Tamoxifen added to lumpectomy and radiation therapy reduced breast cancer events in ductal carcinoma in situ

Fisher B, Dignam J, Wolmark N, et al. **Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial.** Lancet. 1999 Jun 12;353:1993-2000.

Question

In women with noninvasive ductal carcinoma in situ (DCIS), does adding tamoxifen to lumpectomy and radiation therapy (RT) prevent cancer in ipsilateral and contralateral breasts?

Design

Randomized {allocation concealed*,†} blinded {clinicians, patients, outcome assessors, and statisticians*†}, placebo-controlled trial with median 74-month follow-up.

Setting

57 centers in the United States and Canada.

Patients

1804 women who had lumpectomy for DCIS, including those with or without lobular carcinoma in situ, and who were expected to live ≥ 10 years. 16% had positive resection margins. Women with previously diagnosed cancer other than in situ carcinoma of the cervix or basal-cell or squamous-cell carcinoma of the skin were excluded. Follow-up was 99.7%.

Intervention

Lumpectomy and RT (50 Gy) began within 8 weeks of surgery and were allocated to tamoxifen, 10 mg twice/d for 5 years (n = 902), or placebo (n = 902).

Main outcome measures

Invasive or noninvasive tumors as first events in the ipsilateral or contralateral breast.

Main results

Fewer breast cancer events, both invasive and noninvasive, occurred in women who received tamoxifen than in those who received placebo (P < 0.001) (Table). Use of tamoxifen reduced invasive events in the ipsilateral breast (P = 0.03) and noninvasive events in the contralateral breast (P = 0.02) (Table). For total breast cancer events, 20 women would need to be treated with tamoxifen for 5 years to prevent 1 additional occurrence of breast cancer. At 5 years, survival was 97% in each group (P = 0.74).

Conclusion

In women with ductal carcinoma in situ, the addition of tamoxifen to a treatment regimen of lumpectomy and radiation therapy was effective in preventing cancer in the ipsilateral and contralateral breast at 5 years without affecting survival.

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For correspondence: Prof. B. Fisher, National Surgical Adjuvant Breast and Bowel Project (NSABP), 4 Allegheny Center, Suite 602, Pittsburgh, PA 15212-5234, USA. FAX 412-330-4411.

*See Glossary.

†Information provided by author.

Lumpectomy, radiation therapy (RT), and tamoxifen vs lumpectomy, RT, and placebo to prevent first breast cancer events at 5 years‡

Events	Cumulative incidence of events		Relative event reduction (95% CI)
	Tamoxifen	Placebo	
All breast cancer	8.2%	13.4%	37% (17 to 53)
Ipsilateral breast cancer			
Invasive	2.1%	4.2%	44% (5 to 68)
Noninvasive	3.9%	5.1%	18% (–28 to 47)‡
Contralateral breast cancer			
Invasive	1.8%	2.3%	37% (–26 to 69)‡
Noninvasive	0.2%	1.1%	78% (19 to 96)

‡Not significant.

Commentary

Fisher and colleagues show that tamoxifen therapy for 5 years adds to the benefit of lumpectomy and radiation in women with DCIS. Some parts of this study, however, merit discussion before it can be concluded that tamoxifen should be recommended for all women with DCIS.

Tamoxifen decreased the rate of invasive breast cancer in the ipsilateral breast (absolute reduction of 2.1%, from 4.2% to 2.1%). For enrollment, pathologic margins of resection for cancer could be either negative or positive, and 16% of patients had involved residual surgical margins. Patients with residual scattered mammographic calcifications were also eligible for enrollment. Margins of resection have been shown to correlate with recurrence in previous retrospective studies. For example, a nonrandomized trial by Silverstein and colleagues (1) showed only a 4% risk for 8-year ipsilateral recurrence with lumpectomy alone in women whose excised lesions had margin widths of ≥ 10 mm. The benefit of tamoxifen might have been lower if the margins of resection were negative, if patients with suspicious residual calcifications had had further surgery, or if an RT boost to the tumor bed had been given to those with positive resection margins.

Although tamoxifen led to a decrease in noninvasive contralateral DCIS, the absolute reduction was 0.9% (from 1.1% to 0.2%), and no significant effect was seen on the rate of contralateral invasive disease.

Tamoxifen appears appropriate for some women with DCIS, but perhaps not for all. Further well-designed trials should attempt to define the subsets of women who will benefit most from this systemic therapy.

Edith A. Perez, MD
Mayo Clinic Jacksonville
Jacksonville, Florida, USA

Reference

1. **Silverstein MJ, Lagios MD, Groshen S, et al.** N Engl J Med. 1999;340:1455-61.

Author's response

The points raised by Dr. Perez regarding positive margins are similar to those recently published in a letter to the *Lancet*, to which we gave a detailed response (1).

Bernard Fisher, MD

Reference

1. **Chan KC, Bundred NJ.** Lancet. 1999;354:1211-2.