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


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 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).

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.

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

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, 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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