**Key Words**
Ductal carcinoma in situ, secondary prevention, tamoxifen, radiotherapy, risk reduction behavior

**Abstract**
Ductal carcinoma in situ (DCIS) is a premalignant condition that, if left untreated, may progress to invasive breast cancer. After lumpectomy, DCIS can recur, and about half of recurrences are invasive. In 4 randomized trials, radiation has been shown to decrease the local recurrence rate by about half, though it does not change survival. Based on the results of 3 randomized trials, tamoxifen probably decreases cancer recurrence by about 30%, particularly in young women. Low fat diets, weight loss, and physical activity decrease invasive breast cancer recurrence and may be recommended to certain women with DCIS. Prognostic factors include age, extent of DCIS, margin status, grade, and presence of necrosis, although how these affect adjuvant therapy is unclear. Research evaluating other drugs to reduce recurrence risk and on different ways of delivering radiation continues. (*JNCCN* 2010;8:1211–1217)

Ductal carcinoma in situ (DCIS) is “a proliferation of malignant epithelial cells within the breast parenchymal structures with no evidence of invasion across the basement membrane.” It is one fourth as common as invasive breast cancer, with an age-adjusted incidence of 32.5 per 100,000 women in the United States per year. Approximately 500,000 women in the United States are living with DCIS.

Although not all DCIS will progress to invasive cancer, it is clearly a premalignant condition. Understanding of the natural history of untreated DCIS comes from studies of cohorts of women treated with biopsy alone in whom DCIS was not initially recognized. The rate of development of invasive carcinoma was 14% to 60% within a follow-up of up to 30 years. Most recurrences were in the same quadrant of the same breast as the DCIS, suggesting that these represent progression rather than independent cancers. All these studies are from the prescreening era, and whether the natural history of screen-detected DCIS differs from this is unknown and likely will remain unknown.

The ECOG 5194 study explored the natural history of DCIS treated with lumpectomy alone. Women were eligible for this single-arm study if they had DCIS treated with lumpectomy with 3-mm clear margins that was low- or intermediate-grade and between 0.3 and 2.5 cm in diameter, or high-grade and between 0.3 and 1 cm in diameter. The study was stopped early when the enrollment goal for women with low- or intermediate-grade DCIS was met. The study population included 565 women with low- or intermediate-grade DCIS and 105 women with high-grade DCIS. Approximately 30% of women in each group took tamoxifen for some time. After a median follow-up of more than 6 years, the 5-year rate of invasive cancer or DCIS in the same breast was 6.1% in the low-grade group and 15.3% in the high-grade group. In the opposite breast, the rates were 3.7% and 7.4%, respectively. Rates in both groups continued to rise through at least year 7 without signs of a plateau.

Many patients and clinicians consider a 15% risk of breast cancer over 5 years, half of which are invasive, unacceptably high. Therefore, research has focused on strategies to reduce the risk of breast cancer after lumpectomy for DCIS. These strategies must balance the benefit from reducing breast cancer with risks...
to women who are otherwise asymptomatic, most of whom would not develop breast cancer. This article reviews what is known about risk reduction after breast-conserving surgery using tamoxifen and other drugs, radiation, or lifestyle modification.

**Risk Reduction With Tamoxifen**

Tamoxifen is a selective estrogen receptor (ER) modulator that inhibits ER activation in breast tissue while acting as an ER agonist in bone and endometrium. It is FDA-approved for the treatment of metastatic breast cancer, the adjuvant treatment of invasive breast cancer and DCIS, and breast cancer risk reduction in high-risk women. Three randomized trials have examined the benefit of tamoxifen in women with DCIS after surgical resection (Table 1).

NSABP B-24 was a double-blinded, randomized, controlled trial to assess the usefulness of tamoxifen in reducing recurrent breast cancer, either invasive or in situ, in either breast in women with DCIS treated with lumpectomy and radiation. This study randomized 1804 women with DCIS, 80% of whom had nonpalpable tumors 1 cm or smaller detected on screening mammography, to either tamoxifen or placebo. One third of women were younger than 50 years. Tamoxifen, 10 mg twice daily, was started during radiation and continued for 5 years. It reduced the primary end point, which was recurrent invasive or in situ cancer in either breast, by 37% (P = .0009), from 13.4% to 8.2% at 5 years. The relative reduction was similar for invasive and in situ cancers, although the difference was only significant for invasive cancers, likely because of a higher number of events. Overall survival was high (97%) and not significantly different between groups.

In a subgroup analysis, benefit seemed to be higher in women younger than 50 years (33% vs. 20% reduction), and the absolute rate of recurrence was lower (1.3% per year) in women aged 50 years or older than in women younger than 50 years (3.3% per year). Thus, the absolute benefit of tamoxifen in women aged 50 years or older was small (∼ 0.3% per year). Therefore, the number needed to treat for women younger than 50 years was 91 compared with 333 for women aged 50 years and older.

In invasive cancer, only cancers that express ER or progesterone receptor (PR) benefit from hormone therapy. Whether this is also true for DCIS is unproven. One retrospective analysis of a subset of 628 patients from the NSABP B-24 trial, presented at the San Antonio Breast Cancer Symposium in 2002 but never published, showed that the hazard ratio for breast cancer reduction in ER-positive DCIS was 0.45 (95% CI, 0.25–0.65). For ER-negative DCIS, the hazard ratio was 0.8, but it was not statistically significant. The power was limited by a low number of events in the ER-negative group, and results for this group were considered inconclusive. In 2007, an ASCO guideline on tumor markers in breast cancer concluded that evidence was insufficient to recommend ER/PR testing of DCIS.

The UK DCIS trial was an unblinded 2x2 factorial trial of tamoxifen and radiation in 1694 women who are otherwise asymptomatic, most of whom would not develop breast cancer. This article reviews what is known about risk reduction after breast-conserving surgery using tamoxifen and other drugs, radiation, or lifestyle modification.

**Table 1 Comparison of Randomized Trials of Adjuvant Tamoxifen for Ductal Carcinoma In Situ**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NSABP B-24</th>
<th>UK DCIS</th>
<th>EIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of women</td>
<td>1804</td>
<td>1576</td>
<td>160</td>
</tr>
<tr>
<td>Average age</td>
<td>NR</td>
<td>NR</td>
<td>46</td>
</tr>
<tr>
<td>Percent &lt; 50 years</td>
<td>33.4%</td>
<td>9.5%</td>
<td>NR</td>
</tr>
<tr>
<td>Percent negative margins</td>
<td>75%</td>
<td>100%</td>
<td>NR</td>
</tr>
<tr>
<td>Follow-up</td>
<td>5 y</td>
<td>4.4 y</td>
<td>5.5 y</td>
</tr>
<tr>
<td>Ipsilateral DCIS recurrence</td>
<td>5.1%</td>
<td>3.9%</td>
<td>10%</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>4.2%</td>
<td>2.1%</td>
<td>4%</td>
</tr>
<tr>
<td>Contralateral DCIS recurrence</td>
<td>1.1%</td>
<td>0.2%</td>
<td>1%</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>2.3%</td>
<td>1.8%</td>
<td>2%</td>
</tr>
<tr>
<td>Total breast cancer</td>
<td>13.4%</td>
<td>8.2%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Abbreviations: DCIS, ductal carcinoma in situ; EIO, European Institute of Oncology; NR, not reported.
with screen-detected DCIS and less than 1 mm of microinvasion after lumpectomy with negative margins.12 Fewer than 10% of participants were younger than 50 years. Tamoxifen was given at a dose of 20 mg daily for 5 years. The primary end point was ipsilateral invasive breast cancer recurrence. Tamoxifen had no significant effect on any end point except ipsilateral or contralateral DCIS recurrence, which decreased by 32% ($P = .03$). Interestingly, ipsilateral invasive breast cancer was more common in the tamoxifen group than in the placebo group, although the difference was not significant.

The different results between this trial and the NSABP B-24 trial are likely caused by differences in age distribution and margin status between the populations, and differences in the use of radiation. The relative risk reduction for women younger than 50 years was similar in the trials, at approximately 40%, but was not significant in the UK DCIS trial because of a lower number of events. Moreover, because of the smaller sample size, the CIs for the UK DCIS trial were wider than those for NSABP B-24, and overlap occurred. The overall higher rate of relapse in the UK DCIS trial is likely because of the group randomized to no radiation.

A phase II trial by the European Institute of Oncology randomized 235 premenopausal women, 68% of whom had carcinoma in situ, to tamoxifen, 5 mg daily, or fenretinide in a 2x2 factorial design.13 The mean age was 46 years. Most of the women had DCIS that was ER- or PR-positive. Although not powered for efficacy, a nonsignificant 30% decrease in breast neoplasms was seen with tamoxifen and a significant 62% ($P = .03$) decrease in breast neoplasms was seen with fenretinide. The combination had an equivalent rate of breast events to that seen with placebo. Thus, the tamoxifen data support the results of the NSABP B-24 trial, whereas the fenretinide data need confirmation in a larger study.

In summary, these 3 trials suggest that 5 years of tamoxifen decreases the recurrence of DCIS or new invasive cancer in younger women by approximately 30%. The benefit of tamoxifen in older women is smaller both in relative and absolute terms. These studies were underpowered to detect effects on survival, although survival was high in all cases.

Given the lack of statistical significance in 2 trials and lack of survival improvement with tamoxifen, the risks of tamoxifen are important to weigh. Tamoxifen increases the risk for stroke by approximately 50%, venous thromboembolic disease by approximately 90%, and endometrial cancer by 200% to 300%.14 However, the incidence of each of these is much less than 1% per year in women without particular risk factors, particularly in premenopausal women. Evidence is mixed on the effect of tamoxifen on death from myocardial infarction, for which it may be protective, and gastrointestinal cancer, for which it may confer additional risk.14 Tamoxifen can also affect quality of life and cognition, which may be part of the reason that up to 50% of women with breast cancer stop taking it early.15–17 Therefore, an individualized approach to balancing the benefits and risks of tamoxifen is appropriate.

**Risk Reduction With Other Drugs**

Both aromatase inhibitors and human epidermal growth factor receptor 2 (HER2) blockers are natural subjects for DCIS trials because of their success at preventing recurrence of invasive cancer. Anastrozole is being compared with tamoxifen in the NSABP B-35 trial, which closed in 2006 after enrolling its goal of 3000 postmenopausal women with ER-positive DCIS, and in the IBIS-II trial, which is expected to complete accrual at the end of 2010. The National Surgical Adjuvant Breast and Bowel Project (NSABP) is currently evaluating the role of 2 doses of trastuzumab given with radiation therapy in women with HER2-positive DCIS in the NSABP B-43 trial. The primary end point of this trial is prevention of ipsilateral breast events, including breast cancer, skin cancer, and DCIS. The proposed sample size of 2000 patients should give this study the power to detect small differences. As of May 2010, just under 15% of the required sample size had been enrolled.

Although raloxifene has never been studied in women with DCIS, it was almost as efficacious as tamoxifen at preventing breast cancer in high-risk women without DCIS in the STAR trial, and had fewer side effects. In an update with 81 months of follow-up, the relative risk for raloxifene versus tamoxifen was 1.24 (CI, 1.05–1.47) for invasive breast cancer and 1.22 (CI, 0.95–1.59) for noninvasive breast cancer.18 Although women with DCIS were not included in the STAR trial, their recurrence risk is as high as the breast cancer risk of those who qualified through the Gail model. No current studies listed on
The SweDCIS trial randomized 1046 women with DCIS contained in one breast quadrant who underwent lumpectomy to either observation or radiation with 5000 cGy in 25 fractions, 4800 cGy in 20 fractions, or a split course of radiation. Approximately 10% of women had positive margins. The mean age was 56 years, and 80% of women had non-palpable tumors. Radiation reduced the 5-year rate of ipsilateral breast tumor recurrence by 67%, from 22% to 7%. Approximately half of all recurrences in each group were invasive. No difference was seen in contralateral recurrence, distant metastases, or cancer death.

Given the consistency of the results, it is not surprising that several meta-analyses, including a Cochrane review, have concluded that radiation decreases the occurrence of both invasive and non-invasive ductal carcinoma after lumpectomy for DCIS by approximately 50%.22,23 No difference was seen in distant metastases or survival, although only 63 total breast cancer deaths occurred among all 4 studies combined, limiting the power of this analysis. Except for the lack of blinding, the studies were all of high quality and no evidence was seen of heterogeneity or publication bias.

Current randomized studies are evaluating radiation plus hormone therapy versus hormone therapy alone in women with completely excised hormone receptor–positive DCIS; accelerated partial breast irradiation versus whole breast irradiation in low- or intermediate-risk women by Van Nuys Prognostic Index (VPNI); and radiosensitization with trastuzumab. Both intraoperative radiotherapy and intracavitary radiotherapy are being studied in single-arm studies but have not been evaluated in randomized trials.

Risk Stratification
Is there a way to identify women with a low enough risk of recurrence that the 50% relative risk conferred by radiation does not translate to a significant absolute risk reduction? Tumor grade, presence of comedonecrosis, margin status, and age have all been associated with recurrence.24 Issues related to margin status and its management are discussed in another article elsewhere in this issue. One approach to synthesizing these various factors is to use the University of Southern California (USC)/VNPI.25
The VNPI was derived from a prospectively collected single-center cohort of 660 patients. It uses age, tumor size, margin size, and grade/presence of necrosis to calculate a score from 4 to 12. In independent studies, women with a VNPI score of 6 or less had a 5-year recurrence rate less than 5%, and some believe these women may be able to have radiation omitted safely.\textsuperscript{26,27} Not all groups have been able to independently verify the usefulness of VNPI for stratifying patients, however.\textsuperscript{28} Furthermore, most patients have an intermediate risk according to the VNPI, limiting its usefulness.\textsuperscript{29}

Multiple molecular and immunohistochemical biomarkers have been studied in DCIS, including Ki-67, p53, p21, Myc, HER2, and BCL-2.\textsuperscript{30} However, none has been consistently shown to be an independent predictor of recurrence or survival. Therefore, no molecular and immunohistochemical biomarkers are currently part of the standard pathologic evaluation of DCIS. The current status of biomarkers in DCIS is reviewed in greater depth in another article elsewhere in this issue.

**Lifestyle Modification**

Weight gain is associated with an increased risk of invasive breast cancer in observational and case-control studies.\textsuperscript{31–35} Studies on the effect of weight changes in women with DCIS are lacking, and therefore, investigators must extrapolate from studies of invasive breast cancer.

Two studies have examined the effect of diet on recurrence of early-stage breast cancer. The Women's Healthy Eating and Living (WHEL) study randomized 3088 women to a standard diet or an intensive low-fat, high-fiber, high fruit and vegetable diet plus dietary support.\textsuperscript{36} After more than 7 years of follow-up, no difference in breast cancer incidence was seen. Although women in the intervention group ate significantly more vegetables and less fat than the control women, they still averaged more than 25% of calories from fat and did not lose weight. In a post-hoc subgroup analysis, women without hot flashes at baseline had a statistically significant decrease in recurrence by approximately 30%, from 23.6% to 16.1% at 7.3 years.\textsuperscript{37}

The Women's Intervention Nutrition Study randomized 2437 women with early-stage breast cancer to standard care or dietitian counseling, with a goal of less than 20% of calories from fat. Women in the low-fat intervention group lost 2.7 kg more than those in the control group. Relapses at a median follow-up of 5 years were reduced from 12.4% in the control group to 9.8% in the intervention group (\(P = .003\)).\textsuperscript{38} An analysis after a median follow-up of 9 years that was presented at ASCO showed that a low-fat diet conferred a statistically significant improvement in survival for women with ER-positive cancers.\textsuperscript{39}

In contrast, Women's Health Initiative Randomized Controlled Dietary Modification Trial (WHI-DMT) was a primary-prevention randomized trial of a low-fat diet in healthy postmenopausal women.\textsuperscript{40} The groups did not differ in weight after the intervention, and no difference in breast cancer incidence was seen.

Therefore, whether the particular diet or the weight loss is most important for preventing breast cancer recurrence is unclear. Both the Women's Intervention Nutrition Study (WINS) and WHEL programs were difficult logistically and financially. Nonetheless, encouraging a low-fat diet and weight loss are reasonable for women with DCIS.

Physical activity is associated with a decreased risk of invasive breast cancer in observational studies.\textsuperscript{41–43} In one case-control study, exercise was associated with a lower risk of DCIS in women without a family history of breast cancer but not in those who did.\textsuperscript{44} As with weight loss, moderate exercise is reasonable to recommend to women with DCIS given its other health benefits.

**Conclusions**

The only strategies for risk reduction in women with DCIS that have been studied in randomized controlled trials are tamoxifen and radiation. Radiation reduces ipsilateral breast cancer recurrence by 50%. Because 99% of women with DCIS are alive 5 years later, no survival benefit for radiation has been shown. Further improvement in risk stratification is needed to determine if situations exist in which radiation can safely be omitted. In the meantime, radiotherapy should be offered to all women except possibly those with a low VNPI. Given the lack of survival advantage with radiation, the individual benefits and risks or discomforts associated with radiation should be discussed with each woman.
Tamoxifen reduces breast cancer recurrence in either breast by approximately 30%, although this risk reduction is probably modified by ER status. For women younger than 50 years with ER-positive DCIS, particularly those without risk factors for thromboembolic events, the benefits of tamoxifen outweigh the risks. For women older than 50 years, who are more likely to have risk factors for thromboembolic events or endometrial cancer and who have a lower absolute recurrence risk, the benefits of tamoxifen are less clear, and the risks and benefits of treatment require a careful discussion with patients. Whether tamoxifen benefits women with ER-negative DCIS remains unclear and requires more published research.

Although not supported by level I evidence, women should be educated about the possible effects of diet, weight, and physical activity on recurrence risk. Randomized trials of lifestyle interventions in women with DCIS are needed.

In the next few years, results on aromatase inhibitors and trastuzumab may broaden the armamentarium of drugs for risk reduction. In the meantime, research is needed on risk stratification to avoid undertreating or overtreating individual women.

References


