

# COMMENTARY

## Breast cancer and hormone replacement therapy

See page 1047

Women making decisions about hormone replacement therapy (HRT) will find it helpful to have the information from the thorough reanalysis reported in today's *Lancet* of accumulated epidemiological data on the very salient question of whether use of HRT for many years increases the risk of breast cancer. In this study, the results are based on more than 160 000 women from around the world who participated in 51 different epidemiological investigations over the past 25 years or so. More than 900 of the women eligible for this analysis had been on HRT for 15 or more years. This analysis reveals an increased relative risk of breast cancer among current or recent users of HRT for more than 5 years and shows that risk is associated with duration of use.

Strengths of this report include the search for all relevant studies, the reanalysis of the source data for each study using the same variable definitions and statistical methods, the consideration of numerous confounding factors, and the use of conservative 99% confidence intervals for all but the main comparisons. However, despite the large numbers of women included in this analysis, only 12% of hormone users had been exposed to progestagens. Thus, HRT in this report refers predominantly to the use of oestrogen with or without progestagen, and there remains too little information on the use of progestagens with oestrogen for long periods to draw firm conclusions on the combination.

An association between HRT and breast cancer is biologically plausible. On the basis of the pattern of reproductive risk factors for breast cancer (early menarche, late menopause, nulliparity, delayed childbearing), it has been postulated that lengthy exposure to normal concentrations of endogenous oestrogen in the premenopausal years increases risk of breast cancer later on by stimulating excessive proliferation of normal mammary epithelial stem cells, thereby increasing the likelihood of eventual transformation of stem cells into intermediate cells. Excess oestrogen concentrations after the menopause were then postulated to weakly increase the risk of transformation of intermediate cells into tumour cells.<sup>1,2</sup> Recent prospective studies support an association between higher postmenopausal endogenous oestrogen concentrations and risk of breast cancer.<sup>3,4</sup> Furthermore, several recent reports support a strong association between higher bone-mineral density, presumed to be a marker of life-long oestrogen exposure, and increased risk of breast cancer.<sup>5,6</sup> Finally, as the authors of today's report note, an association between long-term HRT and increased risk of breast cancer is internally consistent in this meta-analysis with the finding of reduced risk associated with years since menopause, the two factors having almost identical magnitudes of risk in opposite direction.

The results of this meta-analysis may underestimate the

true magnitude of breast cancer risk associated with HRT. Osteoporotic women, who are also more likely than others to be on HRT, are at considerably lower risk of breast cancer than other women.<sup>5,7</sup> Hence the suggestion that the increased risk of breast cancer seen in many epidemiological studies may underestimate the true magnitude of increased risk that would be observed if oestrogen was taken by a broader spectrum of women, including those with higher bone-mineral density.<sup>8</sup>

Conversely, the results of this meta-analysis may also overestimate the true magnitude of breast-cancer risk associated with long-term HRT. The finding that long-term hormone users had a higher risk of localised, but not metastatic tumours, is consistent with differential screening and earlier ascertainment of breast cancer among hormone users. The potential for detection bias is greater when there are large differences in mammography screening rates between hormone users and non-users. In the Nurses' Health Study, more than 90% of users and non-users had at least one screening mammogram in the 4 years preceding the end of follow-up, making detection bias unlikely in that study.<sup>9</sup> However, among 52 000 women aged 50 and older at Group Health Cooperative of Puget Sound, a large pre-paid health plan in Washington State that systematically solicits women's participation in mammographic screening, 81% of hormone users received at least one mammogram in 1995–96 compared with only 53% of non-users (unpublished). Thus, rates of screening mammography probably varied substantially among the study populations included in the meta-analysis. The impact of differential screening, if it exists, might be lessened by lower sensitivity of screening mammography among women on oestrogen replacement therapy, because of increased radiographic breast density.<sup>10</sup>

During the next decade the best available evidence on HRT and breast cancer is likely to come from epidemiological studies. Some physicians may have found the disparate results from individual epidemiological studies on oestrogen use and breast cancer to be too confusing to warrant counselling women about the possibility of an increased breast-cancer risk. The results of this well-conducted meta-analysis should serve to over-ride debate about the relative merits and plausibility of individual studies and focus attention appropriately on the totality of the epidemiological evidence so far. These findings create an ethical responsibility for physicians and other health-care providers to advise women that the accumulated epidemiological data show an increased risk of breast cancer among those on HRT for 5 or more years. The risk is related to duration of therapy and seems to go away within 5 years of stopping HRT. For long-term hormone users, the findings translate into an extra 12 cases of breast cancer by the age of 70 for every 1000 women

who start taking hormones at the age of 50 and continue to do so for 20 years (75 cases of breast cancer in hormone users compared with 63 in never users). Counselling about these risks must also be placed in the context of what is known about the long-term benefits (prevention of coronary events and fractures) and other long-term risks (such as the possibility of endometrial cancer).

Because the data are based on observation of women rather than controlled experimental trials, the excess risk should be viewed as a possibility but not a certainty. Although epidemiological data are critically important for learning about the long-term risks and benefits of preventive interventions, some questions they raise can be resolved only by rigorous, large, double-blind, randomised controlled trials. The Women's Health Initiative in the USA is such a trial designed specifically to resolve questions about the risks and benefits of long-term hormone therapy among 275 000 women aged 50–79 followed-up for an average of 9 years.<sup>11</sup> At its planned conclusion in 2007, the trial is projected to have 79% power to detect a relative risk of 1.22 for breast cancer in the hormone treatment *vs* the placebo groups.

These are exciting times for women's health in the prevention arena. Health-care providers, researchers, and the pharmaceutical industry share the hope that someday there will be agents that can help prevent the major chronic conditions that cause disability and death in older women—namely, fractures, heart attacks, and women's cancers, including breast cancer. There is the danger that new preventive agents marketed as alternatives to hormone replacement (eg, selective oestrogen-receptor modulators, bisphosphonates) will be assumed to be effective and safer, when in fact there is no information on their long-term risks and benefits. HRT has been, and continues to be, the focus of well-designed studies, both observational and experimental. But it should not be held to a higher standard of evidence than any of the newer agents marketed as alternatives to hormone replacement. Physicians also have an ethical obligation to inform women that what we do not yet know about the newer agents could harm them.

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## ICRF: from mayhem to meltdown

Once more, women have been ill-served by those who claim their trust. The story behind this week's publication of a collaborative reanalysis of data on hormone replacement therapy (HRT) and breast cancer is a familiar one. But this time there is a twist. Through a series of misjudgments, the Imperial Cancer Research Fund (ICRF), the UK charity that paid for the pooling and analysis of the data, now finds itself in some difficulty. ICRF staff have pitted themselves against one another, decisions have been driven by greed for publicity, and the fundraising image of ICRF seems to have become the charity's over-riding priority.

After careful qualitative and statistical peer review leading to acceptance of a revised manuscript, we had planned to publish the HRT article on Oct 18. Then came a telephone call on Friday, Oct 3, informing us that a journalist at *The Sunday Times* had obtained a draft copy of the paper. She had a scoop and intended to write her story for the coming weekend. Clearly, there was a chance that this leak could produce serious confusion among women. Selective reporting of the results before full publication of the research paper might lead to misinterpretation. There was good reason to believe this would happen. A year before, the same journalist had published a report—"Pill-users face 10-year tumour risk"—based on data from the same research group. In an effort to publish the paper as quickly and safely as possible, we liaised with the investigators and the UK Committee on Safety of Medicines to move our publication date forward to Oct 11.

The front-page report in *The Sunday Times* of October 5 was worse than we could have conceivably imagined. Under the headline, "HRT link to breast cancer proved", Lois Rogers reported in her second paragraph that "The investigation found that among some groups of women receiving HRT, the risk of developing breast cancer is 2.3 times higher, or more than double, that of non-users". She had, of course, made a fundamental miscalculation. Among current users of HRT or those who ended use in the previous 5 years, 2 and 3 are the correct digits—but the relative risk was 1.023 per year of use, not 2.3, a hundred-fold error. *The Sunday Times* has a huge circulation. The damage to women's confidence in HRT is likely to be severe.

Rogers also claimed, wrongly, that "research fund officials were told Beral [the principal investigator] had decided to delay publication but they still hoped her findings would be published in full 'before the end of the year'". In fact, "research fund officials" were planning their own press conference to release details of the results. Also, the only spokesperson for the collaborative group in *The Sunday Times* article was Jack Cuzick, ICRF's head of cancer prevention and control. He was sceptical, saying that