Re: Effect of Hormone Replacement Therapy on Breast Cancer Risk: Estrogen Versus Estrogen Plus Progestin

The report by Ross et al. (1) in the February 16, 2000, issue of the Journal concludes that a combination of estrogen and progestin increases the risk of breast cancer over time when compared with estrogen alone. A similar conclusion was recently reported in a paper in the Journal of the American Medical Association by Schairer et al. (2). There is little question that hormone therapy, either estrogen or estrogen/progestin, is associated with an increased risk of breast cancer especially with long-term use (3). However, papers contrasting estrogen therapy with estrogen/progestin therapy have a serious use bias.

When comparing estrogens alone versus estrogen/progestin, the use indication for either therapy must be similar. Estrogen therapy alone is used for women who have had an artificial menopause (i.e., removal of the ovaries and uterus). Such women may be at a lower baseline risk of breast cancer for the following reasons: 1) Because of the oophorectomy and the resulting decreased estrogen levels, these women may remain at a lower risk until the time they are placed on hormone therapy; and 2) the reasons for the hysterectomy or oophorectomy, including aberrant menstrual cycles and/or decreased ovarian function during their premenopausal years place these women at lower risk for postmenopausal breast cancer.

Women on estrogen/progestin usually have an intact uterus, have started on hormone therapy after naturally becoming menopausal, and may be at higher background risk of breast cancer than women who were placed on estrogen therapy alone. Women on estrogen/progestin therapy tend to be better educated, may be older at first pregnancy, and are less likely to be premenopausally obese.

A proper comparison is the relative and absolute risks of breast cancer between estrogen users and control women, i.e., hysterectomy and/or oophorectomy, and women with an intact uterus who are on combination estrogen/progestin versus those with an intact uterus who are not on therapy. The most important comparison is absolute risk and relative risk by duration of exposure in the four arms. Adjustment for oophorectomy or hysterectomy is unlikely to be successful, since very few women would be on long-term estrogen use with an intact uterus. Furthermore, such women must have a unique characteristic—either they do not adhere to the estrogen therapy or they have characteristics that result in either lower estrogen levels or a lack of tissue sensitivity (i.e., they do not develop uterine hyperplasia on long-term estrogen therapy).

The papers in the Journal and the Journal of the American Medical Association have, unfortunately, generated a great deal of interest in the media and, possibly, in the interpretation that estrogens alone are safer than estrogen/progestin (4). This interpretation may be the case but, certainly, the data to date do not support this conclusion. The results from the Women’s Health Initiative, especially the long-term follow-up, including women on estrogen, estrogen/progestin, and placebo therapy will probably provide the only data to test the hypothesis of the risks and benefits of estrogen or estrogen/progestin therapy.

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REFERENCES


Note

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Response

Dr. Kuller is correct that an appropriate comparison of the effects of estrogen replacement therapy (ERT) versus estrogen/progestin hormone replacement therapy (combined hormone replacement therapy [CHRT]) requires comparability of women in terms of their baseline breast cancer risks. Adjustment for age at menopause and for type of menopause, as done in our report (1), may not be sufficient to make such a comparison, if the vast majority of women using one type of therapy (e.g., ERT) have a very different risk factor profile (e.g., have all undergone artificial menopause) from women using the alternative therapy. However, in our study, such adjustments were sufficient. Even when we restrict our analyses to the majority subgroup of women, those with natural menopause, the difference in effect of ERT and CHRT remains virtually unchanged: the odds ratio per 5 years of use of ERT was 1.08 versus 1.22 for CHRT. Adjustment factors were the same as for Table 2 in our original report (1). These results are very comparable to the 1.06 (for ERT) and 1.24 (for CHRT) figures cited in our report for the entire study population. We had insufficient women on long-term CHRT who had undergone hysterectomy and bilateral oophorectomy to adequately compare ERT versus CHRT in this subset of women.

The studies by Magnusson et al. (2) and Schairer et al. (3) confirm the need as raised in the “Discussion” section of our report to establish an adequate delivery system for progestins. The sole goal of progestin administration postmenopausally is to protect the endometrium from carcinogenic transformation. The ideal progestin delivery system will provide the necessary dose to the endometrium to provide such protection, while concurrently minimizing or eliminating exposure to other organs, such as the breast, liver, and cardiovascular system negatively affected by progestins.

We believe that the results of our report combined with those reported by Magnusson et al. and Schairer et al. have changed the standard by which current and subsequent generation progestins and the methods and regimens for their delivery should be evaluated. The bur-
den of proof should no longer be on epidemiologists and other investigators to demonstrate that such agents increase the risk of breast cancer, rather, it should shift to the proponents of systemic use of such agents to demonstrate that they do not.

Although we thank Dr. Kuller for his helpful insights regarding our analysis, we strongly disagree with his opinion that we need results from the Women’s Health Initiative to determine which type of hormone replacement causes more breast cancer, ERT or CHRT, which is incidentally, a curious twist on the usual goals for a prevention trial. In fact, the Women’s Health Initiative suffers from the precise limitation for which Dr. Kuller criticizes our report; women assigned to ERT and CHRT do not have similar baseline risk of breast cancer, since ERT is assigned only to women who have had hysterectomies and CHRT is assigned exclusively to women who have not.

Not only do the epidemiologic data now provide a convincing case that CHRT is substantially more harmful than ERT, highly convincing supportive studies of CHRT versus ERT on cell proliferation indices also exist both in women (4) and in nonhuman primates (5), in addition to the study of mammographic densities cited in our report (6). We believe that it would represent a serious error in judgment with regard to the public health to ignore the clear message from these combined studies.

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REFERENCES


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