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Postmenopausal hormone replacement therapy: what is the risk of breast cancer?

● **Recently, a pharmaceutical company sales rep sent me a reprint of a follow-up study of the E3N cohort, which assessed the risk of breast cancer associated with postmenopausal hormone replacement therapy and attempts to downplay the adverse effects of oestrogen. What should I make of this study, asked Jacques Guitard, General practitioner in France?**

Long-term research evidence on the risk-benefit balance of postmenopausal hormone replacement therapy has taken a long time to emerge. It was in the late 1990s that the results of clinical trials first began to provide estimates of the risks of cardiovascular disease and cancer (1).

Postmenopausal hormone replacement therapy is associated with an increased risk of breast cancer. In 2002 a randomised placebo-controlled trial of hormone replacement therapy based on sulfoconjugated equine oestrogen plus medroxyprogesterone in 16 000 women (the WHI trial) was stopped early because of an excess of adverse effects including breast cancer among the women randomised to hormone use. Similarly, the second part of this study, which compared sulfoconjugated equine oestrogen monotherapy with a placebo in 11 000 hysterectomised women was stopped due to an excess of cerebrovascular adverse effects (2,3). There was, however, no increase in the frequency of invasive breast cancer among women taking oestrogen alone, the yearly incidence of which was about 0.3%.

Recent epidemiological studies also provide data on the risks of breast cancer, albeit with a lower level of evidence than randomised controlled trials. Follow-up of a very large British cohort (the Million Women Study) showed a statistically significant increase in the risk of breast cancer with other types of hormone replacement therapy, such as oestrogen-progestin combinations, oestrogen alone, and tibolone (4). The results of a Swedish cohort study and an American case-control study also suggested an increase in the risk of breast cancer associated with progestin use.

A combination of sulfoconjugated equine oestrogen and medroxyprogesterone is the best-evaluated postmenopausal hormone replacement therapy. Other treatments, especially those commonly used in France, are less well evaluated. In October 2005 the French medicines agency none the less published an estimate of the number of cases of breast cancer and cardiovascular events attributable to postmenopausal hormone replacement therapy in France in 2000-2002 (5).

A French cohort study. This French prospective cohort study (the E3N cohort) involved 98 997 women born between 1925 and 1950, identified from a health insurer's database (MGEN) (6). The women were first asked in 1992 to list any hormone treatments they had taken, and were then questioned regularly every two years.

54 548 postmenopausal women who had not used hormone replacement therapy during the year before their entry to the E3N study were followed for an average of 5.8 years. Invasive breast cancer was diagnosed in 948 women, who had been taking hormone replacement therapy for an average of 2.8 years.

The risk of breast cancer was significantly higher among users of hormone replacement therapy than among non users: the relative increase in the risk was 20%, with a 95% confidence interval of 10% to 40%.

The risk of breast cancer did not seem to increase significantly in women who used oestrogen alone: the 95% confidence interval ranged from a 20% reduction in the relative risk to an increase of 60%.

With oestrogen-progestin combinations there was a 30% relative increase in the risk of breast cancer, with a 95% confidence interval of 10% to 50%. Among users of micronised progesterone, the risk of breast cancer was 10% lower than in non users, but the 95% confidence interval ranged from a 30% reduction to a 20% increase. In women who used synthetic progestins, the risk of breast cancer increased by 40% compared to non users (confidence interval 20% to 70%). The risk of breast cancer was not significantly influenced by the mode of oestrogen delivery (**a**).

These data come from an observational study, meaning that various potential biases could not be controlled and that the level of evidence is weak. In particular, it is unclear whether the women who took micronised progesterone were comparable to those who used a synthetic progestin.

The study report does not mention the incidence of endometrial cancer.

In practice. The risk of breast cancer increases in women taking postmenopausal hormone replacement therapy based on an oestrogen-progestin combination. Data comparing available progestin combinations are sparse and unreliable.

It is possible that micronised progesterone has a different effect in terms of cancer risk than other progestins, but it is equally possible that the relevant results of the E3N study are biased and that, in fact, the cancer risk also increases with micronised progesterone. The authors of the E3N study emphasised the weaknesses of their study and called for additional research to answer these questions (6).

It is therefore better not to use postmenopausal hormone replacement therapy for long periods, whether or not it includes micronised progesterone.

a- A French multicentre case-control study conducted from 1999 to 2004 compared 179 patients hospitalised for pulmonary embolism or deep venous thrombosis, plus 56 non hospitalised patients, with 362 hospitalised controls and 192 non hospitalised controls. The increase in the risk of thrombosis associated with oestrogen use appeared to be smaller when oestrogen was delivered transdermally rather than orally, but the results represent a low level of evidence and comparative trials are lacking (ref 7). Like the E3N study, this study was examined by a task force convened by the French medicines agency, which, in June 2006, considered that the results did not challenge practice guidelines existing prior to these studies (ref 8). ▶▶

1- Prescrire Editorial Staff "Postmenopausal hormone therapy: cardiovascular risks" *Prescrire Int* 2003; **12** (64): 65-69.
2- Prescrire Rédaction "Ménopause: arrêt de l'essai WHI estrogène versus placebo" *Rev Prescrire* 2004; **24** (249): 273.
3- Stefanick ML et al. ''Effects of conjugated equine oestrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy'' *JAMA* 2006; **295** (14): 1647-1657.
4- Prescrire Editorial Staff "Risk-benefit balance of postmenopausal hormone replacement therapy" *Prescrire Int* 2004; **13** (71): 106-109.
5- Prescrire Rédaction "Hormonothérapie de la ménopause et cancers du sein: une évaluation française" *Rev Prescrire* 2005; **25** (267): 829.
6- Fournier A et al. "Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort" *Int J Cancer* 2005; **114**: 448-454.
7- Scarabin PY et al. "Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women. Impact of the route of oestrogen administration" *Circulation* 2005; **112**: 3495-3500.
8- Agence française de sécurité sanitaire des produits de santé "Traitement hormonal de la ménopause. Point d'étape. Juin 2006" 21 pages.

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Clopidogrel and mortality

Several readers challenged our presentation and interpretation of the CHARISMA and CLARITY-TIMI trials. Prescrire justifies its assessment.

Once again your presentation of clinical trial results in issue 273 of la revue Prescrire (translated in Prescrire International n° 85 page 194) adopts a negative ("the glass is half-empty") point of view. With respect to the Clarity TIMI 28 study, you stated that there was no significant effect on mortality at one month, on the basis of an endpoint combining recurrent myocardial infarction, stroke and cardiovascular death. You could just as well have pointed out ("the glass is half-full") that, at one month, study data also show a 20% reduction in an endpoint combining cardiovascular death, myocardial infarction, recurrent ischaemia necessitating revascularisation (p=0.026; confidence interval (CI) 0.65–0.97); or alternatively that at one month there was a statistically significant reduction in an endpoint combining cardiovascular death, myocardial infarction, stroke and recurrent ischaemia necessitating revascularisation (1).

Similarly, you provide details on a subgroup of high-risk patients with no documented cardiovascular events in the Charisma study, and correctly conclude that, in this population, the clopidogrel-aspirin combination is no better than aspirin alone. But then you fail to provide corresponding data for the subgroup of patients who had already had cardiovascular events and who benefited from the two-drug combination compared with aspirin alone, even though the difference was only just statistically significant (p=0.046; CI 0.77 - 0.998) (2).

If you want to maintain the integrity and quality of your journal, as well as the accuracy of the articles you publish, you should provide your readers, especially non specialists, with all the available data from a study and not just selected results. (Drug companies tend to do the same thing, but from "the glass is half-full" perspective.)

I hope these suggestions will contribute to tempering the systematically negative tone you adopt when examining new studies.

Alain Pinzani
Cardiologist
France

I am just a "simple" vascular physician with no shares in Sanofi Aventis. I have the following question: in the first half of the article entitled "Patients at high cardiovascular risk: excess mortality of about 1.6% on aspirin + clopidogrel" (la revue Prescrire issue 273, Prescrire International n° 85), was the study population receiving primary or secondary prevention? Your article is not very clear on this point, nor is the summary of the original publication (2,3). If the patients were receiving dual-agent antiplatelet therapy as primary prevention, the negative results are hardly surprising.

Laurent Marcy
Specialist in vascular medicine
France

In any randomised controlled trial, only a full analysis of the primary endpoint in the entire study population, which is only possible once the trial has been completed, can provide meaningful statistical and clinically relevant conclusions. Analyses of subgroups or secondary endpoints are purely exploratory approaches and can never replace the analysis of the primary endpoint.

The Charisma study compared aspirin + clopidogrel with aspirin + placebo in patients at high risk of atherothrombotic disease (2,3). The primary outcome measure was a composite score combining myocardial infarction, stroke, and death due to cardiovascular causes. These events occurred in 6.8% of patients receiving aspirin + clopidogrel and in 7.3% of patients receiving aspirin + placebo; the confidence interval ranged from 0.83 to 1.05 and the difference was not statistically significant. This means there is no point adding clopidogrel to aspirin in this setting. This much at least is perfectly clear.

Three-quarters of at-risk patients had already had a symptomatic vascular disorder (coronary heart disease, stroke, lower-limb artery disease), and one-quarter of patients had multiple cardiovascular risk factors. When the editors of the Charisma article (or the sponsors) state that there was a significant difference in favour of clopidogrel in patients with symptomatic atheromatous arterial disease, they base their claim on a subgroup analysis that has no clinical relevance. Moreover, the patients were not stratified for this inclusion criterion before randomisation, and this retrospective comparison cannot provide reliable evidence. At best, it might warrant a new clinical trial only focusing on this type of patient.

When Prescrire makes exactly the same mistake (but in reverse), it is just as serious (or perhaps even more serious for strict methodologists). The title of your article "Patients at high cardiovascular risk: excess mortality of about 1.6% on aspirin + clopidogrel" was also based on a subgroup analysis that has no clinical significance. Worse, by focusing on the excess overall mortality in this subgroup you are emphasizing what is only a secondary endpoint. This concerns a "sub-