Int J Fertil, 35(4), 1990 p. 202–204

Scandinavian Association for Studies in Fertility, Falloppius International Society, and the International Society of Reproductive Medicine

1990

EDITORIAL

Estrogen Therapy and Breast Cancer

R. Don Gambrell, Jr., M.D.
Department of Endocrinology
Medical College of Georgia
Augusta, Georgia

IN AUGUST 1989, A STUDY FROM SWEDEN purporting to show an increased risk of breast cancer in estrogen users was published in *The New England Journal of Medicine.*[1] Wide media coverage of this article has created unfounded fears for patients and physicians alike. Patients have stopped their estrogen therapy without consulting physicians, and when they did seek advice, some physicians were uncertain in their recommendations.

The publication of this Swedish study linking estrogen therapy to an increased risk of breast cancer was premature, to say the least. Their mean duration of follow-up (5.7 years) is too short, since most breast cancers develop for seven to eight years before becoming clinically detectable. Only 29 of their 253 patients with breast cancer used estrogens for nine or more years (relative risk, 1.7; 95% confidence interval, 1.1 to 2.7). Yet the 45 women who never used estrogens had a similar relative risk of 1.6 (95% confidence interval, 1.1 to 2.1). Epidemiologic studies such as this can never show a true cause and effect, only a possible association. Confirming some of the methodology problems is this group's previous study of endometrial cancer from the same data base published earlier in 1989.[2] In that phase of their study they observed only a relative risk of 1.8 (95% confidence interval, 1.1 to 3.2) of endometrial cancer after 6 years of unopposed estrogen use. Numerous other epidemiologic studies of endometrial cancer have shown a relative risk from 4.5 to 13.9 in unopposed estrogen users. This group also failed to find the significant protection from endometrial cancer when progestogens were added to estrogen replacement (relative risk, 0.9; 95% confidence interval, 0.4 to 2.0)[2] that has been universally observed.

Their conclusion, that breast cancer is not prevented and may even be increased by added progestogens, is invalid, not only because of the short follow-up (6 years) but also because it is based on only 10 patients with breast cancer (relative risk, 4.4; 95% confidence interval, 0.9 to 22.4). Although not stated in their report, the duration and dosages of the added progestogens may be inadequate. In their previous study of endometrial cancer, the progestogens used were in a seven- to 10-day combination with levonorgestrel, 125 to 250 μg, norethisterone acetate, 5 to 10 mg, or medroxyprogesterone acetate, 5 to 10 mg.[2] Indeed, these dosages and duration of progestogens added to estrogen replacement did not reduce endometrial cancer (relative risk, 0.9; 95% confidence interval, 0.4 to 2.0)[2] to the same magnitude observed in other studies, where 12 to 14 days of medroxyprogesterone acetate, 10 mg, were added.[3–5] In our studies of breast cancer in estrogen users, with and without added progestogen, we observed a slight but insignificant increase in the incidence of breast cancer during the first 5 years of prospective study.[5,6] A significant decrease in the incidence of breast cancer in the estrogen-progestogen users was not observed until the ninth and tenth years of ever-increasing addition of progestogens to estrogen replacement. In another 10-year prospective study from New York, there were four breast cancers in the 84 placebo users and none in the 84 estrogen-progestogen users, with $P \leq .05$.[7] A study from West Germany disclosed a lower incidence of breast cancer in unopposed estrogen users (123 per 100,000 women) when compared to nonusers (154 per 100,000), although this was not statistically significant.[8] The incidence of mammary malignancy in the estrogen-progestogen users (109 per 100,000) was significantly lower ($P \leq .05$) when compared to the nonusers.

The Swedish study reporting the highest risk (rel-

ative risk = 1.8) was from more than 6 years' use of estradiol compounds, but did not specify dosage, type, or route of administration—whether by skin cream, patch, pill, or pellet. However, this relative risk of 1.8 was not significant (95% confidence interval, 0.7 to 4.6), and was based on only 10 cases of breast cancer. They found no increased risk of breast cancer with conjugated or other estrogens. Overall, this study observed about a 10% increase in the relative risk of breast cancer in estrogen users, very similar to those from other larger and longer-term studies, which observed slight decreases in some subgroups, slight increases in other subgroups, with the net relative risk close to 1.0.[9,10] These other studies concluded that estrogen therapy did not increase the risk of breast cancer. The Swedish group, even with multiple warnings interspersed throughout their report, overinterpreted their own data to conclude that "... perimenopausal treatment with estrogens ... seems to be associated with a slightly increased risk of breast cancer..." Finally, this study is not a cohort, long-term study of 23,244 women followed for 133,375 person-years. Only 653 of these women answered their questionnaire to provide detailed information for proper assessment of other risk factors for breast cancer. What this study represents is a case-control analysis of 253 patients with breast cancer, among whom they had complete data on only 196 women.

Bergkvist et al[1] have achieved the notoriety of Pike et al[11] by publishing misleading information regarding hormone use and breast cancer. In 1983, similar public disservice occurred when the Los Angeles group purported to show an increased risk of breast cancer in women diagnosed before age 37 who had used "high progestogen" oral contraceptives before the age of 25 for 4 or more years.[11] That study has been completely refuted by numerous epidemiologic studies; however, wide media coverage caused many young women to stop using their pill, resulting in many unwanted pregnancies. The Swedish study has been and will also be completely refuted, in that over 23 studies have shown that there is no increased risk of breast cancer in postmenopausal estrogen users, except for some small subgroups. Because of the wide media coverage of the Swedish study, many postmenopausal women have ceased using estrogens, which may result in increased osteoporotic fractures and heart attacks. How many women will needlessly suffer from hot flashes, night sweats, vaginal dryness, and the nervous symptoms that are so easily relieved by estrogen replacement? Physicians are concerned, many not knowing what to do, since the Swedish report was released to the press before they even received their journal—let alone had time to assess the study properly.

In the very month this report was published, Bergkvist et al published another paper, in the *American Journal of Epidemiology*, utilizing the same data base, where they observed a significantly higher survival rate in breast cancer patients who had received estrogen treatment.[12] The authors stated that this had not been previously studied; however, their report confirmed several earlier studies, with none to the contrary, indicating an improved prognosis for breast cancer developing in estrogen users.[13–15] Burch et al[13] were the first, in 1976, to observe a 25% reduction in mortality from breast cancer when the malignancy developed in estrogen users followed for 15 years. In our studies of 256 postmenopausal women with breast cancer, the mortality was 22.2% in the 63 hormone users, compared to a death rate of 45.5% in the 165 nonusers, which was statistically significant ($P \leq 0.5$).[14] In a study from England of 4,544 hormone users, the mortality from breast cancer was significantly reduced, with a relative risk of 0.55 (95% confidence interval, 0.28 to 0.96).[15]

The Swedish study observed a significant reduction in mortality from mammary malignancy developing in estrogen users (relative risk, 0.68; 95% confidence interval, 0.52 to 0.87).[12] The lowest risk was in current users (relative risk, 0.54; 95% confidence interval, 0.34 to 0.86); however, they also observed significant reductions with latency (off estrogens for 48–96 months), with a relative risk of 0.58 (95% confidence interval, 0.35 to 0.96), and duration (more than 37 months of estrogen use), with a relative risk of 0.55 (95% confidence interval, 0.31 to 0.97). Unfortunately, these data were not released to the public media; for if they had been publicized, it would probably have diminished the terrible impact their other study had on both patients and physicians. The authors did reference *The New England Journal of Medicine* article in *The American Journal of Epidemiology* as being "in press," but failed to cross-reference this other study in *The New England Journal of Medicine.*

Many of us are very concerned as to how the editorial review process of *The New England Journal of Medicine* could break down so completely as to allow such an erroneous study to be published. It was appalling to learn that they "... encourage au-

thors to suggest the names of possible reviewers. . . ," and one must wonder if this may bias their review process. It is fairly obvious that this paper was not reviewed by clinical oncologists, who understand the biology of breast cancer, or endocrinologists, who are familiar with the hormone relationships. We are also concerned about the press release policies of the journal, which allow the news media access to articles in advance of their being received by physician readers. Although the authors interspersed throughout their report multiple warnings that their data should be interpreted cautiously, these were not picked up by the media. The wide media coverage of this report is devastating to estrogen replacement therapy, and it will take many years to undo the damage that was unnecessarily done. Many of my colleagues feel that *The New England Journal of Medicine* is guilty of medical journal sensationalism, and should be censured for (a) publishing a flawed study and (b) releasing it to the news media before publication. In a sense of fair play, the editors of the journal have been encouraged to issue a similar press release when the letters to the editor are published. The press and the public have a right to know the many controversies surrounding this study. The only redeeming aspect about their publication of this paper was the editorial by Elizabeth Barrett-Conner in the same issue.[16] Unfortunately, most of the media did not heed her warning to interpret the findings in the Swedish study cautiously.

REFERENCES

1. Bergkvist L, Adami H-O, Persson I, et al: The risk of breast cancer after estrogen and estrogen-progestin replacement. *N Engl J Med* 321:293-297, 1989.
2. Persson I, Adami H-O, Bergkvist et al: Risk of endometrial cancer after treatment with oestrogens alone or in conjunction with progestogens: results of a prospective study. *Br Med J* 298:147-151, 1989.
3. Padwick MC, Pryse-Davies J, Whitehead MI: A simple method for determining the optimal dosage of progestin in postmenopausal women receiving estrogens. *N Engl J Med* 315:930-934, 1986.
4. Thom MH, White PJ, Williams RM, et al: Prevention and treatment of endometrial disease in climacteric women receiving oestrogen therapy. *Lancet* 2:455-457, 1979.
5. Gambrell RD, Jr: Use of progestogen therapy. *Am J Obstet Gynecol* 156:1304-1313, 1987.
6. Gambrell RD, Jr, Maier RC, Sanders BI: Decreased incidence of breast cancer in postmenopausal estrogen-progestogen users. *Obstet Gynecol* 62:435-443, 1983.
7. Nachtigall LE, Nachtigall RH, Nachtigall RD, et al: Estrogen replacement therapy. II. A prospective study in the relationship to carcinoma and cardiovascular and metabolic problems. *Obstet Gynecol* 54:74-79, 1979.
8. Lauritzen C, Meier F: Risks of endometrial and mammary cancer morbidity and mortality in long-term estrogen treatment, in van Herendael H, van Herendael B, Riphagen FE, et al (eds): *The Climacteric—An Update.* Lancaster, England, MTP Press Ltd, pp 207-216, 1984.
9. Kaufman DW, Miller DR, Rosenberg L, et al: Noncontraceptive estrogen use and the risk of breast cancer. *JAMA* 252:63-67, 1984.
10. Wingo PA, Layde PM, Lee NC, et al: The risk of breast cancer in postmenopausal women who have used estrogen replacement therapy. *JAMA* 257:209-215, 1987.
11. Pike MC, Henderson BE, Krailo MD, et al: Breast cancer in young women and use of oral contraceptives: Possible modifying effect of formulation and age at use. *Lancet* 2:926-929, 1983.
12. Bergkvist L, Adami H-O, Persson I, et al: Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen-progestogen replacement therapy. *Am J Epidemiol* 130:221-228, 1989.
13. Burch JC, Byrd BF, Vaughn WK: Results of estrogen treatment in one thousand hysterectomized women for 14,318 years, in van Keep PA, Greenblatt RB, Albeaux-Fernet M (eds): *Consensus on Menopausal Research.* Lancaster, England, MTP Press Ltd, pp 164-169, 1976.
14. Gambrell RD, Jr: Proposal to decrease the risk and improve the prognosis of breast cancer. *Am J Obstet Gynecol* 150:119-132, 1984.
15. Hunt K, Vessey M, McPherson K, et al: Long-term surveillance of mortality and cancer incidence in women receiving hormone replacement therapy. *Br J Obstet Gynaecol* 94:620-635, 1987.
16. Barrett-Conner E: Postmenopausal estrogen replacement and breast cancer [editorial]. *N Engl J Med* 321:319-320, 1989.

Address reprint requests to:
Dr. R. Don Gambrell, Jr., M.D.
Department of Endocrinology
Medical College of Georgia
Augusta, GA 30912