Prescription of Tamoxifen for Breast Cancer Prevention by Primary Care Physicians

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Background: Although tamoxifen citrate has been approved for primary reduction of breast cancer risk since 1998, little is known about the prescription of tamoxifen by primary care physicians.

Methods: To investigate the determinants of prescription of tamoxifen for breast cancer prevention by primary care physicians, we mailed a national survey to 350 primary care physicians, including specialties of family practice, obstetrics and gynecology, and general internal medicine, regarding past prescription of tamoxifen, intention to prescribe tamoxifen in hypothetical scenarios, and potential predisposing and enabling factors.

Results: Ninety-six physicians (27.4%) reported having prescribed tamoxifen for breast cancer prevention at least once in the prior 12 months. After multivariate adjustment, having prescribed tamoxifen was associated with the physician having a family member with breast cancer (odds ratio [OR], 2.66; 95% confidence interval [CI], 1.21-5.85), patients who asked for information about tamoxifen (OR, 3.98; 95% CI, 1.44-11.04), and the beliefs that the benefits of tamoxifen outweighed the risks (OR, 1.86; 95% CI, 1.07-3.24) and that eligibility was easy to determine (OR, 2.67; 95% CI, 1.35-5.29). In hypothetical scenarios, the prescription of tamoxifen was affected by the patient’s family history of breast cancer but not by her risk for endometrial cancer (ie, hysterectomy status).

Conclusions: A minority of primary care physicians have prescribed tamoxifen for breast cancer prevention. The decision to prescribe tamoxifen is affected by the ability to determine eligibility, patient demand, and personal experience with breast cancer as much as perceptions of the risks and benefits. A woman’s risk of endometrial cancer from tamoxifen seems to have less impact on prescribing decisions than the magnitude of her breast cancer risk.

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In 1998, the Breast Cancer Prevention Trial was stopped early because of a 49% reduction in the incidence of breast cancer among the women who were assigned to take tamoxifen citrate. Later that year, the US Food and Drug Administration approved tamoxifen for the primary reduction of breast cancer risk among women 35 years or older. Tamoxifen became one of the first drugs to be marketed for the primary prevention of cancer.

Despite the substantial impact of tamoxifen on breast cancer risk, several studies suggest that the use of tamoxifen for primary prevention of breast cancer has been limited. However, these studies concentrated on decision making among selected high-risk women rather than primary care populations. Understanding the prescribing practices of primary care physicians is particularly important because most eligible patients will not be seen in clinics for high-risk patients or oncology practices.

Multiple factors may inhibit primary care physicians from prescribing tamoxifen for primary breast cancer prevention. Tamoxifen has significant adverse effects, including a 2-fold increase in the risks of venous thromboembolism and endometrial cancer. The risk vs benefit equation also depends on an individual woman’s risk of breast cancer, with significantly greater absolute benefits at higher breast cancer risks. Thus, determining eligibility requires calculating a numeric breast cancer risk, which may be cumbersome for some primary care physicians. Lack of patient interest or lack of physician time may also interfere with the prescription of tamoxifen. In addition, the adoption of new therapies by physicians often depends on the behaviors of other physicians in their community.

Given the potential impact of chemoprevention and the paucity of data about the prescription of tamoxifen for primary prevention, we conducted a national survey of primary care physicians to investigate the factors associated with the prescription of tamoxifen for breast cancer prevention.
METHODS

PARTICIPANTS AND PROCEDURES

A random sample of 1000 primary care physicians from the American Medical Association master file was obtained through the AMA’s Medical Marketing Services. The sample was stratified by primary specialty to include an equal number of physicians whose primary practice was internal medicine, obstetrics and gynecology, family medicine, or general practice.

The institutional review board of the University of Pennsylvania, Philadelphia, approved this study. Study subjects were mailed the questionnaire, a cover letter, and a reply envelope with prepaid postage. Multiple strategies were used to maximize the response rate. In the first mailing, subjects were randomized to receive either a handwritten note, a $5 incentive, or both a handwritten note and a $5 incentive. Two subsequent mailings including the questionnaire, cover letter, and a $3 incentive were mailed to nonresponders. Physicians who had not responded to any of the mailings were offered a chance to complete the survey by telephone or fax or to be mailed another packet if they agreed to complete it through the mail. Data collection occurred from June 2002 to June 2004.

Of the original sample of 1000 physicians, 248 physicians were excluded who had incorrect addresses, were no longer practicing, were not primary care physicians, had no female patients, or had died. Twenty-six of the subjects refused to participate. The response rate was 47.2%. Responders did not differ significantly from nonresponders in sex, region of the country, specialty, or type of degree (MD vs DO). However, responders had graduated from medical school more recently than nonresponders (mean year of graduation, 1985 and 1981, respectively; P<.01). Of the 353 surveys returned, 5 (1.4%) were excluded from analyses because they were missing data about the prescription of tamoxifen.

SURVEY INSTRUMENT

The questionnaire included 4 sections: (1) whether the physician had previously prescribed tamoxifen for breast cancer prevention, (2) whether the physician would prescribe tamoxifen in a series of hypothetical patient scenarios, (3) attitudinal and practice factors that may influence the prescription of tamoxifen, and (4) practice and sociodemographic characteristics. Past prescribing behavior was measured by asking, “In the last 12 months, approximately how many times have you prescribed tamoxifen to reduce the risk of breast cancer?”12 Response categories were 0 times, 1 to 6 times, 7 to 12 times, and 13 or more times. Intended prescribing behavior was assessed using 6 case vignettes14-18 of 55-year-old women who varied in the degree of family history of breast cancer (none, mother only, or mother and sister) and hysterectomy history (yes or no). Each vignette, respondents were asked whether they would recommend tamoxifen as a preventive therapy.

Items assessing the attitudinal and practice factors that might influence the prescription of tamoxifen were developed based on interviews with primary care physicians and literature about clinical decision making about tamoxifen. These factors were grouped using the PRECEDE model of health behavior,19,20 in which behaviors are influenced by the presence or absence of predisposing, enabling, and reinforcing factors. Predisposing factors included 3 items assessing beliefs about the risk benefit ratio, including (1) the general belief that the benefits outweighed the risks and specific beliefs about risk of endometrial cancer and risk of venous thromboembolism, as well as individual items assessing the belief that the evidence is controversial; (2) whether patients asked for information about tamoxifen; and (3) whether other physicians in the community prescribed tamoxifen for breast cancer prevention. Enabling factors included an item assessing the ability to determine who is eligible for tamoxifen and an item assessing concern about the time that it takes to counsel a woman about tamoxifen. The response options used a 5-point Likert scale (strongly agree, somewhat agree, neither agree nor disagree, somewhat disagree, and strongly disagree).

Items adapted from other physician surveys were used to assess sociodemographic and practice characteristics, including the number of primary care physicians in the practice, the percentage of patients with Medicaid or Medi-Cal, the average number of patients seen a week, the percentage of the patients who are women, medical school affiliation, and the year of graduation from medical school.13 We also asked if the participant had any family members who had been diagnosed with breast cancer and if so, which family member.

STATISTICAL ANALYSES

All analyses were conducted using Stata statistical software (version 8.0; StataCorp LP, College Station, Tex). The P values are 2-sided. To facilitate the presentation of inferential analyses, prior tamoxifen prescribing behavior was dichotomized into 0 times in the past 12 months and 1 or more times in the past 12 months, and responses to the vignettes were dichotomized into yes vs no or not sure. Similarly, responses to the Likert-scaled items were grouped as agree or strongly agree vs neither agree nor disagree, disagree, or strongly disagree. Alternative categorizations were tested and did not change the main results.

Bivariate associations were examined using ordinary χ2 tests for categorical variables and ordinary independent sample t tests for continuous variables. Multivariate analyses were conducted using logistic regression. Variables were entered into the model if they were associated with the outcome in bivariate analyses (P<.10) or had been specified a priori (ie, age, sex, medical specialty, or percentage of patients in managed care). Variables were retained in the model if they were associated with the outcome with a P value of less than .05 or altered the coefficient for another variable by 15%. To assess the effect of patient characteristics on tamoxifen recommendations in the hypothetical scenarios, hierarchical logistic regression was used with the dependent variable as the recommendation (yes vs no or not sure) and the independent variables as the patient’s breast cancer family history (none, mother only, or mother and sister) and hysterectomy history (yes vs no). The analysis adjusted for the clustering of the 6 vignettes within each respondent.

The sample size of 350 respondents provided 80% power to identify a relative risk of 1.35 or greater for any independent variable assuming a prevalence of 50% in the physicians who had not prescribed tamoxifen and a type I error of .05. The study protocol was approved by the institutional review board at the University of Pennsylvania.

RESULTS

The 350 physicians had a mean age of 45.5 years and just over half had graduated from medical school since 1985 (Table 1); 32.3% were women; 41.4% reported their specialty as family practice, 18.9% as obstetrics and gynecology, and 39.8% as internal medicine. A little more than a tenth of the participants had a family member who had been diagnosed with breast cancer.
Ninety-six physicians (27.4%) reported having prescribed tamoxifen for breast cancer prevention at least once in the prior 12 months. Among these physicians, 82 (85.4%) had prescribed tamoxifen 1 to 6 times; 12 (12.5%), 7 to 12 times; and 3 (3.1%), more than 12 times. Physicians who had prescribed tamoxifen were older, less likely to be women, and more likely to see more than 100 patients per week and to be in practice with 5 or fewer primary care physicians. Physicians who had prescribed tamoxifen were more likely to have a family member with breast cancer.

Several physician attitudinal and practice factors were correlated with having prescribed tamoxifen to reduce the risk of breast cancer (Table 2). Physicians were more likely to have prescribed tamoxifen if they reported that it was easy to determine who was eligible for tamoxifen, that other physicians in the community were prescribing tamoxifen for breast cancer prevention, that the benefits of tamoxifen outweighed the risks, and that their patients were asking for information about tamoxifen. Interestingly, concerns about the risk of endometrial cancer or thromboembolism being too great were neither common nor associated with having prescribed tamoxifen. After multivariate adjustment, the factors that remained associated with having prescribed tamoxifen were having a family member with breast cancer and beliefs about the benefits outweighing the risk, the ease of determining eligibility, and patients asking for information (Table 3). Associations with age, sex, number of primary care physicians in the practice, and belief that physicians in the community were prescribing tamoxifen were no longer statistically significant after multivariate adjustment.

The decision to prescribe tamoxifen in scenarios describing 55-year-old women with varying family history and hysterectomy status was influenced more by the strength of the family history than whether the woman still had her uterus (Table 4). As predicted, participants were significantly more likely to recommend tamoxifen to a woman who had a mother with breast cancer than to a woman with no family history of breast cancer (P = .001) and significantly more likely to recommend tamoxifen if the woman had a mother and sister with breast cancer than only a mother with breast cancer (P = .001). Although participants were slightly more likely to recommend tamoxifen at each level of family history if the woman had a hysterectomy, these differences were not statistically significant (P > .10 for all).

The Breast Cancer Prevention Trial P-1,2 demonstrated that use of tamoxifen for 5 years in women at increased risk for breast cancer was associated with a 49% reduction in the incidence of breast cancer but a 2-fold in-

### Table 1. Participant Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n = 350)</th>
<th>Had Prescribed Tamoxifen Citrate (n = 350)</th>
<th>Had Not Prescribed Tamoxifen Citrate (n = 254)</th>
<th>( P ) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>45.6</td>
<td>48.7</td>
<td>44.3</td>
<td>.002</td>
</tr>
<tr>
<td>Specialty</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family practice</td>
<td>32.3</td>
<td>21.9</td>
<td>35.8</td>
<td>.01</td>
</tr>
<tr>
<td>Obstetrics/gynecology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal medicine</td>
<td>39.8</td>
<td>34.4</td>
<td>41.4</td>
<td></td>
</tr>
<tr>
<td>PCPs in practice, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>19.3</td>
<td>24.7</td>
<td>17.1</td>
<td></td>
</tr>
<tr>
<td>2-5</td>
<td>33.9</td>
<td>41.2</td>
<td>31.0</td>
<td>.31</td>
</tr>
<tr>
<td>6-10</td>
<td>21.7</td>
<td>14.1</td>
<td>24.8</td>
<td>.045</td>
</tr>
<tr>
<td>11</td>
<td>25.1</td>
<td>20.0</td>
<td>27.1</td>
<td></td>
</tr>
<tr>
<td>Patients in managed care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75-99</td>
<td>17.8</td>
<td>13.5</td>
<td>19.7</td>
<td></td>
</tr>
<tr>
<td>25-49</td>
<td>44.5</td>
<td>45.8</td>
<td>44.9</td>
<td>.51</td>
</tr>
<tr>
<td>50-74</td>
<td>15.5</td>
<td>16.7</td>
<td>12.6</td>
<td></td>
</tr>
<tr>
<td>75-100</td>
<td>24.2</td>
<td>24.0</td>
<td>22.8</td>
<td></td>
</tr>
<tr>
<td>Patients/wk, mean, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>34.9</td>
<td>23.3</td>
<td>39.3</td>
<td>.02</td>
</tr>
<tr>
<td>75-99</td>
<td>24.4</td>
<td>18.9</td>
<td>26.5</td>
<td></td>
</tr>
<tr>
<td>100-139</td>
<td>32.0</td>
<td>46.7</td>
<td>26.9</td>
<td></td>
</tr>
<tr>
<td>&gt;140</td>
<td>8.4</td>
<td>11.1</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>Medical school affiliation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family member with breast cancer</td>
<td>11.9</td>
<td>19.8</td>
<td>8.7</td>
<td>.004</td>
</tr>
</tbody>
</table>

Abbreviation: PCPs, primary care physicians.
*Data are given as a percentage of participants except where noted.
†From 2-tailed test.

### Table 2. Attitudes About Tamoxifen Citrate*

<table>
<thead>
<tr>
<th>Attitude</th>
<th>Overall (n = 350)</th>
<th>Had Prescribed Tamoxifen Citrate (n = 96)</th>
<th>Had Not Prescribed Tamoxifen Citrate (n = 254)</th>
<th>( P ) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>The benefits of tamoxifen in breast cancer prevention outweigh the risks.</td>
<td>45.7</td>
<td>62.5</td>
<td>39.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>The evidence that tamoxifen significantly reduces breast cancer risk is controversial.</td>
<td>27.7</td>
<td>30.2</td>
<td>27.0</td>
<td>.55</td>
</tr>
<tr>
<td>Physicians in my community are prescribing tamoxifen for breast cancer prevention.</td>
<td>21.4</td>
<td>33.3</td>
<td>16.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>It is too time consuming to discuss taking tamoxifen with women in my practice.</td>
<td>19.3</td>
<td>15.6</td>
<td>20.1</td>
<td>.30</td>
</tr>
<tr>
<td>It is easy for me to determine who is eligible to take tamoxifen for breast cancer risk reduction.</td>
<td>15.6</td>
<td>28.1</td>
<td>10.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>The risk of endometrial cancer is too great to prescribe tamoxifen for breast cancer risk reduction.</td>
<td>15.0</td>
<td>16.6</td>
<td>13.7</td>
<td>.48</td>
</tr>
<tr>
<td>The risk of thromboembolic disease is too great to prescribe tamoxifen for breast cancer risk reduction.</td>
<td>12.3</td>
<td>11.6</td>
<td>12.9</td>
<td>.75</td>
</tr>
<tr>
<td>Many of my female patients ask for information about taking tamoxifen for breast cancer risk reduction.</td>
<td>7.8</td>
<td>14.6</td>
<td>4.8</td>
<td>.002</td>
</tr>
</tbody>
</table>

*A data are presented as percentage of respondents who indicated that they agree or agree strongly.
†From 2-tailed test.

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crease in the incidence of endometrial cancer and thromboembolic disease. Guidelines for the prescription of tamoxifen have been developed by several advisory organizations, including the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and the Canadian Task Force on Preventive Health Care. These guidelines support offering tamoxifen to women with a 5-year breast cancer risk of more than 1.66% in the setting of an informed discussion of risks and benefits. The guidelines also recognize that the most favorable risk vs benefit ratio for tamoxifen occurs in women at higher risk of breast cancer, women without a uterus, and younger women.

To our knowledge, this is the first national survey of primary care physicians regarding their prescription of tamoxifen for the chemoprevention of breast cancer. In this sample, approximately a quarter of primary care physicians had prescribed tamoxifen for breast cancer prevention in the prior 12 months. This proportion is higher than might have been predicted based on literature about patient uptake but lower than might be expected based on the estimated proportion of women who would experience a net benefit from tamoxifen. Prior studies of high-risk women have found that approximately 20% (range, 1%-42%) are interested in taking tamoxifen in a hypothetical scenario or actually begin tamoxifen after risk counseling. On one hand, because many of these patients are likely to be seen by physicians who provide counseling for individuals at high-risk for breast cancer, it is potentially surprising that the prescription of tamoxifen for breast cancer prevention among primary care physicians is as prevalent as our results suggest. On the other hand, analyses of US women aged 30 to 79 years suggest that 4.9% of white women and 0.6% of black women will experience a net benefit from tamoxifen. Based on this estimate, most primary care physicians in clinical practice would care for women who would receive a net benefit from tamoxifen.

These results indicate that the prescription of tamoxifen by primary care physicians is strongly associated with logistical factors, such as patient demand and the ability to determine eligibility. Although a relatively small percentage of participants reported that patients asked for information about tamoxifen, of all the factors that we examined, this factor was the most strongly associated with having prescribed tamoxifen. The growing consumerism of medical care has been widely discussed, and these results provide more evidence that patient involvement can have a direct impact on what health care interventions they receive. Perceptions about the ease of determining who is eligible for tamoxifen were also strongly associated with having prescribed tamoxifen, and only 15.6% of physicians thought that it was easy to determine eligibility. Because eligibility is based on a 5-year breast cancer risk of 1.66% or greater, determining eligibility requires a breast cancer risk prediction model, generally the Gail model. Although the Gail model is available online and was widely distributed as a handheld calculator at the time of this study, primary care physicians may not be aware of this tool or may find it cumbersome to incorporate in their daily practice. Basing eligibility on a calculated risk number rather than on relatively simple subgroups (eg, women older than 50 years with a first-degree relative) increases the precision of eligibility criteria but may contribute to the relatively low uptake of tamoxifen. Strategies to increase the uptake of chemoprevention in the future should educate patients and physicians about the availability of these interventions and develop simple ways for patients and physicians to determine eligibility.

In addition to logistical factors, a physician’s personal experience with breast cancer in his or her own family was strongly correlated with their decision to prescribe tamoxifen to their patients. Physicians with a family member with breast cancer (usually their mother) were more than 2 times more likely to have prescribed tamoxifen to a patient than physicians without a family member with breast cancer. Although it is generally accepted that personal experience makes breast cancer risk more salient, to our knowledge, this is the first study to demonstrate that personal experience with breast cancer in a physician’s family may spill over into their clinical practice.

The observed association between having prescribed tamoxifen and perceptions of the balance of risk vs benefit is not surprising; however, it is interesting that this correlation seems to be driven more by the absolute reduction in breast cancer risk than by the risks of endometrial cancer or thromboembolism. The prior prescription of tamoxifen was not correlated with concerns about endometrial cancer or thromboembolism, and the re-
sponses to the hypothetical scenarios did not depend on a woman's risk of endometrial cancer. This finding is unexpected given that the risks of these events play a significant role in prior assessments of the risk benefit ratio from tamoxifen and influence patient decision making about the use of tamoxifen as primary prevention.5-7,9 Furthermore, most general approaches to primary prevention emphasize the need to minimize adverse events in a healthy population rather than the need to maximize the impact on the target disease.27 Although we did not explore the reasons for this discrepancy, it is possible that it reflects the perception that endometrial cancer is largely a curable disease and that this finding would not be true for other drugs with different adverse effects.

This study has several limitations. We had a relatively small sample size that limited our ability to find small effects. However, this sample size was adequate for detecting factors that increased the probability that a physician would have prescribed tamoxifen by a third or more—a reasonable cutoff for factors that would be considered clinically significant. The prescription of tamoxifen was measured by self-report and may either overestimate or underestimate actual behavior. Because the study hypotheses were guided by a relatively small number of interviews and a behavioral model, we may have overlooked some factors that are associated with tamoxifen prescribing. We did not address the question of whether histopathologic risk factors, such as atypical hyperplasia and lobular carcinoma in situ, change physicians' attitudes toward prescribing tamoxifen. The National Surgical Adjuvant Breast and Bowel Project P-1 Study1,2 demonstrates a more pronounced effect on breast cancer risk reduction in women with atypical ductal hyperplasia. A previous study6 found enhanced offering and uptake of tamoxifen in women with lobular carcinoma in situ or atypical ductal hyperplasia. In addition, the effect of a patient's age or thromboembolic risk factors on prescribing practice or the effect of a patient's characteristics on physician attitudes was not examined. Although our response rate of 47.2% is close to the mean (SD) response rate of 54% (17%) found in a 1997 review28 of physician surveys published in medical journals, nonresponders may have differed from responders in ways that may have influenced our results. For example, if responders were more likely to have a family history of breast cancer and were more likely to have prescribed tamoxifen, we may have overestimated the association between having a family history of breast cancer and tamoxifen prescribing. However, in sensitivity analyses examining the potential effect of this type of selection bias, even assuming that physicians with a family history were twice as likely to respond and twice as likely to prescribe tamoxifen, the effect on the main results is relatively small (from an odds ratio of 2.66 [95% confidence interval, 1.21-5.85] in the study analyses to an odds ratio of 2.11 [95% confidence interval, 0.98-4.75] after adjusting for the selection effect).29

Although tamoxifen remains the only medication that the Food and Drug Administration approved for primary breast cancer risk reduction, the Study of Tamoxifen and Raloxifene30 trial recently demonstrated that, for postmenopausal women, use of raloxifene hydrocholride is as effective as tamoxifen for breast cancer prevention but has a lower risk of endometrial cancer and thromboembolic disease. It is possible that primary care physicians may be more willing to use raloxifene for breast cancer prevention because of the improved risk benefit profile. However, many of the issues with determining eligibility and patient awareness are likely to be similar for tamoxifen and raloxifene. These issues must be addressed before the availability of breast cancer chemoprevention will be translated into a reduction in breast cancer mortality in the United States.

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