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## Tibolone and breast cancer

● **Tibolone is a synthetic steroid marketed for the treatment of menopausal symptoms.**

● **A cohort study of women with no history of breast cancer showed that tibolone was associated with an increased risk of breast cancer.**

● **In women with a history of breast cancer, a placebo-controlled trial showed a higher risk of breast cancer recurrence with tibolone.**

● **A placebo-controlled trial of half the standard dose of tibolone showed no increased risk of breast cancer but was interrupted due to an increased risk of stroke.**

● **In practice, it is better simply not to use tibolone.**

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**T**ibolone is a synthetic steroid with oestrogenic, progestogenic and androgenic properties. It is marketed for symptomatic relief of menopausal symptoms (1-3).

In the Women's Health Initiative (WHI), a randomised double-blind trial including 16 000 postmenopausal women with a mean age of 63 years at enrolment and who were monitored for 5.2 years on average, oestrogen-progestogen treatment was associated with 8 additional invasive breast tumours per 10 000 woman-years compared to placebo (4).

This review examines the latest data on the risk of breast cancer in women treated with tibolone.

**Postmenopausal women with no history of breast cancer: increased risk of breast cancer.** The British Million Women Study involved a cohort of postmenopausal women aged 50 to 64 years who were monitored for an average of 2.6 years. Among the women who used hormone replacement therapy, 6% took tibolone.

Among women treated with tibolone, the risk of being diagnosed with invasive breast cancer was 1.5 times higher than

in women who did not use hormone replacement therapy (relative risk (RR): 1.45; 95% confidence interval (CI): 1.25 to 1.68) (1-5)(a).

**A placebo-controlled trial: increased risk of breast cancer recurrence.** The Liberate study, a randomised double-blind multicentre trial, compared tibolone 2.5 mg/day versus placebo in terms of the risk of breast cancer recurrence. It included 3148 women with a mean age of 53 years and a history of surgically treated breast cancer. Most of the women were receiving tamoxifen, an oestrogen antagonist.

After a median follow-up of 3.1 years, a statistically significant increase in the rate of breast cancer recurrence was observed in the tibolone group (237 cases, versus 165 cases in the placebo group; RR: 1.4; 95% CI 1.1-1.7) (6).

**An uninformative trial of half the standard dose of tibolone.** The Lift study, a randomised double-blind trial, compared tibolone versus placebo for fracture prevention in 4538 osteoporotic postmenopausal women aged 60 to 85 years. The daily tibolone dose was half that recommended in the marketing authorisation (1.25 mg instead of 2.5 mg) (7).

The trial was interrupted because of an excess of strokes in the tibolone group, after a median treatment period of 3 years (RR: 2.19; 95% CI%; 1.14-4.23; p=0.02).

The risk of breast cancer was one of the secondary endpoints. The incidence of invasive breast cancer was lower in the tibolone group than in the placebo group, with respectively 6 cases (0.9 per 1000 patient-years) and 19 cases (2.8 per 1000 patient-years) (RR: 0.32; 95% CI; 0.13-0.80; p=0.02) (b)(8). These results are not very reassuring, however, given the low dose regimen (c).

**In practice.** Tibolone appears to increase the risk of breast cancer in postmenopausal women when used at the standard dose. A trial evaluating a lower dose was stopped because of an increased risk of stroke in the tibolone

arm. In summary, the risks associated with tibolone outweigh its benefits.

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**a-** A UK case-control study showed no increase in breast cancer in women taking tibolone. However, the risk was higher in the subset of women who switched to tibolone from oestrogen-progestogen therapy (9).

**b-** This trial was funded by Organon, the company that markets tibolone (ref 7).

**c-** By convention, prior definition of a primary endpoint authorises the use of a p value of <0.05 to define statistical significance, while for secondary endpoints a threshold of 0.01 more closely reflects the 5% error risk (ref 10).

### Selected references from Prescrire's literature search.

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