Commentary

Estrogen–progestin replacement therapy: regulatory action needed

Malcolm C Pike and Ronald K Ross

Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California, USA

Correspondence: Malcolm C Pike, Department of Preventive Medicine, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA. Tel: +1 323 865 0405; fax: +1 323 865 0125; e-mail: mcpike@usc.edu

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Abstract

It is now established that the most commonly prescribed estrogen–progestin replacement therapy regimen significantly increases breast cancer risk. What are the risks associated with other regimens? Studies with breast cancer as the outcome cannot answer these questions in the right timeframe. It is incumbent on us to agree that some intermediate marker of risk must be used to show the probable effect of a regimen. We should then act as if the effect on the marker is a quantitative guide to the probable effect on breast cancer risk. Regulatory authorities need to require such studies on all current regimens.

Keywords: breast cancer, estrogen, postmenopause, progestin

Introduction

In her review on hormone replacement therapy and breast cancer, published in the present issue of *Breast Cancer Research* [1], Catherine Schairer concludes that studies "suggest, for the most part, that estrogen–progestin replacement therapy has a more adverse effect on breast cancer risk than estrogen replacement therapy". This relatively tentative conclusion has now been amply confirmed by the recent publication of the results of the Women's Health Initiative (WHI) trial [2] in the case of the most commonly prescribed estrogen–progestin replacement therapy (EPRT) regimen. The WHI large, randomized trial compared continuous combined EPRT (conjugated equine estrogen at 0.625 mg/day with medroxyprogesterone acetate at 2.5 mg/day) with placebo and found that, after a mean duration of use of 5.2 years, this EPRT regimen increased the rate of breast cancer by 26%. This is not a small increase; if all postmenopausal women used this regimen for 5 years then, during the 5 years of use, every four current breast cancer cases would become five. Epidemiological studies suggest that there would be further excess cases extending possibly for many years after the EPRT was stopped.

Minimizing progestin exposure

As noted by Schairer, it was predicted some 14 years ago, based on the epidemiology and biology of breast cancer, that EPRT would be more harmful to the breast than estrogen replacement therapy [3,4]. An epidemiologic study from Scandinavia published in 1992 [5] supported this view and, as remarked on in the WHI report, the WHI results are completely compatible with the most definitive epidemiological studies.

Why was the epidemiological evidence on the higher risk from EPRT effectively ignored by prescribers and regulatory authorities for so long? In a situation of admittedly incomplete evidence, should we not have acted as if EPRT quite possibly increased breast cancer risk more than estrogen replacement therapy? If this possibility had

EPRT = estrogen–progestin replacement therapy; WHI = Women's Health Initiative.

been taken seriously, we would have had an aggressive scientific effort to find ways to deliver progestins to the endometrium (the whole point of delivering progestins) in such a way as to minimize exposure to the breast. A direct endometrial route of administration with minimal progestin exposure to the breast was shown to be possible as early as 1991 [6], and this has been confirmed in a recent study [7]. If this is unacceptable to a woman, then a vaginal route of administration shows great promise [8,9]. If this is also unacceptable, then giving progestins by mouth (or transdermally) for 10–12 days every 3–4 months should provide satisfactory protection to the endometrium if the estrogen dose is kept to no more than standard-dose conjugated equine estrogen [10–12].

Conclusion

Schairer [1] and the WHI report [2] note that many questions remain to be answered regarding the breast cancer risk from EPRT. In particular, what are the risks associated with the many different regimens of EPRT that have been licensed by the regulatory authorities? These regimens cover transdermal delivery, the use of different estrogens and progestins, and quite different sequences of delivery of the progestins. Epidemiological breast cancer case–control studies cannot answer all these questions in the right timeframe (i.e. before many tens of thousands of women have taken the regimens) and clinical trials with breast cancer as the outcome are not going to be performed to cover all the regimens available. It is therefore incumbent on us to agree that some intermediate marker of breast cancer risk must be used to show the probable effect of a regimen and then, if this shows that the regimen affects the intermediate marker in a manner to suggest increased breast cancer, that we act accordingly. We should in fact be prepared to act as if the effect on the marker is a quantitative guide to the probable effect on breast cancer risk.

There is considerable evidence in support of using changes in mammographic densities as such a marker [13]. A large, randomized trial with changes in mammographic density as the endpoint has already shown that the usual sequential EPRT regimen with conjugated equine estrogen and medroxyprogesterone acetate is likely to increase breast cancer risk as much as the continuous combined regimen used in the WHI trial, and that replacing medroxyprogesterone acetate with micronized progesterone does not significantly alter the added risk. Regulatory authorities need to require such studies on all current regimens so that women can have an evidence-based guide to the probable effects of different regimens. We should not allow regimens that are not covered by the current epidemiological and WHI evidence to be presented in such a way as to suggest that they may not increase breast cancer risk without evidence of this type.

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