LETTERS TO THE EDITOR

Mortality Associated with Hormone Replacement Therapy in Younger and Older Women

To the Editor:—Salpeter et al.'s meta-analysis included 30 randomized controlled trials of hormone replacement therapy (HRT) with at least 1 death and claimed a reduction in total mortality in younger women.¹ Not a single one of these studies had found a statistically significant effect on total mortality. Of the 17 trials listed for women with a mean age under 60, the largest double-blind study, PEPI 1995, had 701 HRT-treated women and a mortality odds ratio of 1.75 (0.09 to 34.01), but was allocated only 2.3% of the weight in the meta-analysis. An overall beneficial result was achieved by allocating 4 trials, containing 685 treated women, 72.2% of the total weighting, because they had most of the deaths. These studies were either open-label design or contained only hospitalized or ovarian cancer patients. Guidozi's 1999 study involved 62 HRT-treated women with ovarian cancer. More than half of both HRT-treated and control women died during the follow-up period; therefore, this small study was allocated 41% of the weighting. Several studies have found that estrogen-HRT increases the risk of fatal ovarian cancer.

If only randomized double-blind trials containing more than 100 previously healthy, HRT-treated women are included in the meta-analyses, a different result can be obtained. The 5 trials of younger women which fulfill these criteria are PEPI 1995, Angerer 2000, Arrenbrecht 2002, Giske 2002, and Watts 2000, totaling 1,450 HRT-treated women and 479 controls. No deaths occurred in the controls but 7 deaths occurred in the HRT-treated women.

Most studies have serious problems because few women have never taken hormones and few studies give the numbers for this only valid control group.^{2,3} Most control volunteers have used progestones or estrogens at some time, either for contraception or menopause, and the exact duration of exogenous hormone exposures, either past or current, is also often missing. Follow-up duration is not the same as current use duration. Thickened endometrial arterioles and dilated sinusoids match generalized vascular side effects, and clotting factors alter, during therapy. Therefore, vascular deaths would be expected to be increased in current users. However, extra cancer deaths would still be occurring for decades because breast cancer is still the main cause of death in women up to 20 years after it has been diagnosed.—**Ellen C.G. Grant, MBChB**, Kingston-on-Thames, Surrey, UK.

REFERENCES

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2. Grant ECG. Epidemiologists' long-term underestimation of harm from hormones. Available at: <http://bmj.com/cgi/eletters/329/7456/2#65645>. Accessed July 3, 2004.
3. Grant ECG. Pill and HRT epidemiologists. Available at: <http://bmj.com/cgi/eletters/329/7463/467#72387>. Accessed August 27, 2004.

In Reply:—I appreciate the opportunity to respond to Dr. Grant's letter concerning our meta-analysis on mortality associated with hormone replacement. It is true that no single trial of younger women has shown a significant reduction in mortality with hormone use. In fact, no trial of hormone replacement has shown a decrease or increase in mortality. Death is a very rare event, especially in younger postmenopausal women, and it would require a very large trial to provide the statistical power necessary to produce significant results. A more precise estimate can be made by pooling the results of many smaller trials in the form of a meta-analysis.

In the analysis of younger women, approximately one half of the deaths were from one trial with ovarian cancer survivors that provided 40% of the weight. However, as described in the article, when this trial was excluded from the analysis there still was a significant reduction in mortality for the younger age group, with an odds ratio of 0.56 (confidence interval [CI], 0.31 to 0.99). Since our analysis was published, the Women's Health Initiative estrogen-only trial has shown a hazard ratio for total mortality of 0.73 (CI, 0.47 to 1.13) in those 50 to 59 years old.¹ If these data were added to our meta-analysis, it would provide 50% of the weight, with a revised odds ratio for mortality in the younger age group of 0.67 (CI, 0.49 to 0.92).

It is not possible to completely control for previous exposure to hormone replacement in clinical trials, but randomized trials help to reduce baseline differences between the treatment and control groups. In this meta-analysis, the women in the younger age group had a mean age of 53.7 years and had no recent exposure to hormone replacement, which indicates that their previous exposure to hormone replacement was probably minimal. Longer trials of hormone replacement will be needed in the future to assess whether this mortality benefit seen in younger women persists over the years.—**Shelley Salpeter, MD, FACP**, Santa Clara Valley Medical Center, San Jose, CA.

REFERENCE

1. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291:1701–12.