

## EMAS Comment on the Last WHI Paper

### **Fall in breast cancer risk following stopping combined HRT: update from WHI.**

Data on breast risk and combined HRT use from the WHI studies are published on the 5 February 2009 issue of the New England Journal of Medicine. Both the randomized trial and observational study cohorts are analyzed [1]. In the randomized trial, there were fewer breast-cancer diagnoses in the group receiving estrogen plus progestogen than in the placebo group in the initial 2 years of the study, but the number of diagnoses increased over the course of the 5.6-year intervention period. The elevated risk decreased rapidly after both HRT and placebo users stopped taking the study pills, despite a similar frequency of mammography. The number of breast-cancer diagnoses in the HRT group decreased by 28% from the last year of the intervention phase to the first year of the postintervention phase. In the observational study, the incidence of breast cancer was initially about two times as high in the group receiving HRT as in the placebo group, but this difference in incidence decreased rapidly in about 2 years, coinciding with year-to-year reductions in combined hormone use.

This rapid fall in breast cancer risk on stopping HRT is reassuring but is faster than that found in other studies. The authors conclude that 'the rapid decrease in breast cancers during the postintervention period suggests that withdrawal of estrogen-plus-progestin therapy leads to a regression of preclinical cancers.'

**Comment:** This rapid effect on stopping HRT appears bizarre because one would have expected a rapid increase in breast cancer risk in the early years of the randomized trial when there were fewer diagnoses. Also the fall in breast cancer risk in placebo users is unexpected as the major risk factor for breast cancer is increasing age. Analysing in detail the data there are some intriguing observations: the annualized percentage rate of breast cancer in the non treated group fluctuates according to time suggesting confounding factors. In addition, the rate of use of diagnostic tools (mammograms and biopsies) was higher in both groups. This suggests that the diagnostic approach to breast cancer may be linked to factors which can lead to fluctuation in the number of events over short periods.

In addition, it may be premature to attribute the decrease of breast cancer, as observed in some countries, to the unique effect of decreased HRT consumption. Indeed a relation does not imply necessarily a causality, especially as it is not known whether similar observations will be reported in patients using estrogen only, or different combined regimens, as discussed in the recent EMAS statement(2).

1. Chlebowski RT, Kuller LH, Prentice RL et al; WHI Investigators. Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med. 2009 Feb 5;360(6):573-87.
2. Gompel A, Rozenberg S, Barlow DH; EMAS board members [The EMAS 2008 update on clinical recommendations on postmenopausal hormone replacement therapy.](#) Maturitas. 2008 Nov 20;61(3):227-32

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