The influence of combined estrogen–progestin replacement therapy on breast cancer risk is important in the risk–benefit equation associated with hormone replacement therapy. Thus, the lack of data on this relationship is of considerable concern to the millions of treated women. Therefore, it was with great interest we read the report in the Journal by Ross et al. (1). Last year, we published results from a case–control study conducted in Sweden (2), where combined estrogen–progestin therapy has been the predominant therapy for many years. We thought it might be of interest to make a comparison between the only two studies where the influence of sequential estrogen plus progestin replacement therapy (SEPRT) and continuous combined estrogen plus progestin replacement therapy (CCRT) has been explored. The Swedish study included 3345 case patients and 3454 control subjects, with response rates of 84% and 82%, respectively (2). We reported that risk of breast cancer increased with duration of use of both SEPRT and CCRT, yet, in contrast to the findings of Ross et al. (see Table 1), the relative risk (RR) associated with SEPRT was substantially lower (RR = 1.03 per year of use; 95% confidence interval [CI] = 0.94–1.13) than the corresponding risk associated with CCRT (RR = 1.19 per year of use; 95% CI = 1.09–1.31). These estimates were statistically significantly different from one another (P for heterogeneity = .03).

To correctly interpret these differences, some comments are needed. First, our data refer to the use of mainly estradiol plus testosterone-like progestin, while the use of conjugated estrogens plus progesterone-like progestin (medroxyprogesterone acetate) is most common in the United States. Second, we chose to restrict our analyses to exclusive use of the different regimens (excluding women with mixed use), whereas Ross et al. adjusted their estimates for the use of one type of regimen for other types. However, it is not clear to us how detailed this adjustment was carried out (i.e., whether adjustment was made only for ever use or for duration of use of other regimens). The estimates presented from our study (Table 1) were not adjusted for as many other breast cancer risk factors as those described in study by Ross et al. (Table 1). We examined the additional risk factors as described by Ross et al. (i.e., age at menarche, family history of breast cancer, history of benign breast disease, use of oral contraceptives, and alcohol con-
In extensive analyses and found that they did not improve the model fit; thus, they were excluded from the final models. The data in Table 1 also pertain to a subset of all women included in the Swedish study, excluding women with a history of invasive cancer, premenopausal women, women with premenopausal hysterectomy, and women unable to recall their age at menopause. Lastly, our estimates for continuous duration of use of SEPRT and CCRT were calculated after the exclusion of never users to minimize recall bias in short-term users. It was not stated in the report by Ross et al. whether they obtained their estimates in a similar way.

We believe that neither our study (2) nor the study by Ross et al. (1) provides the full picture regarding the possibly different effects of SPRT and CCRT on breast cancer risk but only that a comparison between the two is interesting. Indeed, this important question needs further investigation.

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REFERENCES


NOTES

Editor’s note: Ronald K. Ross et al. declined to respond to the correspondence of Cecilia Magnusson et al.

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