The Use of Chemoprevention Following Breast Biopsy in Women at High Risk for Developing Breast Cancer

By

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ABSTRACT

Context: Breast cancer chemoprevention is recognized as an effective strategy for risk reduction in women at high risk for the future development of breast cancer. Women with a history of breast biopsy revealing atypical hyperplasia or lobular carcinoma in situ are at particularly high risk for developing breast cancer. The rates of chemoprevention counseling and prescribing in this population are unknown.

Objective: To determine the practice patterns of general surgeons who perform breast biopsies with regard to breast cancer chemoprevention counseling and prescribing.

Design: Cross-sectional descriptive study based on the results of a self-administered questionnaire mailed to general surgeons.

Participants: General surgeons living in and licensed to practice in North Carolina. In the data analysis, we will exclude those respondents whose practice does not include breast care.

Main Outcome Measures: Rates of breast cancer chemoprevention counseling and prescribing. Description of surgeon and practice characteristics related to counseling and prescribing. Description of referral patterns for chemoprevention counseling and prescribing.

Results: Pending at this time. Once data collection is complete, we may anticipate the following results:
1. Surgeons are not discussing chemoprevention with high risk patients OR
2. Surgeons discuss or recommend chemoprevention but do not prescribe it OR
3. Surgeons discuss and prescribe chemoprevention

Conclusions: If surgeons are not discussing chemoprevention with high risk patients, an educational intervention may be appropriate. If surgeons discuss chemoprevention but refer to another provider for prescribing, it will be necessary to survey these other providers to determine if patients are getting chemoprevention medications. If we find high rates of chemoprevention counseling and prescribing in North Carolina, repeating the survey on a national level would define geographic variations.
INTRODUCTION

Breast cancer presents a significant public health problem. The American Cancer Society estimates that 211,300 women will be diagnosed with invasive breast cancer and 55,700 will be diagnosed with in situ cancer in the US in 2003. Almost 40,000 deaths are expected.¹ In North Carolina, 6385 cases and 1370 deaths are expected in 2003.² Risk factors for breast cancer include increasing age, previous diagnosis of breast cancer, family history of breast cancer, young age at menses, older age at first birth, nulliparity, and history of breast biopsy. In particular, a breast biopsy revealing atypical ductal hyperplasia (ADH) or lobular carcinoma in situ (LCIS) places a woman at significantly increased risk.

Because there are few modifiable risk factors for breast cancer, early detection has been the principle approach to breast cancer control. Recently, preventive efforts have focused on using medications to decrease a woman’s risk of breast cancer. This is known as chemoprevention. Breast cancer treatment studies found the incidence of contralateral breast cancers in women treated with tamoxifen to be much lower than expected. This led to the idea that tamoxifen may be effective as a chemopreventive agent. Several large clinical trials of tamoxifen for breast cancer chemoprevention found that the drug does prevent some breast cancers, especially in women at high risk for developing the disease.

Histopathologic factors found on benign breast biopsies place a patient at increased risk for the future development of breast cancer. These include the atypical hyperplasias and lobular carcinoma in situ. Atypical hyperplasia is a breast lesion that has some but not all of the features of carcinoma in situ.
Current pathologic classification divides the atypical hyperplasias into atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH). Lobular carcinoma in situ (LCIS) is a lesion generally considered to be a marker for increased risk of future breast cancer. These histopathologic changes are present in 5-10% of all breast biopsy specimens.

Chemoprevention is one of three treatment options for women with a breast biopsy revealing atypical hyperplasia or LCIS. The other two are careful surveillance with regular mammograms and clinical breast exams, and bilateral prophylactic mastectomy. Surveillance is the most common option. Mastectomy is reserved for those women who have intense fear and distress about breast cancer. The rate of chemoprevention use in this high risk population of patients is unknown.

BACKGROUND

Pathology and Future Risk of Breast Cancer

The evolution of premalignant breast disease into invasive breast cancer is not completely understood. There may be a continuum of carcinogenesis from normal terminal duct lobular units to ADH/ALH to DCIS/LCIS to invasive cancer. Many genetic changes have been identified in the atypical hyperplasias, including loss of heterozygosity, allelic imbalance, p53 tumor suppressor gene mutations and estrogen receptor overexpression. In fact, 95% of samples of ADH and LCIS overexpress the estrogen receptor. This may explain why tamoxifen, a drug that acts as an antiestrogen, is more effective in preventing breast cancer in
those women with ADH or LCIS as compared to the high-risk population as a whole.

The atypical hyperplasias and LCIS were historically considered to be markers of increased risk overall, rather than premalignant lesions themselves. However, review of the literature shows that in some series the increased risk was actually about two-thirds in the ipsilateral breast and one-third in the contralateral breast. Recently published results from the Nashville Breast Studies found the risk of invasive cancer following ALH to be almost three times higher in the ipsilateral breast. According to the authors, “Our findings suggest a model of premalignancy for ALH intermediate between a local precursor and a generalized risk for both breasts.”

In the pre-mammographic era, the prevalence of atypical hyperplasia in benign breast biopsies was 4 - 5%. The prevalence increases to approximately 10% of benign biopsies in the mammographically-screened population. In a sample within the Nurses Health Study, the mean age of biopsy revealing atypical hyperplasia was 43 years and the time from first biopsy to diagnosis of breast cancer was 8-10 years. In the Nashville Breast Studies, invasive breast cancer was diagnosed 14.8 years after biopsy showing ALH.

In a case-control study done within the Breast Cancer Detection and Demonstration Project, atypical hyperplasia increased the risk of future development of breast cancer by four times (OR=4.3, 95% CI 1.7-11). This is consistent with a previous study by the same authors that found the odds of breast cancer increased 5.3 times compared to benign biopsies without proliferative
disease. History of breast cancer in a first degree relative doubled the risk of breast cancer, and appears to be synergistic with atypical hyperplasia. Thus, in a woman with a family history of breast cancer and a biopsy with atypical hyperplasia, the odds of breast cancer are eight to ten times higher than the general population.  

A nested case-control study of biopsy-confirmed breast disease in a cohort within the Nurses Health Study divided the atypical hyperplasias into atypical ductal hyperplasia and atypical lobular hyperplasia. Overall, atypical hyperplasia increased the risk of breast cancer 3.4 times (95% CI, 2.0-5.9). ALH increased the risk of breast cancer (OR=5.3, 95% CI, 2.7-10.4) more than ADH (OR=2.4, 95% CI, 1.3-4.5). The difference between the two was significant (p=0.05).  

The absolute risk of invasive breast cancer following a biopsy with atypical hyperplasia is reported to be 10-15% in 15-20 years. In a patient with atypical hyperplasia and one first degree relative with breast cancer, the absolute risk increases to 20-30% over the next 15-20 years. By contrast, the absolute risk of invasive breast cancer in a woman who carries the BRCA-1 mutation is 80-85%.  

Lobular carcinoma in situ is less common than the atypical hyperplasias. It represents 0.5% of symptomatic and 1% of screen-detected breast lesions. The absolute risk of invasive breast cancer following a diagnosis of LCIS is 25-40% in 15-20 years. Over that time period, the absolute risk of breast cancer in the same breast is 15-20% and it is 10-15% in the contralateral breast.
Tamoxifen

Tamoxifen is a selective estrogen receptor modulator that has antiestrogenic effects on breast tissue and estrogenic effects on bone, endometrium, lipids and clotting. In the breast, it is a nonsteroidal antiestrogen that competitively inhibits estrogen binding to the estrogen receptor. Thus, it modulates the expression of estrogen related genes that influence breast cell growth and apoptosis.\(^9\) It increases natural killer cell activity and antibody production. It decreases insulin-like growth factor and increases TGF-beta.\(^{10}\) It is effective in the prevention and treatment of breast cancers that overexpress the estrogen receptor (ER\(^+\)). Overall, 60-70% of breast cancers are ER\(^+\) -- 50% of premenopausal cancers and 80% of postmenopausal cancers.\(^9\)

Tamoxifen has been shown to decrease the incidence of breast cancer in three important clinical settings. Women with invasive breast cancer who are treated with tamoxifen have a 47% reduced incidence of contralateral breast cancer.\(^{11}\) In women with DCIS, the addition of tamoxifen following lumpectomy and whole breast radiation therapy decreases the incidence of invasive and non-invasive carcinoma in both the ipsilateral and contralateral breasts.\(^{12}\) Finally, in women at elevated risk for the future development of breast cancer, tamoxifen prevents 69% of estrogen-receptor positive tumors.\(^{13}\)

Tamoxifen, approved by the FDA for treatment of metastatic breast cancer in 1977, has a favorable side-effect profile when viewed as a breast cancer treatment drug. However, when viewed as a preventive agent, the side effects seem more significant. Side effects of tamoxifen include climacteric symptoms,
increased risk of endometrial cancer, increased thromboembolic events (stroke, deep vein thrombosis, pulmonary embolism) and increased cataracts. Tamoxifen use is associated with decreased fractures. It does not appear to have any effect on heart disease, liver cancer, colorectal cancer or ovarian cancer.\textsuperscript{13}

Following the results of the Breast Cancer Prevention Trial (BCPT), tamoxifen received FDA approval for breast cancer risk reduction. Tamoxifen is the first drug to get FDA approval for the primary prevention of cancer.\textsuperscript{9} It is approved for use in both premenopausal and postmenopausal women age 35 and older whose five-year risk of breast cancer is greater than or equal to that of the average 60 year old. This corresponds to a Gail risk score of >1.66%.\textsuperscript{14}

Tamoxifen reduces the risk of developing estrogen-receptor positive breast cancer by 69%. It has no effect on the incidence of estrogen-receptor negative tumors. Estrogen-receptor positive tumors occur in 51% of premenopausal women and in 80% of postmenopausal women.\textsuperscript{14} Thus, tamoxifen is potentially more beneficial in postmenopausal women. However, the adverse events associated with tamoxifen also increase with age.

In the BCPT, tamoxifen also reduced the incidence of benign breast disease (RR= 0.72, 95% CI 0.65-0.79) and reduced the number of breast biopsies in the treatment group (RR=0.71, 95% CI 0.66-0.77). The risk was especially decreased in women less than 50 years old. There was also a decrease in symptomatic complaints of breast pain and swelling.\textsuperscript{15}

CHEMOPREVENTION TRIALS
In the evidence summary performed for the United States Preventive Services Task Force (USPSTF), Kinsinger et al.\textsuperscript{16} examined the benefits and harms of breast cancer chemoprevention. Four randomized controlled trials were included in the analysis: the Royal Marsden Hospital Tamoxifen Chemoprevention Trial; the Italian Tamoxifen Prevention Study; the Breast Cancer Prevention Trial (BCPT); and the Multiple Outcomes of Raloxifene Evaluation (MORE). A fourth tamoxifen trial, the International Breast Cancer Intervention Study (IBIS-1) has since been completed. The authors concluded that the evidence supports a substantial effect of chemoprevention in reducing the incidence of estrogen-receptor positive tumors. Based on the results of this summary, the USPSTF recommends that clinicians discuss breast cancer chemoprevention with all women who are at high risk for breast cancer and at low risk for adverse events.

The four tamoxifen prevention trials and the single raloxifene prevention trial will now be reviewed in more detail.

**Breast Cancer Prevention Trial**

The largest trial of tamoxifen for breast cancer chemoprevention is the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-01 Trial,\textsuperscript{13} also known as the Breast Cancer Prevention Trial (BCPT). The BCPT randomized 13,388 high-risk women either to treatment with tamoxifen (20mg/day for 5 years) or to placebo. In this trial, high-risk was defined as 1) age greater than or equal to 60 years; 2) history of lobular carcinoma in situ; or 3) age 35-59 with a
five-year modified Gail model risk of at least 1.66%. Of these women, 6.3% had a history of LCIS and 9.1% had a history of ADH. Overall, invasive breast cancer was reduced 49% (RR=0.51, 95% CI 0.39-0.66). Through 69 months of follow-up, the cumulative incidence of invasive breast cancer was 43.4 cases per 1000 women in the placebo group and 22.0 cases per 1000 women in the treatment group. Absolute 5-year risk decreased from 2.6% in the placebo group to 1.3% in the treatment group. Tamoxifen reduced the occurrence of in situ breast cancer (DCIS and LCIS combined) by 50% (RR=0.50, 95% CI 0.33-0.77). The reduction in breast cancer cases comprised estrogen-receptor positive, but not estrogen-receptor negative, tumors.

Specifically, in the group with a history of LCIS, breast cancer was reduced 56% (RR=0.44, 95% CI 0.16-1.06) and in the group with a history of ADH, breast cancer decreased by 86% (RR= 0.14, 95% CI 0.03-0.47). One possible explanation for this is that LCIS and ADH are most often estrogen-receptor positive. The BCPT is the only one of the four to report subgroup analysis of LCIS and ADH patients.

There were meaningful risks associated with tamoxifen use (see Table 1). Specifically, the treatment group had higher rates of endometrial cancer, stroke, deep vein thrombosis, pulmonary embolus and cataracts. These adverse events were more common in women older than 50 years. There was no increase in the incidence of other cancers or ischemic heart disease. There was a non-statistically significant decrease in fractures of the hip and radius in the treatment group. Overall quality of life scores were similar between the two groups, although
women in the treatment group reported significantly more bothersome hot flashes and vaginal discharge.

**TABLE 1: RISKS AND BENEFITS OF TAMOXIFEN IN THE BCPT**

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate/1000 women Placebo</th>
<th>Rate/1000 women Tamoxifen</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial Cancer</td>
<td>0.91</td>
<td>2.30</td>
<td>2.53*</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.92</td>
<td>1.45</td>
<td>1.59*</td>
</tr>
<tr>
<td>Deep Vein Thrombosis</td>
<td>0.84</td>
<td>1.34</td>
<td>1.60</td>
</tr>
<tr>
<td>Pulmonary Embolus</td>
<td>0.23</td>
<td>0.69</td>
<td>3.01*</td>
</tr>
<tr>
<td>Cataracts</td>
<td>21.72</td>
<td>24.82</td>
<td>1.14*</td>
</tr>
<tr>
<td>Fractures</td>
<td>5.28</td>
<td>4.29</td>
<td>0.81</td>
</tr>
<tr>
<td>Noninvasive Breast Cancer</td>
<td>15.9</td>
<td>7.7</td>
<td>0.50*</td>
</tr>
<tr>
<td>Invasive Breast Cancer</td>
<td>43.4</td>
<td>22.0</td>
<td>0.51*</td>
</tr>
</tbody>
</table>

* statistically significant

Methodologically, the BCPT is the strongest of the 4 trials. It is the largest and attrition was much lower than in the other studies. In fact, the combination of a lower-than-expected occurrence of breast cancer events and the high rate of attrition likely left the European studies underpowered to detect a difference. The BCPT had strict, well-defined inclusion and exclusion criteria. Specifically, "high-risk" was rigorously defined. Most importantly, women in the
BCPT were not allowed to take hormone replacement therapy (HRT) concurrently. The European trials did allow enrolled women to take HRT. Allowing enrolled women to take estrogen supplements at the same time confuses the results in two ways. First, given that tamoxifen’s action as a breast cancer preventive agent is likely because of its anti-estrogenic effects, the combination of an anti-estrogen with estrogen supplementation leads to unknown biologic effects. Second, the results of the Women’s Health Initiative now show that HRT use is associated with an increased incidence of breast cancer.\textsuperscript{17}

The BCPT does not address low-to-average risk patients. A major weakness of the study is that 96.5\% of those enrolled were white; the risk reduction seen in this study may not be generalizable to non-whites. Also, it does not include a subset analysis of women with BRCA1 or BRCA2 mutations, and so it does not contribute to our understanding of tamoxifen’s effectiveness in these women.

**Royal Marsden Trial**

The Royal Marsden Hospital randomized controlled trial\textsuperscript{18} compared tamoxifen (20mg per day) for 8 eight years with placebo in women with a family history of breast cancer. It was designed as a pilot study for the International Breast Cancer Intervention Study. Of 1200 women randomized to treatment, over 570 of them discontinued the medication and only 79 completed 8 years of treatment at the time the results were published, at an average of 70 months of follow-up. Although this study did not find a difference between the groups
(RR=1.06, 95% CI, 0.7-1.7), it was likely underpowered to detect a difference even if one exists.

Other reasons why the Royal Marsden results differed from the BCPT results are probably attributable to the differing study populations. The women in this trial were high risk because of a family history of breast cancer. In fact, over half of the patients in the treatment group had a first degree relative diagnosed with breast cancer prior to age 50. Genetic risk factors are more likely to be associated with estrogen-receptor negative tumors, which tamoxifen would be ineffective against. Subjects in the BCPT were more likely to be high risk because of nongenetic risk factors, which are more often associated with estrogen-receptor positive tumors. Finally, about half of the women in the Royal Marsden trial took hormone replacement therapy at some point while enrolled in the trial.

**International Breast Cancer Intervention Study**

The International Breast Cancer Intervention Study (IBIS-1)\(^1\) randomized 7000 high-risk women to tamoxifen (20mg per day) for 5 years or placebo. The complex inclusion criteria included combinations of family history, hormonal factors and previous biopsy-proven diagnosis of ADH or LCIS that placed women at significantly elevated risk for breast cancer. Participants were allowed to take HRT. This study found a 32% risk reduction in the treatment group (RR=0.68, 95% CI, 0.5-0.92). They also found a 31% reduction in benign breast disease and a 32% reduction in breast pain. There was no difference in risk reduction based on age, degree of risk, or HRT use.
There was a significant increase in thromboembolic events and a non-significant increase in endometrial cancer in the treatment group. There was no difference in the incidence of cataracts or fractures. Of note in this study, there was a statistically significant increase in all-cause mortality in the tamoxifen group. This result is different from the BCPT and the Italian trials, which found non-significant decreases in all-cause mortality. The increased deaths were attributable to many different causes, leading the investigators to speculate that this finding may be due to chance.

**Italian Tamoxifen Prevention Study**

The Italian tamoxifen trial\(^2\) randomized 5200 women at low-to-average risk of breast cancer to treatment with tamoxifen or placebo. Inclusion criteria demanded that the woman be post-hysterectomy; 49% also had bilateral salpingoophorectomy. At a mean follow-up of over 80 months, there was no difference in breast cancer incidence between the two groups (p=0.215). Participants were allowed to take HRT. There was a significant difference in breast cancer events between the HRT users in the tamoxifen group (0.92%) and the HRT users in the control group (2.58%). This study was hampered by a high attrition rate and fewer-than-expected breast cancer events, which probably left it underpowered to detect a difference even if one exists. However, given that this represents a lower-than-average risk population, tamoxifen use for chemoprevention of breast cancer is not likely appropriate.
Multiple Outcomes of Raloxifene Evaluation

Raloxifene is a selective estrogen receptor modulator similar to tamoxifen. The major difference is that in addition to having antiestrogenic effects on the breast, it also has antiestrogenic effects on the uterus. The Multiple Outcomes of Raloxifene Evaluation\(^2\) considered breast cancer incidence as one of multiple outcomes. The trial randomized 7700 North American and European postmenopausal women with osteoporosis to one of three arms: placebo; raloxifene 60mg for 3 years; or raloxifene 120mg for three years. The primary endpoint was fracture occurrence.

The MORE trial found a significant decrease in the incidence of invasive breast cancer (RR=0.24, 95%CI, 0.13-0.44). The decrease was seen in ER+ but not in ER- tumors. There was an increase in thromboembolic events, but no increase in endometrial cancer. The breast cancer risk reduction was similar with 60mg and 120mg doses of raloxifene. The NSABP is currently conducting a randomized controlled trial comparing tamoxifen and raloxifene. The Study of Tamoxifen and Raloxifene (STAR) trial will enroll 22,000 women and results are expected in 2008.

Meta-analysis

In 2003 the investigators associated with the Royal Marsdan and Italian studies published a meta-analysis of the five studies outlined above.\(^2\) Overall, breast cancer incidence decreased 38% (95% CI 28-46%). The risk reduction was confined to ER+ tumors. There was no effect on ER- tumors. There was no
difference in risk reduction based on age. The risk of endometrial cancer was 2.4 (95% CI, 1.5-4.0), and the increased risk was most prominent in women over 50 years of age. Thromboembolic events also increased (RR 1.9, 95% CI 1.4-2.6). Incidence of fractures was not evaluated. There was no effect on all-cause mortality, but there was an increase in death from pulmonary embolism in women treated with tamoxifen.

BREAST CANCER RISK

Risk assessment

For decades, investigators have tried to estimate an individual woman’s risk for developing breast cancer. However, breast cancer risk assessment is an imperfect science. The tool most commonly used to assess breast cancer risk is the model developed at the National Cancer Institute. Gail et al. developed the model using case control data from the Breast Cancer Detection and Demonstration Project. The model includes age, age at menarche, age at first live birth, age at menopause, number of first-degree relatives with breast cancer and number of previous breast biopsies. It was later modified to include race and history of ADH. It is not appropriate to use the Gail model for women with a history of breast biopsy revealing LCIS; they are by definition high-risk.

The Gail model was validated recently in a sample of women from the Nurses Health Study. The model predicted risk well in at the population level, although risk was underpredicted in younger women. The model was less effective at predicting individual risk. That is, it has poor “discriminatory
accuracy” at the individual level. If the Gail model is considered as a diagnostic test for future development of breast cancer, it has a sensitivity of 0.44 and a specificity of 0.66. While it does perform better than chance, it is a poor predictor of whether or not an individual woman with a given set of risk factors will actually develop breast cancer. This is one of the fundamental difficulties in applying population based risk assessment tools to individuals.

One of the challenges for advocates of chemoprevention is to better identify those women who may benefit from treatment. While attempting to develop a risk/benefit index, Gail et al. found that tamoxifen was most beneficial for women less than 50 years old with a 5-year risk greater than 1.5%. They conclude that “tamoxifen causes very few adverse events among black and white women under age 50 years and has the potential to prevent invasive breast cancers and in situ breast cancers among high-risk women in this age range.”

The breast cancer risk prediction models currently in use do not attempt to discriminate between those who will develop ER+ tumors and those who will develop ER- tumors. Veronesi et al. used the results of the Italian Tamoxifen Trial to attempt to determine a risk profile that predicts the development of an ER+ tumor. They found a subset of breast cancer patients (13% of the total sample) with a profile that placed them at “high-risk” for ER+ tumors. The risk factors included height above 62 inches, age at menarche less than or equal to 13, age at first birth greater than or equal to 24, overall parity, and the presence of ovaries. Tamoxifen decreased the incidence of breast cancer in this high-risk group by 81%.
Although the results of this subset analysis need to be repeated in other populations, this is intriguing information. If we were better able to predict who might get an ER+ breast cancer, we could restrict the use of tamoxifen to those women who have a higher likelihood of benefit. This would increase the cost-effectiveness of the drug and may tilt the risk/benefit ratio toward overall benefit.

High risk

The definition of “high-risk” for breast cancer varies. Family history, hormonal factors and known genetic mutations can all increase a woman’s risk of breast cancer, as can previous breast biopsies revealing proliferative changes. FDA approval of tamoxifen for breast cancer risk reduction is based on the definition of high risk used in the BCPT – age greater than or equal to 35 and 5-year risk greater than 1.66%. This is a somewhat arbitrary definition of high risk, based on statistical power calculations for the BCPT. Regardless, any woman with a biopsy revealing atypical hyperplasia or LCIS should be considered at increased risk for the future development of breast cancer.

Women who have a mutation in the BRCA1 or BRCA2 gene are at very high risk of developing breast cancer. Their absolute lifetime risk is 80-85%. Tamoxifen has not been studied for breast cancer prevention in this group. However, a case-control study showed that it does offer protection against subsequent contralateral breast cancer following diagnosis of breast cancer. Risk was decreased 62% in BRCA1 carriers and 37% in BRCA2 carriers. The effect of tamoxifen was independent of oophorectomy.27
POTENTIAL PUBLIC HEALTH BENEFIT

Estimates of the potential public health benefit of chemoprevention for breast cancer vary widely. The wide variation in estimates is largely attributable to differing assessments of the number of women who would have a favorable risk/benefit profile. The National Cancer Institute used results from the Cancer Control Module of the National Health Interview Survey to estimate that 15.5% of US women aged 35-79 years would be eligible for tamoxifen based on a 5-year risk of greater than 1.5%. They then used a risk/benefit tool created by Gail et al. based on the results of the BCPT to create an overall risk/benefit index. About 5% of white women (2.4 million women) have a positive risk/benefit ratio. They estimate that 28,500 cases of invasive breast cancer could be prevented over 5 years.25

This estimate differs from the estimate by the authors of the BCPT, who calculated that 700,000 cases of invasive and in situ breast cancers could be prevented in 5 years. The estimate is based on the assumption that all US women who meet eligibility criteria for the BCPT take the full 5-year course, regardless of the woman's potential for adverse events.28

Using a cohort from the Nurses Health Study and very conservative criteria to estimate who might have a net health benefit from tamoxifen, one group concluded that only 3.3% of cases of invasive breast cancer arose from women who would have benefited from tamoxifen. Therefore, only 1.6-1.7% of breast cancers would be prevented by 5 years of tamoxifen.24
In a survey of North Carolina primary care offices, 7-10% of women age 40-69 were identified as appropriate for counseling about tamoxifen use. These women had both a 5-year risk greater than or equal to 1.66% and a low risk of adverse events. Also, 9% reported a history of an abnormal breast biopsy. These authors found that a primary care provider can screen for women who are at high risk by asking about family history and history of biopsy. A woman who answers yes to one of these questions should undergo formal risk assessment using the Gail model. By their estimates, only 6-8% of all breast cancers among women age 40-69 could be prevented with 5 years of tamoxifen treatment. This represents a very conservative estimate, in that any woman with hypertension or diabetes was considered to be at high risk for adverse events.

In an attempt to further define potential benefits of tamoxifen for breast cancer chemoprevention, Col et al. used a patient-specific Markov modeling strategy to calculate gains in life expectancy in women aged 50 or older. For women without a uterus, gains in life-expectancy were two to six months, depending on breast cancer risk. For women with a uterus, there were smaller gains; depending on breast and endometrial cancer risk factors, some losses in life expectancy were noted. The potential gains in life expectancy for postmenopausal women at high risk for breast cancer compare favorably to other preventive measures. For example, mammographic screening every other year from age 50 to age 60 results in average gains of 0.8 months. Cervical cancer screening every three years leads to life-expectancy gains of three months.
TABLE 2: NUMBER NEEDED TO TREAT WITH TAMOXIFEN FOR 5 YEARS TO PREVENT ONE CASE OF BREAST CANCER

<table>
<thead>
<tr>
<th>BREAST CANCER RISK</th>
<th>Average (5-year = 0.99%)</th>
<th>High (5-year = 1.66%)</th>
<th>Highest (5-year = 3.18%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNT</td>
<td>85</td>
<td>51</td>
<td>27</td>
</tr>
</tbody>
</table>

The NNT to induce one case of endometrial cancer in women at average risk for endometrial cancer is 208.

Another potential benefit of tamoxifen for breast cancer chemoprevention involves reducing the morbidities and costs associated with the diagnosis and follow-up of benign breast disease in a high-risk population. Benign breast disease in this population has both economic and psychological consequences. In the BCPT, there was a decrease in invasive breast cancer, in situ breast cancer and benign breast disease. There was a 36% reduction in atypical hyperplasia. The annual rate of breast cancer in women with atypical hyperplasia was 10 per 1000 women in the placebo group, and 4 per 1000 in the treatment group. This implies that tamoxifen effects breast carcinogenesis at an early, preventive phase and also at a later, treatment phase.

CURRENT RECOMMENDATIONS

A search of the National Guidelines Clearinghouse and Medline indicates that the following are the available recommendations for chemoprevention counseling and use.
The United States Preventive Services Task Force recommends that clinicians discuss chemoprevention with women both at high risk for breast cancer and at low risk for adverse effects. These women should be informed of potential benefits as well as potential risks. This is a grade B recommendation. They do not recommend chemoprevention for low-to-average risk women. While chemoprevention may have some benefit for these women, the risks outweigh the benefits. The Canadian Task Force on Preventive Health Care offers similar recommendations.

The American Society for Clinical Oncology says that tamoxifen (20mg per day for 5 years) may be offered for risk reduction in women who have a 5-year risk greater than or equal to 1.66%. The best risk/benefit profile is seen in premenopausal women, those who have had a hysterectomy, or those who are at higher risk. They state that the discussion of chemoprevention should involve informed decision making and should attempt to define individual risks and benefits. Use of tamoxifen with HRT and use of other chemopreventive agents such as raloxifene, aromatase inhibitors or fenretinide is not recommended outside of a clinical trial.

The National Comprehensive Cancer Network recommends that risk reduction therapy counseling should be offered to women with a 5-year risk greater than or equal to 1.7% who have a life expectancy of more than 10 years and no contraindications to tamoxifen. Contraindications to tamoxifen listed are: history of DVT, PE, stroke or TIA; concurrent estrogen and/or progestin use; pregnancy; and pregnancy potential without effective contraception.
THE SURGEON'S ROLE

The surgeon's role in the care of breast patients is multifaceted. Women with benign breast complaints such as pain or fibrocystic changes are often referred to surgeons for clinical breast exam and follow-up. Women with breast masses are seen in consultation by surgeons and undergo radiographic examination to determine the need for biopsy. Women with mammographic abnormalities either see a surgeon for open or percutaneous core breast biopsy, or see a radiologist for percutaneous core breast biopsy. Women with genetic mutations are referred to surgeons for discussion of prophylactic mastectomies. And, the surgeon is involved in the initial and long-term care of breast cancer patients.

In this study, we are particularly interested in women who undergo breast biopsy and are found to have atypical hyperplasia or LCIS – those women whose biopsy results do not reveal cancer but do reveal lesions that place them at high risk for the future development of breast cancer. Each of those women should be cared for by a surgeon at some point during her care.

Radiologists perform percutaneous core breast biopsies in some communities. These are biopsies done for nonpalpable mammographic abnormalities. About 5% of these biopsies will reveal ADH. On average, 16% (range 10-25%) of percutaneous biopsies that reveal ADH will be upstaged to cancer on open biopsy. Therefore, women who have percutaneous biopsies showing ADH should always be referred to a surgeon for open surgical biopsy.
Other studies in the surgery, radiology and pathology literature support this recommendation.

It is also unlikely that a woman with one of the pathologic entities of interest, atypical hyperplasia or LCIS, would be cared for exclusively by a primary care provider. Family practitioners routinely perform aspiration of breast cysts. However, guidelines indicate that women with solid rather than cystic breast lesions should be referred to a surgeon.\textsuperscript{35}

Given that women who have breast biopsies with atypical hyperplasia or LCIS are at increased risk for breast cancer and that chemoprevention studies show that they benefit from tamoxifen, and given that the surgeon who performs the breast biopsy has the first opportunity to discuss chemoprevention, we sought to determine the practice patterns of North Carolina surgeons with respect to breast cancer chemoprevention in these high risk women.

MATERIALS AND METHODS

Subject Selection

The subjects in this study are general surgeons living in North Carolina and licensed to practice by the North Carolina Medical Board. Subjects were recruited from the list of all general surgeons licensed by the North Carolina Medical Board, as listed on the North Carolina Health Professions Data System list maintained by the Cecil G. Sheps Center for Health Services Research.

The inclusion criteria for this study are as follows: Currently a resident of North Carolina; licensed to practice medicine by the North Carolina Medical
Board; listed on the NC Health Professions Data System list maintained by the 
Cecil G. Sheps Center for Health Services Research; and self-reported specialty as 
“surgeon – general” or “surgeon – oncology.” All other medical specialties were 
excluded from this study. In the data analysis, we excluded those respondents 
whose practice does not include breast care.

Research Protocol

This is a single-center cross-sectional, descriptive study based on a self-
administered questionnaire. Subjects were asked to complete one survey, 
expected to take 10-15 minutes to complete. An initial letter and survey were 
mailed to all general surgeons licensed by the North Carolina Medical Board; they 
were sent to the address provided on the NC Health Professions Data System list 
maintained at the Sheps Center. Three weeks later, a reminder post card was sent 
to those subjects who had not responded. Three weeks after that, a follow-up 
letter and another copy of the survey were sent to non-respondents. A follow-up 
letter communicating the results of the survey will be sent to all of the general 
surgeons on the NC Health Professions Data System list to whom the original 
survey was sent.

The survey consisted of two pages of questions. It was designed 
specifically for this study and pilot tested on a small group of general surgeons 
and surgical oncologists. See Appendix.
This protocol was declared exempt from Institutional Review Board review by the Institutional Review Board of the School of Medicine at the University of North Carolina at Chapel Hill.

**Data Analysis**

Data collected include practice type and location, residency and post-residency training, age, gender, amount of practice devoted to breast disease, familiarity with chemoprevention studies and chemoprevention guidelines, and practice patterns and referral patterns for follow-up of chemoprevention. The demographic data were included in the NC Health Professions Data Set and are available for both respondents and nonrespondents.

Univariate analysis will be performed to describe rates of chemoprevention counseling and prescribing. Bivariate analysis will examine relationships between chemoprevention counseling/prescribing and other factors such as volume of breast care, practice type, participation in multidisciplinary clinics or tumor boards, and surgeon factors like age, gender, and post-residency training. If bivariate analyses reveal any significant associations, linear/logistic regression will be performed as appropriate.
RESULTS

TABLE 3: CHARACTERISTICS OF SURGEONS AND THEIR PRACTICE SETTINGS

<table>
<thead>
<tr>
<th></th>
<th>Respondents N= (%)</th>
<th>Nonrespondents N= (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PHYSICIAN CHARACTERISTICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Male)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race (White)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Board Certified</td>
<td></td>
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<tr>
<td>Fellowship Training</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical School Affiliation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; or = 50 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PRACTICE CHARACTERISTICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metropolitan Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Practice Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single Specialty Group</td>
<td></td>
<td></td>
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<tr>
<td>Multispecialty Group</td>
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</tbody>
</table>
TABLE 4: CHEMOPREVENTION PRACTICES

<table>
<thead>
<tr>
<th></th>
<th>N= (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgeons who counsel about chemoprevention</td>
<td></td>
</tr>
<tr>
<td>Surgeons who refer for counseling</td>
<td></td>
</tr>
<tr>
<td>Surgeons who prescribe chemoprevention</td>
<td></td>
</tr>
<tr>
<td>Surgeons who refer for chemoprevention prescriptions</td>
<td></td>
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</tbody>
</table>

Once data collection is complete, we may anticipate the following results:

1. Surgeons are not discussing chemoprevention with high risk patients OR
2. Surgeons discuss or recommend chemoprevention but do not prescribe it OR
3. Surgeons discuss and prescribe chemoprevention OR
4. Surgeons prescribe raloxifene rather than tamoxifen

DISCUSSION

If North Carolina surgeons are counseling high risk women about breast cancer chemoprevention and prescribing chemoprevention, it would be worthwhile to repeat this study in a national sample. It is well established that there is regional variation in the surgical treatment of breast cancer; there may be regional variation in chemoprevention practices as well. It would also be interesting to assess if there are differences in chemoprevention practices between general surgeons and those with additional training in surgical oncology. It is
unlikely that our North Carolina sample will have adequate power to detect this difference.

Even if women at high risk for the future development of breast cancer are being appropriately counseled, patient reluctance to take tamoxifen may be a barrier to the effectiveness of chemoprevention. In a single-institution study of 43 women eligible to take tamoxifen, only two were treated. After undergoing a neutral (although not standardized) physician administered educational session about tamoxifen, 15 women declined immediately and the 26 who were initially undecided eventually declined. Most declined because of a fear of side effects or a reluctance to discontinue HRT. Perhaps most interestingly, after the educational session, more than half were able to accurately describe the risk reduction, but 73% substantially overestimated the risk of complications.\(^\text{36}\)

If we find that North Carolina general surgeons are recommending chemoprevention but not prescribing it, two questions will need to be answered. First, to whom are these patients referred? Referral patterns may vary in different communities; women may be referred to their primary care providers, obstetrician/gynecologists, medical oncologists, or others. Second, are the patients actually receiving the chemoprevention medication? In 2001, 56% of community physicians in North Carolina were not familiar with using the Gail model for breast cancer risk prediction and 69% were not comfortable discussing tamoxifen with high risk women. (Kinsinger, personal communication)

We may find that surgeons are not discussing chemoprevention with these high risk patients. A discussion of chemoprevention options is complicated and
time consuming. There may be a need for an educational intervention to increase surgeons’ familiarity with chemoprevention trial results and current recommendations. Communicating individual risk to patients is difficult because the tools we have are imperfect and because both doctors and patients have a hard time understanding risk. Several studies have shown that women tend to overestimate their breast cancer risk in particular.\(^{37}\)

In a community based sample of 1273 North Carolina women aged 40-55 years insured by Blue Cross/Blue Shield, 23% of women reported that they would be interested in taking a drug to prevent breast cancer. Only 8% of this sample would potentially be eligible for tamoxifen, using a 5-year Gail risk score of >1.66% to define eligibility. However, interest in chemoprevention was not associated with actual risk of breast cancer; it was associated with perceived risk. Thus, interest in chemoprevention appears to arise more from worry than from actual risk.\(^{38}\) This study underscores the importance of appropriately counseling those women who would benefit from chemoprevention while also allaying the fears of those who are not actually at high risk.

Finally, we may find that surgeons are discussing and prescribing chemoprevention, but that they tend to use raloxifene rather than tamoxifen. This would also necessitate an educational intervention. There are a variety of reasons why tamoxifen is preferable to raloxifene at this point in time. While breast cancer was a carefully assessed outcome on the MORE trial and the results are likely to be true, it was a secondary endpoint. Currently, tamoxifen has an FDA indication for breast cancer risk reduction but raloxifene does not. Those
guidelines that address the question recommend raloxifene only within a clinical trial. Perhaps most importantly, tamoxifen’s effectiveness has been replicated in multiple studies, while there is only one study to support the use of raloxifene. Until results of ongoing trials such as STAR and RUTH (Raloxifene Use for The Heart) offer more evidence for the use of raloxifene, tamoxifen will remain the standard of care.

There are unresolved issues regarding chemoprevention of breast cancer. The effect on mortality is unknown; longer follow-up of the randomized trials will allow us to assess disease-specific and overall mortality. Adjuvant studies offer convincing evidence for the optimal length of treatment, but the optimal dose of tamoxifen for prevention, the minimum effective dose, is unknown. The length of ongoing effect is also unknown; adjuvant studies indicate that tamoxifen’s protective effect continues for 5-10 years after the 5 years of treatment. Questions of generalizability to average-risk women and those with BRCA1 and BRCA2 mutations persist. Although minority enrollment in the BCPT was low, results from adjuvant studies with 10-15% minority enrollment indicate that there were similar decreases in contralateral tumors in whites and blacks.

While the overall public health benefit of breast cancer chemoprevention is still debated, it is clear that chemoprevention offers benefit to some subsets of women at high risk for the future development of breast cancer. Advice from surgeons about chemoprevention use following breast biopsy is likely to be important in the patient’s decision to use chemoprevention. There is no evidence available in the medical literature about the surgeon’s effect in this particular
situation. It is known that primary care physician recommendation was the most important factor in a woman's decision to enroll in the BCPT. The surgeon's recommendation to women with breast cancer regarding treatment with breast conserving therapy versus modified radical mastectomy is one of the most powerful factors in her decision. Finally, surgeons play a key role in the recruitment of breast cancer patients to adjuvant therapy clinical trials.
REFERENCES


Please circle the number next to the answer that most accurately reflects your beliefs and practice patterns. Please return this questionnaire no later than MM/DD/YYYY. Thank you for your help.

1. Approximately what percentage of your practice is breast surgery?
   (0) None
   (1) 0-20%
   (2) 21-40%
   (3) 41-60%
   (4) 61-80%
   (5) >80%

If you answered "none" to question #1, please stop now and return your survey in the enclosed self-addressed envelope. Your response is important to us. Thank you.

2. Approximately how many breast biopsies do you perform in an average month? __

3. Of those breast biopsies, approximately what percentage are atypical ductal hyperplasia, atypical lobular hyperplasia or LCIS?
   (0) 0-5%
   (1) 6-10%
   (2) 11-15%
   (3) 16-20%
   (4) >20%

4. As a surgeon, do you think you have a role in discussing breast cancer chemoprevention with patients (i.e. the use of tamoxifen, raloxifene, or other medications for the prevention of breast cancer)?
   (0) No role
   (1) Minor role
   (2) Some role
   (3) Major role

5. Do you bring up the topic of breast cancer chemoprevention with patients who have biopsies that show ADH, ALH or LCIS?
   (0) Never
   (1) Rarely
   (2) Sometimes
   (3) Often
   (4) Always

6. If you DO NOT bring up the topic of chemoprevention with a specific patient, do you ask another healthcare provider to discuss chemoprevention?
   (0) Never
   (1) Rarely
   (2) Sometimes
   (3) Often
   (4) Always

Which healthcare provider do you ask to discuss chemoprevention with these patients? (You may choose more than one answer)

(1) Family Practice
(2) Internal Medicine
(3) Medical Oncology
(4) OB/GYN
(5) Other ___

7. How often do patients ask you about breast cancer chemoprevention?
   (0) Never
   (1) Less often than once a month
   (2) About once a month
   (3) Between once a week and once a month
   (4) One time per week or more
8. Are you comfortable discussing chemoprevention with those patients who bring it up?
   (3) Very comfortable
   (2) Somewhat comfortable
   (1) Not very comfortable
   (0) Not comfortable at all

If you are NOT comfortable discussing chemoprevention, to whom do you refer these patients? (You may choose more than one answer)
   (1) Family Practice
   (2) Internal Medicine
   (3) Medical Oncology
   (4) OB/GYN
   (5) Other

9. As a surgeon, do you think you have a role in prescribing breast cancer chemoprevention drugs?
   (3) Major role
   (2) Some role
   (1) Minor role
   (0) No role

If it IS NOT your role to prescribe chemoprevention, who should prescribe these drugs? (You may choose more than one answer)
   (1) Family Practice
   (2) Internal Medicine
   (3) Medical Oncology
   (4) OB/GYN
   (5) Other

10. If you DO prescribe chemoprevention, approximately how many women have you prescribed it for in the last 6 months? ________

11. If you DO prescribe chemoprevention, which drug(s) do you prescribe? (You may choose more than one answer)
    (0) Tamoxifen
    (1) Raloxifene
    (2) Other

12. How familiar are you with the results of the NSABP P-1 Breast Cancer Prevention Trial, the randomized controlled trial of tamoxifen for breast cancer prevention?
    (0) Not at all familiar
    (1) Somewhat familiar
    (2) Not very familiar
    (3) Very familiar

13. To whom do you look for national recommendations regarding breast cancer prevention? (You may choose more than one answer)
    (1) American College of Surgeons
    (2) American Cancer Society
    (3) National Cancer Institute
    (4) National Comprehensive Cancer Network
    (5) Society of Surgical Oncology
    (6) US Preventive Services Task Force
    (7) Other

14. Do you routinely participate in a multidisciplinary breast cancer clinic or tumor board?
    (0) Never
    (1) Occasionally
    (2) Sometimes
    (3) Almost always
    (4) Always

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE. PLEASE RETURN IT IN THE ENCLOSED SELF-ADDRESSED, STAMPED ENVELOPE BY MM/DD/YYYY.