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Progestagen-only treatment before menopause: increased risk of breast cancer

● **A prospective cohort study (E3N) conducted in France included approximately 100 000 women aged 40 to 64 years who were regularly questioned about their use of hormone and other treatments. More than 70 000 of the 100 000 women responded to the questionnaire. The study showed an increase in breast cancer among women using an oral progestagen alone for more than 4.5 years before menopause (low-dose progestagens were excluded from the study).**

● **The risk of developing breast cancer was approximately 1.5 times higher than among women who had not taken progestagen. After progestagen discontinuation, regardless of treatment duration, the risk of breast cancer dropped to levels similar to those of non-users.**

● **There is widespread use of progestagen-only products before menopause in spite of the lack of robust evidence concerning their risk-benefit balance, particularly with long-term treatment. It is advisable to evaluate drugs before their use provokes adverse reactions in patients.**

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In France, various oral progestagens have long been used for various benign menopause-related disorders, in spite of the lack of robust clinical trial evidence on the risk-benefit balance of long-term treatment (1,2,3).

However, the WHI trial and other studies showed that hormone replacement therapy with the oestrogen/progestagen combination for menopause leads to an increased risk of breast cancer (1,2). Progestagens play an important role, but the progestagens examined in these studies of menopausal women are not the ones most commonly prescribed in France.

Although low-dose progestagens were excluded from the analysis, French epidemiological data published in 2007 provide interesting insights.

A French cohort study. A French study based on data from the E3N cohort included about 100 000 women aged 40 to 64 years, who were covered by complementary health insurance (the *Mutuelle générale de l'éducation nationale* [MGEN]) (3,4).

Since 1990, these women have been questioned every two years about their lifetime use of hormone therapy. More than 70 000 women responded to the questionnaire.

Progestagens taken alone before menopause lead to an increase in breast cancer. 28 370 women had used progestagen-only products; low-dose progestagens were not analysed in this study.

An increase in the risk of breast cancer was observed in women taking oral progestagen without oestrogen for more than 4.5 years before menopause. These women had an approximately 1.5 times higher risk of developing breast cancer than women who did not take progestagen. After progestagen discontinuation, the risk of breast cancer again fell to levels similar to those of non-users, regardless of treatment duration (3,4).

This epidemiological study provided a low level of evidence. But the results are in keeping with data from clinical trials, which showed an increase in breast cancer risk among menopausal women using hormone replacement therapy. This increased risk appears to be linked to the progestagen component of the combination.

Drugs should be assessed before they cause adverse effects. These data suggest that progestagen treatment should be avoided, and that women taking progestagen should be closely monitored.

There has been widespread use of hormone replacement therapy for menopause in spite of the lack of robust evidence on the risk-benefit balance of long-term treatment. Post-authorisation evaluation revealed the magnitude of the risk associated with this therapy. Similarly, there seems to be an increased risk of breast cancer in premenopausal women treated with progestagens.

These examples illustrate the importance of thoroughly evaluating the risk-benefit balance of drugs before marketing authorisation is granted. If, due to the general lack of caution, the risk-benefit balance turns out to be negative after the drug is on the market, it is often too late for patients.

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Selected references from Prescrire's literature search.

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3- Institut national de la santé et de la recherche médicale "Impact de la prise de progestatifs oraux seuls avant la ménopause sur le risque de cancer du sein" 5 April 2007. www.inserm.fr accessed 24 December 2007: 2 pages.

4- Fabre A et al. "Oral progestagens before menopause and breast cancer risk" *Br J Cancer* 2007; **96** (5): 841-844.

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