Endometrial cancer and venous thromboembolism in women under age 50 who take tamoxifen for prevention of breast cancer: a systematic review


CRD summary
This review concluded that the risks of endometrial cancer, deep vein thrombosis, and pulmonary embolism were low in women younger than 50 who take tamoxifen for chemoprevention of breast cancer. Limitations of the evidence base and in the reporting methods of the review suggest that these conclusions may not be reliable or applicable to all women in this population.

Authors' objectives
To evaluate the risks of endometrial cancer, deep vein thrombosis, and pulmonary embolism in women younger than 50 years taking tamoxifen for chemoprevention of breast cancer.

Searching
The Cochrane Central Register of Controlled Trials, the National Library of Medicine (PubMed) and clinical trial registries were searched up to November 2010 for articles in any language. Key words used in the search were reported. Grey literature, conference proceedings and reference lists of relevant publications were also searched. Additional data were obtained through contact with manufacturers and principal investigators of clinical trials.

Study selection
Randomised placebo-controlled trials that investigated the use of a standard daily dose (20mg) of tamoxifen among women (aged <50 years) with no pre-existing breast cancer or ductal carcinoma in situ were eligible for inclusion. To be included, trials were also required to have a duration of at least five years with the goal of chemoprevention. Trials solely containing women older than 50 years were excluded, as were trials of post-menopausal women and those which included women with a prior hysterectomy.

Primary outcomes of interest included the incidences of endometrial cancer, deep vein thrombosis, and pulmonary embolism. The secondary outcome of interest was mortality resulting from the primary outcomes.

The included trials were conducted in the USA, Canada, the UK (two trials), other European countries (not specifically stated), Australia, and New Zealand. All trials enrolled women with increased risks of breast cancer; the criteria used in the risk assessments for breast cancer varied. Other inclusion criteria relating to women's age and clinical characteristics also varied across the studies. Treatment duration ranged from five to eight years.

Two reviewers independently selected the studies for inclusion in the review; any disagreements were resolved by a third reviewer.

Assessment of study quality
Trial quality was assessed according to the Cochrane risk of bias criteria for: randomisation; allocation concealment; blinding of personnel, participants and outcome assessors; incomplete outcome data reporting; selective reporting; and other bias. Each trial was categorised as having a low, high or unclear risk of bias. The overall quality and applicability of the data was categorised as good, fair, or bad (criteria not reported).

The authors did not state how many reviewers assessed the quality of the studies.

Data extraction
Data on the outcomes (numbers of events per trial arm) were extracted to calculate risk ratios using the Fisher's exact test.

Two reviewers independently extracted the data.

Methods of synthesis
Relative risks, 95% confidence intervals, and two-sided p-values for the individual trials were estimated (no further details reported).

Subgroup analyses were performed according to age (<50 years versus ≥50 years) and menopausal status (pre-menopausal versus post-menopausal) to provide combined relative risks, 95% confidence intervals and p-values; these were only performed for two of the three included trials because one trial did not report sufficient data. A sensitivity analysis was performed according to risk of bias results.

**Results of the review**

Seven publications describing three randomised controlled trials were included in the review (22,800 women). One trial was rated as having low risks of bias for all domains, except for the domain of other bias (rated as high risk). The other two trials were rated as having low risks of bias for randomisation, allocation concealment and blinding, and high risks of bias for incomplete outcome data, selective reporting, and other bias.

One trial (13,175 women) found that the overall relative risks were statistically significantly higher among the tamoxifen group than the control group for endometrial cancer (RR 2.46, 95% CI 1.35 to 4.48) and pulmonary embolism (RR 3.01, 95% CI 1.20 to 1.58). Another trial (7,154 women) found a statistically significantly higher risk of deep vein thrombosis among tamoxifen participants (RR 1.68, 95% CI 1.13 to 2.51). No other statistically significant differences between the tamoxifen and control groups were found in the individual trials.

Subgroup analyses of women younger than 50 years (two trials) showed that there were no statistically significant differences between tamoxifen and control groups for the risks of endometrial cancer (RR 1.19, 95% CI 0.53 to 2.65) and pulmonary embolism (RR 1.16, 95% CI 0.55 to 2.43). A statistically significantly higher risk of deep vein thrombosis was observed among tamoxifen groups in the active phase of treatment (RR 2.30, 95% CI 1.23 to 4.31), but by the follow-up phase this difference was no longer statistically significant (RR 1.00, 95% CI 0.38 to 2.67).

Further results were reported in the review.

**Authors' conclusions**

The risks of endometrial cancer, deep vein thrombosis, and pulmonary embolism were low in women younger than 50 who take tamoxifen for chemoprevention of breast cancer.

**CRD commentary**

The review question was clear and the inclusion criteria were sufficiently replicable. Attempts were made to locate published and unpublished literature, and no language restrictions were imposed; this reduced the risk of missing relevant studies.

A suitable quality assessment tool was used; the results showed that the quality of included trials was variable. Trial details (particularly participant characteristics) were reported in limited detail. The statistical synthesis was limited by the clinical differences between the trials plus not all of the results appeared to have been reported. The authors acknowledged that two of the three included trials did not report on the ethnicity of their participants, and that the remaining trial's population were mostly Caucasian/white (96%). The authors also stated that hormone replacement therapy was used alongside tamoxifen in two trials and this may have had additive effects on venous thromboembolic events related to tamoxifen treatment. The lack of screening methods at enrolment meant that women who were at increased risk of the outcome conditions may have been enrolled. There was a slight discrepancy between the authors' conclusions reported in the review abstract and the main text; those used in this abstract were based on the main text.

Limitations of the evidence base and in the reporting methods of the review suggest that the authors' conclusions may not be reliable or generalisable to all women younger than 50.

**Implications of the review for practice and research**

Practice: The authors stated that information regarding actual rates of endometrial cancer, deep vein thrombosis, and pulmonary embolism may be helpful for young, high-risk women considering tamoxifen for chemoprevention of breast cancer.

Research: The authors stated that a randomised controlled trial is required to compare the risks of serious adverse
effects associated with a short course of low-dose tamoxifen versus a traditional 5-year course.

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