</tr>
<tr>
<td>Family members with breast cancer†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>120 (89.6)</td>
<td>160 (83.3)</td>
<td>162 (83.9)</td>
</tr>
<tr>
<td>1</td>
<td>13 (8.7)</td>
<td>30 (15.6)</td>
<td>24 (12.4)</td>
</tr>
<tr>
<td>≥ 2</td>
<td>1 (0.7)</td>
<td>2 (1.0)</td>
<td>7 (3.6)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage of column total). Total sample size across variables varies because of missing data.
†Mothers, daughters, and sisters.
black women in the same age group (Table 2). Among women in their 40s, 9.0% (95% confidence interval [CI], 5.1%-15.2%) of white women and 2.9% (95% CI, 0%-15.0%) of black women had an estimated 5-year breast cancer risk of 1.66% or greater. This proportion increased to 24.0% (95% CI, 18.2%-31.0%) for white women and 7.1% (95% CI, 1.1%-24.4%) for black women in their 50s and 53.4% (95% CI, 46.1%-61.3%) for white women and 13.0% (95% CI, 3.1%-34.3%) for black women in their 60s.

To confirm the findings in a larger sample, we analyzed data collected earlier in the same study from the same practices on a larger number of women in their 40s. In this sample of 1452 women, 8.0% (95% CI, 6.8%-9.8%) of white women and 4.0% (95% CI, 2.7%-5.2%) of black women had estimated breast cancer risks of 1.66% or higher (R.P.H., oral communication, August 9, 2000), similar to the proportions already reported. Earlier data were not collected from women aged 50 to 69.

**WOMEN WITH WHOM DISCUSSION ABOUT TAMOXIFEN IS APPROPRIATE**

Three (25.0%) of the women aged 40 to 49 with increased breast cancer risk had 1 or more conditions that could potentially increase adverse events from tamoxifen. Among women with increased breast cancer risk in their 50s and 60s, 30 (65.2%) and 87 (85.3%), respectively, had 1 or more such conditions.

Nearly 7% (6.7%) (95% CI, 3.1%-11.8%; n=9) of white women in their 40s had an increased risk of breast cancer and no conditions that would increase their likelihood of adverse events from tamoxifen (Table 3). Six percent (95% CI, 2.9%-10.7%; n=12) of women in their 50s and 9.8% (95% CI, 6.2%-14.9%; n=19) of women in their 60s met these requirements for discussions about tamoxifen.

We then considered how worried the women eligible for discussion about tamoxifen were about breast cancer. Most (8/9) of the women in their 40s, many (8/12) women in their 50s, and slightly more than half (10/19) of the women in their 60s with increased breast cancer risk and low risk for adverse events reported being very or somewhat worried about breast cancer (Table 3).

**ACCURACY OF QUESTIONS ABOUT FAMILY HISTORY AND BREAST BIOPSIES TO IDENTIFY HIGH-RISK WOMEN**

To determine if clinicians could accurately estimate the breast cancer risk level of women without applying the full Gail model calculation, we examined the predictive value of the absence of 2 risk factors—a family history of breast cancer and previous breast biopsy—in identifying women who were not at increased risk of breast cancer. No women in their 40s (negative predictive value, 100%) and only 3 women in their 50s (negative predictive value, 97%) who had an estimated 5-year risk of breast cancer less than 1.66% reported a family history of breast cancer or history of breast biopsy (Table 4). Most women in their 40s (73.1% [95% CI, 64.8%-80.1%]) and 50s (64.1% [95% CI, 57.2%-70.6%]) would have needed no
further risk assessment, as they did not have either risk factor. In a strategy of calculating full Gail model risk estimates only for women who had at least 1 of these risk factors, about a quarter of women in their 40s and slightly more than one third of women in their 50s would require further risk assessment.

**BREAST CANCERS POTENTIALLY PREVENTABLE WITH TAMOXIFEN**

We calculated the potential effect of identifying women eligible for discussions about tamoxifen from a hypothetical cohort of 10000 white women similar to the women in this study and offering all of them treatment. We did not calculate the effect for black women because of the small number of black women in our sample.

In a hypothetical cohort of 10000 white women aged 40 to 49 whose 5-year risk estimates correspond to the levels of risk of white women in this study, 109 women at all risk levels would be expected to be diagnosed with invasive breast cancer for 5 years, based on Gail model calculations (Figure). For 10000 women in their 50s, 149 cancers would be expected in the coming 5 years; 217 cancers during 5 years would be expected for 10000 women in their 60s.

If clinicians discussed chemoprevention with all eligible women and all of these women took tamoxifen for 5 years (assuming a relative risk reduction of 49% as in the BCPT), 6.0% to 8.3% (9-15 cases per 10000 women) of all breast cancers in women aged 40 to 69 would be prevented. These percentages represent the maximum effect to at least 1 of these questions.

The study further found that 18% or fewer of white women had an increased breast cancer risk and a low risk for tamoxifen adverse events and thus met criteria for discussions about tamoxifen. If all of these women adhered to tamoxifen use for 5 years, the maximum effect in these age groups would be to reduce the number of invasive breast cancers during the next 5 years by 6.0% to 8.3%. If chemoprevention with a drug such as raloxifene could be safely offered also to women in their 50s and 60s who had not had a hysterectomy, the percentage of breast cancers potentially preventable would increase to 11.0% to 13.2%. In actual practice, probably not all such women would take tamoxifen for 5 years; therefore, the actual number of cancers prevented would be smaller. In the 4 trials of breast cancer chemoprevention with tamoxifen, 24% to 40% of the women in the treatment group discontinued the drug. The inclusion of hypertension and diabetes mellitus as risk factors for adverse events is a cautious approach and leads to a more conservative estimate of the number of women who could potentially benefit from tamoxifen use. Practitioners may be concerned about prescribing tamoxifen for women whose risk of stroke is increased because of such comorbid conditions.

To our knowledge, this study is the first to assess breast cancer risk and the effect of tamoxifen for breast cancer prevention in women from primary care practices. In a study of BlueCross BlueShield of North Carolina enrollees, about 3% of women aged 40 to 45 and 12% aged 50 to 55 had risks of 1.66% or greater. This study’s corresponding estimates were 6.3% for women aged 40 to 45 and 18.0% for women aged 50 to 55. Analyses of the Nurses’ Health Study found that 3.3% of all breast cancers (in women of all ages) occurred in women who were aged 45 to 74 and were appropriate candidates for tamoxifen (based only on the absence of a uterus). Theoretically, tamoxifen could prevent about half of these, or 1.6%, assuming that all eligible women took tamoxifen for 5 years. Our study estimated instead the proportion of potentially preventable cancers within each age group, excluding older women at higher risk of adverse events from tamoxifen. The maximum benefit found ranged from

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**Table 4. Responses by White Women to 2 Questions About Breast Cancer Risk Compared With Estimated 5-Year Breast Cancer Risk**

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Estimated 5-Year Breast Cancer Risk</th>
<th>No. (% of Total)</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49 (n = 134)</td>
<td>Family history of breast cancer or ≥1 breast biopsy</td>
<td>12 (26.9)</td>
<td>33%</td>
<td>NA</td>
</tr>
<tr>
<td>40-49 (n = 134)</td>
<td>No family history or breast biopsy</td>
<td>0 (0.0)</td>
<td>100%</td>
<td>NA</td>
</tr>
<tr>
<td>50-59 (n = 192)</td>
<td>Family history of breast cancer or ≥1 breast biopsy</td>
<td>43 (69.5)</td>
<td>62%</td>
<td>NA</td>
</tr>
<tr>
<td>50-59 (n = 192)</td>
<td>No family history or breast biopsy</td>
<td>3 (53.6)</td>
<td>97%</td>
<td>NA</td>
</tr>
<tr>
<td>60-69 (n = 193)</td>
<td>Family history of breast cancer or ≥1 breast biopsy</td>
<td>66 (71.0)</td>
<td>85%</td>
<td>NA</td>
</tr>
<tr>
<td>60-69 (n = 193)</td>
<td>No family history or breast biopsy</td>
<td>37 (79.1)</td>
<td>68%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

*Five-year breast cancer risk calculated by the Gail et al model.*
sider use of tamoxifen for chemoprevention is un-
known. The potential effect of chemoprevention on breast
cancer incidence may be smaller than might seem likely
from the large relative risk reduction in the BCPT. The
reasons for the small effect are different for women in
different age groups. For women in their 40s, a small propor-
tion of breast cancers occurs in the group of women with
increased risk. Therefore, despite the fact that these
younger women have a lower likelihood of adverse ef-
fects from tamoxifen, the overall effect of chemopreven-
tion is small. For women in their 50s and 60s, the poten-
tially larger number of women with increased breast
cancer risk is reduced by a larger number of these women
who have a substantial likelihood of adverse effects. Again,
the magnitude of effect on the total societal burden of
breast cancer is small. Whether women with higher lev-
els of breast cancer worry would be more likely to con-
sider use of tamoxifen for chemoprevention is un-
known.

This study has several limitations. First, the number
of women in each age category was small, and black
women, women with lower education, and women with
no health insurance were not well represented in the
sample. Similar studies involving larger numbers of such
women would be helpful. Second, although the study
achieved high response rates, the respondents were from
only a small number of primary care practices in one state.
Therefore, the generalizability of this study is uncertain;
further study using a larger number of women in more
primary care practices is needed to confirm these
results. Third, there was no way of determining how many
of the women who reported having an abnormal biopsy
finding actually had atypical hyperplasia. Two different
approaches to estimate the overall risk distributions were
used, each approach providing a similar result.

The 5-year breast cancer risk distributions in this
study demonstrate that the Gail model estimates for black
women are significantly lower than those for white women
with similar risk factors. For example, a 55-year-old
woman with “average” Gail model variables would have
a 5-year breast cancer risk of 1.1% if she were white, com-
pared with 0.6% if she were black.

The Gail model is one way to identify women at high
risk for breast cancer. Other models have been devel-
oped18 and may be more accurate for some subgroups of
patients. All of these models have deficiencies, how-
ever. Improved approaches to assessing breast cancer risk
could help better target chemoprevention.19

Whether chemoprevention will find an important
place in our armamentarium against breast cancer is still
uncertain. Many questions remain, including tamoxi-
fen’s effects on breast cancer mortality and other non-
cancer conditions. Much also depends on whether US
women will embrace chemoprevention as many have
embraced screening mammography. If future chemopre-
ventive agents have fewer adverse effects (including such
quality-of-life effects as hot flashes) and if more older
women at higher breast cancer risk can be added to those
who might be appropriate for these drugs, a greater pro-
portion of breast cancers could be prevented.
REFERENCES