The effects of exogenous hormones on diseases that are hormonally related, particularly breast cancer, cause concern. Breast cancer is common and the relation with hormones complex. Millions of women have taken menopausal oestrogen and progesterone (hormone therapy, HT) for prolonged periods to alleviate menopausal symptoms, to prevent osteoporosis, and to prevent coronary heart disease too.

The breast cancer risk of HT has been investigated since the 1970s in some 50 studies. It has been known that it was associated with an increase in breast cancer, but there has been confusion because of the possible differential effect of different hormones as well as of different durations, methods of application, and the effect of past use. It was none the less argued that the risk was small. It is surely a public health responsibility to clarify these risks as far as possible. This is particularly so when the marketing imperatives are so strong.

Use of combined therapy became common in the 1980s, after years of use of oestrogen alone were found to increase endometrial cancer risk, which the addition of progesterone eliminated. Thus epidemiological data on combined therapy were less mature and often confused with data on unopposed therapy, which had been the subject of most studies. The addition of progesterone could, in theory, have had a differential effect on breast cancer risk in any direction.

The million women study, published in 2003, showed that five years or more of use of combined HT doubles the risk among current users, which is more extreme than oestrogen alone. Such a risk has important public health implications, when 25% of menopausal women were estimated to use HT by 2000. How much could we have known, by when, of the effect of long term combined HT use, with better pharmacovigilance? To investigate this question we have used quick and efficient statistical methods that require simple analyses of published data, and thus were available to all.

**METHODS**

We undertook a systematic review of the published research literature of all studies that examined the relative risk of breast cancer with five or more years of recent combined HT use. Some studies did not distinguish between unopposed or combined use and we included them only if the proportion of combined use was stated as being 30% or more. We pooled the risk estimates; using conventional fixed effect meta-analysis, calculated cumulative pooled estimates after each eligible study was published (final three columns in table 1). Where studies reported risk for several categories of use over five years we similarly pooled these estimates to provide one weighted estimate for each study. Relative statistical weights were estimated from the stated confidence limits of odds ratio (OR) estimates. Also where risks were only reported separately for subgroups, we pooled the estimated effects for the category closest to current use of five or more years of combined HT.

**RESULTS**

It may be seen in table 1 that the million women study dominates any final estimates statistically as it was so large. It however estimates higher risks (significantly) than the synthesis of all other previous studies. Some small individual studies estimate risk higher than 2.0, but this is to be expected by chance. However by 1989 a pooled relative risk of around two was significant and hence should have been
The long term safety of medicinal products designed to alleviate common symptoms in the short term and that therefore have an enormous potential market require rigorous and routine assessment. Epidemiological studies should always report findings separately for drug type and categorised into meaningful duration groups. The paucity of epidemiological data in some groups early in the experience of a product is not a special problem when subjected to proper meta-analysis across studies as they accumulate. Indeed it is an essential part of such assessment. But it is necessary to be rigorous about sensible subgroups of exposure and outcome, a priori. This should be routine.

Authors’ affiliations
K McPherson, R Mant, Nuffield Dept of Obstetrics and Gynaecology, Oxford University, UK

Funding: none.

Conflicts of interest: none.

Correspondence to: Professor K McPherson, Oxford University, John Radcliffe Hospital Womens Centre, Level 3 Headington Oxford OX3 9DU, UK; klim.mcpherson@obs-gyn.ox.ac.uk

Accepted for publication 26 March 2005

REFERENCES


