Tamoxifen reduced breast cancer risk but increased risks of thromboembolic events and all cause mortality in women

IBIS investigators. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. *Lancet* 2002;360:817-24.

QUESTION: In women with an increased risk of breast cancer, does tamoxifen reduce the risk of breast cancer and what are the associated harms?

Design

Randomised (allocation concealed*), blinded (clinicians, patients, data collectors, outcome assessors)†,* placebo controlled trial with median follow up of 50 months.

Setting

Europe, Australia, and New Zealand.

Patients

7152 women 35-70 years of age (mean age 51 y, 49% postmenopausal) who had an increased risk of breast cancer. Exclusion criteria included previous invasive cancer, previous deep vein thrombosis or pulmonary embolism, anticoagulant use, and pregnancy. Follow up was 99.8%.

Intervention

Women were allocated to receive tamoxifen, 20 mg/day (n=3578), or matching placebo (n=3574) for 5 years.

Main outcome measures

Breast cancer, endometrial cancer, thromboembolic events, cardiovascular events, and mortality.

Main results

Analysis was by intention to treat. Tamoxifen reduced the risk of breast cancer more than did placebo (table); age (<50 or ≥50 y), hormone replacement therapy use (during or before the trial, or never), and definition of invasiveness (ductal carcinoma in situ or invasive disease) did not affect this reduction. Tamoxifen increased the rates of thromboembolic events and all cause mortality (table), but no difference existed for rates of endometrial cancer or cardiovascular events (table).

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Tamoxifen v placebo at median follow up of 50 months‡

Outcomes	Tamoxifen	Placebo	RRR (95% CI)	NNT (CI)
Breast cancer	1.9%	2.8%	32% (8 to 50)	111 (61 to 502)
			RRI (CI)	NNH (CI)
Endometrial cancer	0.31%	0.14%	119% (-20 to 503)	Not significant
Thromboembolic events	1.2%	0.48%	152% (45 to 338)	138 (85 to 320)
Cardiovascular events	2.0%	1.8%	15% (-17 to 61)	Not significant
All cause mortality	0.70%	0.31%	127% (13 to 353)	256 (133 to 1530)

‡Abbreviations defined in glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.

Conclusion

In women with an increased risk of breast cancer, tamoxifen reduced the risk of breast cancer but increased the risks of thromboembolic events and all cause mortality.

*See glossary.

†Information provided by author.

COMMENTARY

The IBIS investigators report the results of a well done study of tamoxifen as chemoprevention for breast cancer. Similar to 3 previously reported studies,¹⁻³ tamoxifen was associated with a 2 fold increase in endometrial cancers and thromboembolic events, the usual anti-oestrogenic side effects, and a comparable risk reduction in invasive and non-invasive breast cancers. An unexpected increase in overall mortality was seen; the most likely explanation for this is either chance or an increase in deaths caused by thromboembolic events. The risk of the latter (and deaths) was greatest during a 3 month postoperative period in patients having major surgery. The authors suggest that stopping tamoxifen preoperatively may be useful. It is premature to recommend this in the absence of other information. It is possible that adequate antithrombotic prophylaxis may be all that is necessary. Clearly, more data are required. Adjuvant trials of tamoxifen should also look at this issue. This large study will contribute useful information in the area of chemoprevention, but longer follow up is needed. Researchers also need to better identify high risk groups, show a survival advantage, and test agents with lower toxicity profile. Newer agents such as the aromatase inhibitors hold promise in this area and need to be tested.

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- 1 Powles T, Eeles R, Ashley S, *et al*. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. *Lancet* 1998;352:98-101.
- 2 Fisher B, Costantino JP, Wickerham DL, *et al*. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998;90:1371-88.
- 3 Veronesi U, Maisonneuve P, Costa A, *et al*. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Italian Tamoxifen Prevention Study. *Lancet* 1998;352:93-7.