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Postmenopausal Hormone-Replacement Therapy — Time for a Reappraisal?

In this issue of the *Journal*, Grodstein and colleagues¹ present important data from a large study of the risks and benefits associated with postmenopausal hormone-replacement therapy. Like previous investigators, they found a significantly reduced risk of death from all causes among recent hormone users. This reduction in mortality is the consequence of a profound decrease in the risk of death from coronary heart disease and a somewhat smaller reduction in mortality from cancer, although this reduction was not evident for all types of cancer. The study showed that the reduction in mortality from cardiovascular disease and cancer was probably not due to patterns of selective prescribing of estrogens for women without these diseases or to the discontinuation of hormone therapy at the onset of the fatal disease. It is less clear that these issues of bias were addressed with respect to other causes of death. In addition, questions remain about the extent to which reduced mortality from cancer may reflect earlier disease detection among hormone users. Furthermore, since the study considered only exposures before the development of fatal diseases, it did not address the issue of hormone use after the diagnosis of disease, a particularly important issue with regard to cardiovascular disease.

One strength of this study is the assessment of mortality in relation to both how recently and for how long hormones were used. The protective effect of hormones was lost five years after the discontinuation of use, and extended exposure provided no additional benefit among current users. In fact, there was some attenuation of the protective effect with long duration of use, which was attributable primarily to a 43 percent increase in deaths from breast cancer among women who had used hormones for 10 or more years. However, the proportion of deaths due to breast cancer was higher in the study cohort than in the general population, possibly limiting the generalizability of the results.

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Mortality from breast cancer was reduced overall in this latest study, a finding consistent with those of other studies, but the increased mortality among current users who had been taking hormones for 10 or more years is a matter of concern, particularly given that some studies have shown an increased incidence of breast cancer among long-term or current users.^{2,3,4} A curious finding was that short-term users had a reduced risk of death from breast cancer, which more than offset the increased risk in long-term users. It is possible that the inconsistency in the results for short- and long-term users reflects the small number of deaths in each category. However, if the adverse effect of long-term hormone use on breast-cancer mortality is confirmed by additional research, this will argue against the notion that hormones predispose women to low-risk breast tumors, as suggested by studies showing better survival⁵ and diagnosis of less advanced disease³ in hormone users than in nonusers.

The study provides important data on the increasingly popular regimen of estrogens in conjunction with progestins, showing substantial reductions in overall mortality among users of the combined regimen as well as users of estrogens alone. These results indirectly address the concern aroused by experimental data that progestins may diminish the apparently cardioprotective effect of estrogen therapy. This issue was addressed more directly in a recent report from the Nurses' Health Study,⁶ which showed a reduction in coronary heart disease among users of estrogens with progestins equal to or greater than that among users of estrogens alone. It would also be of interest for studies to assess mortality from breast cancer in relation to the use of estrogen combined with progestin, particularly because there is some concern, although based on limited^{2,4} and inconsistent⁷ epidemiologic data, that combined therapy may increase the incidence of breast cancer more than estrogen alone. As the number of deaths from endometrial cancer accrues in this cohort, it will also be important to assess the mortality from this disease, given evidence that the addition of progestins may not completely counteract the adverse effect of estrogens on the endometrium.⁸

Given that a white woman's cumulative absolute risk of death from the ages of 50 to 94 years has been estimated to be 31 percent from coronary heart disease, 2.8 percent from breast cancer, and 2.8 percent from hip fracture,⁹ the benefits of estrogen use appear to far outweigh the risks. Notably, in this study long-term hormone users had a 20 percent reduction in mortality. However, for many women the benefits of hormone use may not compensate for the fear of acquiring breast cancer and living with its repercussions. Furthermore, in some women at low risk for cardiovascular disease but at high risk for breast cancer, the benefits of hormone therapy may not outweigh the risks.¹⁰ Unfortunately, the issues of risks versus benefits do not easily lend themselves to simple formulas for calculating who should take estrogen and for how long. Decisions need to be personal ones and should involve detailed discussions between a woman and her physician. These discussions should consider individual risk profiles,¹⁰ such as the one discussed in the article by Grodstein et al. However, a number of unresolved questions about individualized risks remain. Although the latest findings show the greatest reductions in hormone-associated mortality among women at high risk for coronary disease, previously published findings from this cohort showed hormone use to result in similar reductions in major coronary disease regardless of a woman's risk-factor profile.⁶ The study addresses an important question by showing that hormone users with a family history of breast cancer are not at any greater risk of death than hormone users without such a history. However, in terms of making decisions about the risk of breast cancer, it might be more

useful to evaluate breast-cancer mortality, specifically assessing hormone-related risks for women at high risk for breast cancer as compared with those at low risk and considering not only the factors mentioned but also others known to have a major impact on the risk of breast cancer (e.g., reproductive behavior and benign breast disease).

Given the findings that hormone use is associated with reduced mortality for multiple causes of death¹¹ and that there are marked lifestyle differences between hormone users and nonusers,¹² there continue to be lingering questions regarding the extent to which reductions in mortality are due to hormone use itself as opposed to the characteristics of the user. Some of the unresolved issues must await the results of ongoing intervention trials of menopausal hormones. However, since these trials may not continue long enough to accrue large numbers of patients in whom cancer develops, it will also be important to evaluate data from large observational studies. If the protective effect of long-term use continues to dissipate with time and adverse effects on breast-cancer mortality are confirmed, the optimal duration of hormone-replacement therapy will need to be reconsidered. That the beneficial effects of hormones are dependent on recent use raises questions about when to initiate use. It is encouraging that hormone use begun later in life offers bone-conserving benefits nearly equal to those conferred by use initiated earlier.¹³ Furthermore, it is important, as Grodstein et al. and others have pointed out, that other means of reducing the incidence of cardiovascular diseases and osteoporosis have been identified. Physical activity is one such approach,¹⁴ of interest in that it may also reduce the incidence of breast cancer.¹⁵ Although further research is needed to clarify the relative benefits of various interventions as compared with hormone-replacement therapy, it may now be the time to question seriously whether hormone-replacement therapy should be prescribed for life or whether for some women, it should be more restricted in duration and combined with other effective disease-prevention techniques.

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References

1. Grodstein F, Stampfer MJ, Colditz GA, et al. Postmenopausal hormone therapy and mortality. *N Engl J Med* 1997;336:1769-1775. [[Abstract/Full Text](#)]
2. Bergkvist L, Adami H-O, Persson I, Hoover R, Schairer C. The risk of breast cancer after estrogen and estrogen-progestin replacement. *N Engl J Med* 1989;321:293-297. [[Abstract](#)]
3. Brinton LA, Hoover R, Fraumeni JF Jr. Menopausal oestrogens and breast cancer risk: an expanded case-control study. *Br J Cancer* 1986;54:825-832. [[Medline](#)]
4. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995;332:1589-1593. [[Abstract/Full Text](#)]
5. Bergkvist L, Adami H-O, Persson I, Bergstrom R, Krusemo UB. Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen-progestogen replacement therapy. *Am J Epidemiol* 1989;130:221-228. [[Abstract](#)]
6. Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996;335:453-461. [Erratum, *N Engl J Med*

- 1996;335:1406. [[Abstract/Full Text](#)]
7. Newcomb PA, Longnecker MP, Storer BE, et al. Long-term hormone replacement therapy and risk of breast cancer in postmenopausal women. *Am J Epidemiol* 1995;142:788-795. [[Abstract](#)]
 8. Beresford SA, Weiss NS, Voigt LF, McKnight B. Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women. *Lancet* 1997;349:458-461. [[CrossRef](#)][[Medline](#)]
 9. Cummings SR, Black DM, Rubin SM. Lifetime risks of hip, Colles', or vertebral fracture and coronary heart disease among white postmenopausal women. *Arch Intern Med* 1989;149:2445-2448. [[Abstract](#)]
 10. Col NF, Eckman MH, Karas RH, et al. Patient-specific decisions about hormone replacement therapy in postmenopausal women. *JAMA* 1997;277:1140-1147. [[Abstract](#)]
 11. Schairer C, Adami H-O, Hoover R, Persson I. Cause-specific mortality in women receiving hormone replacement therapy. *Epidemiology* 1997;8:59-65. [[Medline](#)]
 12. Matthews KA, Kuller LH, Wing RR, Meilahn E, Plantinga P. Prior to use of estrogen replacement therapy, are users healthier than nonusers? *Am J Epidemiol* 1996;143:971-978. [[Abstract](#)]
 13. Schneider DL, Barrett-Connor EL, Morton DJ. Timing of postmenopausal estrogen for optimal bone mineral density: the Rancho Bernardo Study. *JAMA* 1997;277:543-547. [[Abstract](#)]
 14. Kushi LH, Fee RM, Folsom AR, Mink PJ, Anderson KE, Sellers TA. Physical activity and mortality in postmenopausal women. *JAMA* 1997;277:1287-1292. [[Abstract](#)]
 15. Thune I, Brenn T, Lund E, Gaard M. Physical activity and the risk of breast cancer. *N Engl J Med* 1997;336:1269-1275. [[Abstract/Full Text](#)]

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- Csizmadia, I., Benedetti, A., Boivin, J.-F., Hanley, J. A., Collet, J.-P. (2002). Use of postmenopausal estrogen replacement therapy from 1981 to 1997. *Can Med Assoc J* 166: 187-188 [[Full Text](#)]
- KOUKOULIS, G. N. (2000). Hormone Replacement Therapy and Breast Cancer Risk. *Annals NYAS Online* 900: 422-428 [[Abstract](#)] [[Full Text](#)]
- Liu, Y., Ding, J., Bush, T. L., Longenecker, J. C., Nieto, F. J., Golden, S. H., Szklo, M. (2001). Relative Androgen Excess and Increased Cardiovascular Risk after Menopause: A Hypothesized Relation. *Am. J. Epidemiol.* 154: 489-494 [[Abstract](#)] [[Full Text](#)]

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