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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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Tibolone 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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