

# Estrogen replacement therapy in women with previous breast cancer

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**OBJECTIVE:** We sought to review the status of patients with breast cancer who were treated with estrogen replacement therapy and compare the results with those of nonestrogenic hormone users and women not treated with hormone replacement.

**STUDY DESIGN:** The study group consisted of 76 patients with breast cancer, including 50 using estrogen replacement for up to 32 years, 8 using nonestrogenic hormone replacement for up to 6 years and followed for up to 11 years, and 18 using no hormones for up to 10 years. In addition to estrogen use, 40 of the 50 hormone users were treated with androgens, usually in the form of implantation of testosterone pellets. Forty-five subjects were also given progestogens, usually megestrol acetate 20 to 40 mg for 10 to 25 days each month. The 8 nonestrogen hormone users were treated with various combinations of testosterone pellets, tamoxifen, and progestogens. Forty-two of the 50 estrogen users are still being treated in our clinic, as are 2 of the 8 subjects using nonestrogen hormone. Follow-up was done through the tumor registry at University Hospital, and those whose tumor records were not current were telephoned.

**RESULTS:** Of the 50 estrogen users, 3 have died (a mortality rate of 6%), and the rest have been followed for 6 months to 32 years, with a mean duration of follow-up of  $83.3 \pm 8.81$  months. One of the 8 nonestrogen hormone users has died (a mortality rate of 12.5%), and the rest have been followed for 2 to 11 years, with a mean duration of follow-up of  $72.0 \pm 5.93$  months. Six of the 18 women not using hormone replacement have died (a mortality rate of 33.3%), and the rest have been followed for 6 months to 10 years, with a mean duration of follow-up of  $50.5 \pm 6.01$  months.

**CONCLUSION:** Estrogen replacement therapy apparently does not increase either recurrences or mortality rates. Adding progestogens may even decrease recurrences. Women with early breast cancer should be offered hormone replacement therapy after a full explanation of the benefits, risks, and controversies. (Am J Obstet Gynecol 1999;181:288-95.)

**Key words:** Breast cancer, hormone replacement therapy, estrogen, progestogen

Breast cancer is the most common malignancy in the United States, composing 29% of all female cancers and 16% of all female cancer deaths.<sup>1</sup> In 1999, it is expected that 176,300 new cases of breast cancer will be diagnosed, and 43,300 women will die of this disease. Carcinoma of the breast will develop in 1 of every 8 women in their lifetime if they live to be 85 years old. The good news is that the number of new cases is decreasing, down from 184,300 new cases in 1996, and the even better news is that the number of deaths has declined from 46,000 in 1995. This could be attributable to public awareness, increasing use of mammography, and regular examinations. The mortality rate from breast cancer in the United States is 21.1 per 100,000 women, which ranks

15th in the world. The frequency of breast cancer increases continuously in the female life span.

It is assumed that estrogens promote carcinoma of the breast, hasten recurrences, and cause metastases. However, there are no direct data to indicate that estrogen replacement therapy (ERT) will worsen the prognosis of this malignancy. Premenopausal women in whom breast cancer develops continue to produce endogenous estrogen for many years yet are denied ERT when they reach menopause.<sup>2</sup> Many breast cancers are diagnosed early, and women survive the tumor only to die of heart disease or osteoporotic fractures. There have been several studies published recently regarding the use of ERT after diagnosis of breast cancer to treat postmenopausal symptoms and protect against osteoporosis and heart disease.<sup>3-10</sup> This is a report of 76 patients with breast cancer, 50 of whom have been followed in our clinic and treated with ERT for many years.

## Material and methods

The study group consisted of 76 patients ranging in age from 34 to 83 years who were diagnosed with breast

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**Table I.** Deaths among estrogen users from breast cancer and other causes

Subject No.	Length of HRT before diagnosis (y)	Interval before resuming HRT (y)	Therapy during interval	Length of HRT before death	Therapy
1	15½	2	Testosterone pellets, tamoxifen, megestrol	3 wk*	Testosterone plus estradiol pellets, tamoxifen, megestrol
2	16	5	Testosterone pellets, norethindrone acetate	5 y	Testosterone plus estradiol pellets, norethindrone acetate
3	18	0	—	1 y	Testosterone plus estradiol pellets, megestrol

\*Patient died of a myocardial infarction 3 weeks after resuming HRT (no evidence of disease).

cancer (mean age, 61.8 ± 2.56 years). All 73 of the occurrences of breast cancer diagnosed in this patient population for the past 20 years (since 1978) are included in this study. Three patients, those who had used estrogen for 21.5 years, 24 years, and 32 years, were already using estrogen after previous carcinoma of the breast when we joined our current practice. There were 50 patients undergoing hormone replacement therapy (HRT) from 6 months to 32 years, 8 patients using nonestrogenic HRT for 6 months to 3 years, and 18 patients using no hormones for up to 10 years. The mean age at diagnosis of breast cancer in the 50 estrogen users was 57.6 ± 3.36 years. There were 3 nulliparous women (6%) in this group, and the mean parity was 2.2 ± 1.17. The mean body weight was 148.8 ± 4.97 lb, and the mean body mass index expressed in [kilograms/meter]<sup>2</sup> was 25.7 ± 2.00. In the 8 nonestrogenic hormone users, the mean age at diagnosis was 60.3 ± 2.89 years. There were no nulliparous women in this group, and the mean parity was 2.9 ± 1.13. The mean body weight was 156.8 ± 5.06 lb, and the mean body mass index was 27.0 ± 2.14. In the 18 nonhormone users, the mean age at diagnosis of breast cancer was 64.7 ± 3.27 years. There were 3 nulliparous women (16.7%) in this group, and the mean parity was 1.7 ± 1.02. The mean body weight was 155.1 ± 5.50 lb, and the body mass index was 27.7 ± 1.10. In the 50 hormone users, 45 were also given progestogens, mostly megestrol acetate. At the beginning of HRT, all hormone users had stage I disease, with the exception of subject 3, and only 3 of the 50 had 1 to 2 positive axillary nodes. In the 19 patients in whom receptor status was known, 12 had positive estrogen receptors and 8 had positive progesterone receptors. Two of the patients with negative estrogen receptors had positive progesterone receptors, and 1 patient in the positive estrogen receptor group had negative progesterone receptors.

Of the 50 estrogen users, 42 are still being treated in our clinic, 3 have died, 1 is still using estrogen after 6 years, and 4 have stopped using estrogen for the past 3 to 4 years after 9 to 32 years of use. Only 2 of the 8 users of nonestrogenic HRT are still being treated in our clinic. None of the 18 subjects not using hormones still attend our clinic. Follow-up of these 28 patients not still attend-

ing our clinic was done through the tumor registry at University Hospital. Those whose tumor records had not been updated in the past year were telephoned to determine their current status. Two of the 20 subjects not using hormones, last seen in 1988 and 1990, were not contacted, and therefore they are not included in this report. Informed consent was not obtained because no therapy was changed for the purpose of this study. Patients were counseled in detail, and this was noted in the record.

### Results

Mean age at diagnosis of breast cancer was 57.6 years (range, 31-68 years), and the follow-up was from 6 months to 32 years. Seven patients had lumpectomy and irradiation, and 43 had mastectomy. There were 24 occurrences of breast cancer each in the right and the left breast, and 2 were bilateral. Forty-seven of the 50 patients are living and well, and there were 3 deaths in this group (Table I).

**Subject 1.** Carcinoma was diagnosed in the right breast (stage I, negative nodes, positive progesterone receptor, negative estrogen receptor) at age 49 after 15½ years of ERT. A modified radical mastectomy was performed, and the patient was treated with 2 pellets of testosterone (150 mg), tamoxifen 10 mg given twice daily, and megestrol acetate 40 mg for 15 days each month. After 2 years of this interval treatment, 1 pellet of estradiol 25 mg was added, and the patient died 3 weeks later of a myocardial infarction without any known cardiovascular risk factors.

**Subject 2.** At age 66, this patient, who had been receiving estrogen-androgen-progestogen replacement for >16 years, had a left modified radical mastectomy for stage I cancer with negative nodes. ERT was stopped, and interval therapy began with 2 pellets of testosterone (150 mg) implanted every 6 months, with norethindrone acetate 5 mg given 13 days each month. During the next 3 years without the estrogen therapy, total cholesterol, triglycerides, low-density lipoprotein cholesterol, and total cholesterol/high-density lipoprotein ratio all increased, whereas high-density lipoprotein cholesterol decreased. At age 69, after 3 years without ERT, a myocardial infar-

**Table II.** Estrogen therapies for patients with breast cancer

Therapy	No. of patients	Duration	
		Range	Mean $\pm$ SEM (y)
Testosterone 150 mg, estradiol 25 mg, progestogen	19	6 mo–24 y	5.7 $\pm$ 2.36
Testosterone 150 mg, estradiol 50 mg, progestogen	8	2.5–7 y	3.7 $\pm$ 1.16
Oral estradiol, progestogen	4	6 mo–2 y	1.0 $\pm$ 0.78
Testosterone 75 mg, estradiol 25 mg, progestogen	3	1.5–9 y	4.5 $\pm$ 1.80
Oral estrogen, testosterone, progestogen	3	1.5–3.5 y	2.3 $\pm$ 0.92
Testosterone 225 mg, estradiol 50 mg, progestogen	2	3–4.5 y	3.5 $\pm$ 0.71
Transdermal estrogen, progestogen	4	2–5 y	3.2 $\pm$ 1.14
Testosterone 75 mg, estradiol 50 mg	2	16–17 y	16.5 $\pm$ 0.71
Testosterone 75 mg, estradiol 25 mg	1	32 y	—
Testosterone 150 mg, estradiol 50 mg	1	21.5 y	—
Estradiol 75 mg, progestogen	1	2 y	—
Testosterone 225 mg, estradiol 75 mg, progestogen	1	1.5 y	—
Oral estradiol	1	5 y	—
TOTAL	50	6 mo–32 y	5.5 $\pm$ 2.53

**Table III.** Interval hormone therapy between diagnosis of breast cancer and estrogen use

Therapy	No. of patients	Duration (y)	
		Range	Mean $\pm$ SEM
Testosterone pellets 150 mg, megestrol acetate	11	1–12	3.4 $\pm$ 1.69
Testosterone pellets 150 mg, megestrol acetate, tamoxifen	5	1–3	1.7 $\pm$ 0.87
Testosterone pellets 150 mg	4	0.5–4	2.9 $\pm$ 1.20
Testosterone pellets 150 mg, progestogen	3	2–5	4.0 $\pm$ 1.19
Testosterone pellets 150 mg, tamoxifen	2	1–2	1.5 $\pm$ 0.71
Tamoxifen	2	2.5–5	3.8 $\pm$ 1.12
Tamoxifen, progestogen	2	1–3	2.0 $\pm$ 1.00
None	12	4–25	9.7 $\pm$ 2.47
Estrogen not discontinued (or no interval therapy)	9	0	—

tion occurred, and she was treated with coronary bypass surgery. Two years after the myocardial infarction, one 25-mg estradiol pellet was added to the androgen-progestogen replacement therapy. Bone metastases developed 4½ years later, and she died within 6 months.

**Subject 3.** After 18 years of HRT, at age 62 this patient had a mammogram that was suspicious for malignancy in March 1994, and special compression view mammogram or biopsy was recommended by the radiologist. Surgical consultation was sought diligently many times and finally obtained in May 1995. In July 1995 a needle core biopsy was performed and demonstrated extensive ductal carcinoma in situ with focal comedocarcinoma. She was treated in September 1995 with lumpectomy but no irradiation. HRT was continued with 2 pellets of testosterone (150 mg) and 2 pellets of estradiol (50 mg) every 6 months, and megestrol acetate 40 mg was added for 25 days each month after the lumpectomy in September 1995. In September 1996, axillary, shoulder, and vertebral metastases were discovered because of shoulder pain, and the patient died in November 1996.

Table II shows the HRT given to the 50 estrogen users for 6 months to 32 years after diagnosis of breast cancer. The majority were treated with some combination of estradiol and testosterone pellets plus oral progestogens.

Testosterone and estradiol pellets were implanted every 4½ to 6 months in 38 of the 50 women (76%), and 45 of the 50 women (90%) were given oral progestogen. The most frequently used progestogen was megestrol acetate 20 to 40 mg given from 10 to 25 days each month to 29 of the 45 progestogen users (64%). Medroxyprogesterone acetate 10 mg from 10 to 13 days was given to 8 patients, and norethindrone acetate 2.5 to 5 mg was given to the other 8 patients along with the estrogen.

Table III indicates the interval hormone therapy used between diagnosis of breast cancer and either starting, resuming, or continuing ERT. The majority were treated with testosterone pellets, usually 150 mg every 5 to 6 months, for relief of menopausal symptoms. This was the therapy used by 25 of the 50 patients (50%), and 16 of these 25 were also given megestrol acetate 20 to 40 mg for 10 to 15 days each month. Tamoxifen 10 mg given twice daily was prescribed for 11 women. There were 21 patients not given any HRT, including 12 first seen with menopausal symptoms 4 to 25 years after diagnosis and treatment of breast cancer. There were 9 estrogen users diagnosed with carcinoma of the breast while using HRT in whom estrogen was continued without stopping.

Table IV lists the 8 patients treated with alternative therapies to estrogens for menopausal symptoms. These

**Table IV.** Alternative hormone therapies to estrogen

Subject No.	Therapy	Duration	Current status
1	Testosterone pellets 150 mg	1½ y	NED 8½ y
2	Testosterone pellets 150 mg, megestrol	6 y	NED 6 y
3	Testosterone pellets 150 mg, megestrol, tamoxifen	6 mo	NED 11 y
4	Testosterone pellets 150 mg, megestrol, tamoxifen	1½ y	NED 9 y
5	Testosterone pellets 150 mg, megestrol	1 y	NED 6½ y
6	Testosterone pellets 150 mg, megestrol, tamoxifen	3 y	NED 7½ y
7	Testosterone pellets 75 mg, megestrol	2 y	Died at 3 y
8	Testosterone pellets 150 mg, norethindrone acetate, tamoxifen	2 y	NED 2 y

NED, No evidence of disease.

**Table V.** Patients not treated with HRT

Status	No. of patients	Duration (y)	
		Range	Mean ± SEM
Living with no evidence of disease	10	0.5-10	4.6 ± 1.75
Died with cancer	5	0.5-9	3.3 ± 1.74
Died of cerebral vascular accident	1	1	—
Living with cancer	1	7	—
Living, receiving tamoxifen	1	4.5	—
TOTAL	18	0.5-10	3.8 ± 1.63

women had used HRT for 2 to 31 years before carcinoma of the breast was diagnosed (mean duration, 16.3 ± 3.16 years). When breast cancer occurred, estrogen therapy was stopped, and they were given testosterone pellets to alleviate menopausal symptoms. Megestrol acetate was given to 6 and 4 patients who were also treated with tamoxifen. Only 2 patients (subjects 2 and 8) are still receiving the listed therapy in our clinic. There was 1 death, subject 7, who died of breast cancer 1 year after being treated for 2 years with implantation of testosterone pellets 75 mg every 5 months and megestrol acetate 20 mg on a daily cycle on days 13 to 25. Seven of the 8 patients (87.5%) are living with no evidence of breast cancer for 2 to 11 years after diagnosis.

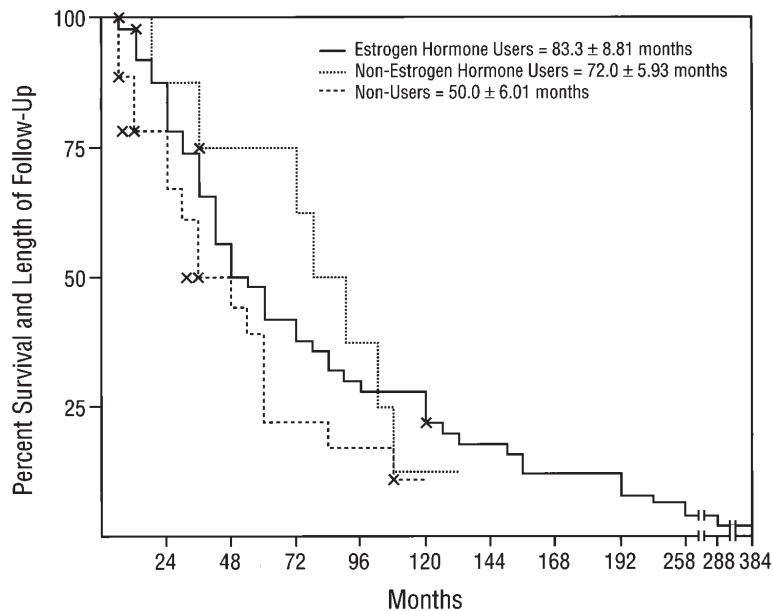
Table V lists the 18 patients who have not received any HRT since receiving the diagnosis of breast cancer. These patients underwent HRT for 2 to 31 years (mean duration, 14.4 ± 2.75 years) before the malignancy was diagnosed. After treatment for breast cancer, none have been seen in our clinic again. Six have died (a mortality rate of 33.3%), 5 of breast cancer and 1 of a cerebral vascular accident 1 year after stopping ERT. Another patient had a stroke 13 months after the last pellet implantation, resulting in right-side paralysis and aphasia. There are 11 patients who are living with no evidence of disease, one finishing the fifth year of tamoxifen. One is still being treated for metastatic breast cancer 7 years after diagnosis.

Fig 1 shows the percentage of survival and length of follow-up for the 3 groups of patients. With 3 deaths in the 50 estrogen users, the overall mortality rate is 6%. These patients have been treated with HRT for 6 months

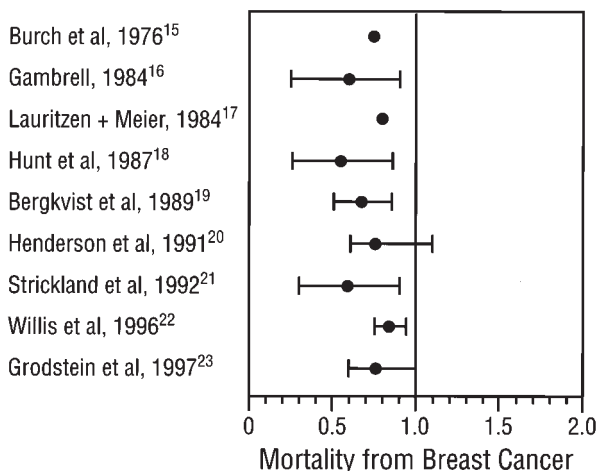
to 32 years, with a survival rate of 94% and mean duration of follow-up of 83.3 ± 8.81 months. In the 8 non-estrogenic hormone users, 1 has died (a mortality rate of 12.5%). These patients have been followed for 2 to 11 years, with a survival rate of 87.5% and a mean duration of follow-up of 72 ± 5.93 months. Among the 18 women not receiving HRT, 6 have died (a mortality rate of 33.3%). They have been followed for 6 months to 10 years, with a survival rate of 66.7% and a mean duration of follow-up of 50.5 ± 6.01 months.

**Comment**

ERT after breast cancer has evolved in our clinic over the years. During the 1980s, when a hormone user developed carcinoma of the breast, estrogen was stopped for 5 years, and menopausal symptoms were treated with androgens and progestogens. Progestogens, including medroxyprogesterone acetate and norethindrone acetate, were given only to women with an intact uterus, usually for 13 days each month or cycle. In the 1990s, as evidence increased that tamoxifen was effective in reducing recurrences, this hormone was added to the androgen. Tamoxifen was added, although the medical or surgical oncologist did not deem it necessary for in situ or intraductal lesions. Also during the 1990s, megestrol acetate was increasingly used as the progestogen of choice because it was found to be more acceptable to the oncologists than either medroxyprogesterone acetate or norethindrone acetate. During the 1990s, as more evidence accumulated that ERT did not increase the risk for breast cancer, especially in estrogen-progestogen users,<sup>11-13</sup> the interval between cancer diagnosis and resumption of



**Fig 1.** Percent survival and length of follow-up in 3 groups of patients—estrogenic hormone users, nonestrogenic hormone users, and nonhormone users. X represents when death occurred for each patient in the 3 groups.



**Fig 2.** Mortality from breast cancer in 9 studies. Filled circles, Relative risk of dying when malignancy develops during estrogen use compared with control subjects. Horizontal lines, 95% Confidence interval when available or calculable.

ERT was shortened. When the article of Eden et al<sup>4</sup> was published in 1995, ERT was no longer stopped but the progestogen was increased. The Australian study used conjugated estrogen 0.625 mg continuously combined with medroxyprogesterone acetate 50 mg. Because continuous combined HRT does not fully protect from endometrial cancer,<sup>14</sup> meggestrol acetate 40 mg for 25 days was prescribed.

All 9 studies that have examined survival from breast cancer developing in estrogen users have observed lower mortality (Fig 2). The relative risks in this figure were ob-

tained from each individual study, as calculated by the authors, along with the 95% confidence interval. Two studies, Burch et al<sup>15</sup> and Lauritzen and Meier,<sup>17</sup> did not report risk estimates but did show a percentage reduction in mortality (25% and 20%, respectively), and therefore these relative risks are shown as 0.75 and 0.80. Burch et al<sup>15</sup> were the first in 1976 to observe a 25% reduction in mortality when carcinoma of the breast developed in estrogen users followed for up to 15 years. In the original study from Wilford Hall<sup>16</sup> with 2 to 8 years of follow-up, the mortality was 22.2% in the 63 hormone users compared with a death rate of 45.5% in the 165 nonusers, which was statistically significant ( $P \leq .005$ ). A German study<sup>17</sup> observed a 20% reduction in mortality from breast cancer in estrogen users. In a study of 4544 hormone users in England, the mortality from carcinoma was likewise reduced (relative risk, 0.55; 95% confidence interval, 0.26-0.87).<sup>18</sup> The Swedish study observed a significantly improved prognosis from mammary malignancy developing in hormone users (relative risk, 0.68; 95% confidence interval, 0.52-0.87).<sup>19</sup> The lowest risk was in current users (relative risk, 0.54; 95% confidence interval, 0.34-0.86). However, they also observed significant reductions with latency (estrogen treatment stopped for 46 to 96 months: relative risk, 0.58; 95% confidence interval, 0.35-0.96) and duration of >37 months of estrogen use (relative risk, 0.55; 95% confidence interval, 0.31-0.97).

The study from Leisure World<sup>20</sup> likewise observed a reduction in deaths from breast cancer developing in estrogen users; however, it was not a significant reduction (relative risk, 0.81; 95% confidence interval, 0.62-1.10).

**Table VI.** HRT in women with breast cancer: Review of literature

Authors	No. of patients	Duration (mo, mean and range)	No. of recurrences	No. of deaths
Stoll and Parbhoo, <sup>5</sup> 1988	50	≥24	0	0
DiSaia et al, <sup>6</sup> 1993	77	27 (1-233)	7	3
Wile et al, <sup>7</sup> 1993	25	35.2 (24-82)	3	1
Powles et al, <sup>8</sup> 1993	35	43	2	0
Bluming et al, <sup>9</sup> 1994	70	8 (1 to ≥18)	2	0
Eden et al, <sup>4</sup> 1995	90	18 (4-144)	6*	0†
DiSaia et al, <sup>10</sup> 1996	41	68.9 (12-108)	6	2
Dew et al, <sup>25</sup> 1998	167	19.2 (3-264)	Relative risk 0.67	2

\*Seven percent compared with 17% of control subjects.

†None compared with 9.9% of control subjects.

In most of these studies the improved prognosis of breast cancer was due to closer surveillance in the estrogen users, and that was true in the study by Strickland et al.<sup>21</sup> In this study the presence of estradiol and progesterone receptors was a good prognostic indicator. When both estradiol and progesterone receptors were positive, 83.3% of the women survived for 8 to 18 years after surgical treatment for mammary malignancy. When both receptors were negative, only 46.3% were still alive. More of the current hormone users (64.7%) had tumors that were positive for both estradiol and progesterone receptors than either the past users (43.8%) or the nonusers (34.8%), which was statistically significant ( $P \leq .05$ ).

The very large American Cancer Society study<sup>22</sup> of 422,373 postmenopausal women showed that ever-use of ERT was associated with a significantly decreased risk of fatal breast cancer (relative risk, 0.84; 95% confidence interval, 0.75-0.94). This decreased risk was most pronounced in women who experienced natural menopause before the age of 40 years (relative risk, 0.59; 95% confidence interval, 0.40-0.87). The 18-year study of mortality with postmenopausal hormone use from the Nurses' Health Study<sup>23</sup> also observed a decrease in death from breast cancer that was of borderline significance (relative risk, 0.77; 95% confidence interval, 0.59-1.00).

Several physicians, particularly gynecologic oncologists, have been advocating ERT in women with previous breast cancer. Now the medical oncologists are joining in on this recommendation.<sup>3</sup> Pregnancy also has been considered contraindicated after breast cancer; however, a recent Danish study of 97 term pregnancies in breast cancer survivors actually found a nonsignificant decrease in death (relative risk, 0.55).<sup>24</sup> Although definitive prospective studies, which may take 10 to 20 years to complete, are currently being done to show that estrogens are safe in survivors of breast cancer, there are some data to support its safety (Table VI). Stoll and Parbhoo<sup>5</sup> were the first to advocate the use of estrogen with progestogen in patients with carcinoma of the breast. In their report of 50 patients given both hormones for ≥2 years, there were no recurrences or deaths. In 77 breast cancer survivors given HRT by gynecologic oncologists

for up to 15 years (median duration, 27 months), there were 7 recurrences and 3 deaths.<sup>6</sup> Surgeons from Southern California reported their experience with 25 women previously treated for breast cancer who subsequently received HRT for 24 to 82 months.<sup>7</sup> There were 3 recurrences and 1 death, but the overall survival in this study was 96%. In England, 35 patients with breast cancer were given HRT for an average of 43 months, with 2 recurrences and no deaths.<sup>8</sup> In a short-term study of 70 patients with carcinoma of the breast (mean duration, 8 months), there were 2 recurrences and no deaths.<sup>9</sup>

The longest and best study was from Australia where 90 patients with previous breast cancer were treated with continuous combined low-dose estrogen (conjugated estrogen 0.625 mg) and moderate-dose progestogen (medroxyprogesterone acetate 50 mg) for up to 12 years.<sup>4</sup> There were significantly fewer recurrences in the hormone users, 7% compared with 17% of the nonusers (relative risk, 0.4; 95% confidence interval, 0.17-0.93). There were no deaths among the hormone users, whereas 9.9% of the control subjects died. Because continuous combined estrogen-progestogen replacement therapy may not be fully protective of the endometrium, this regimen should be modified to cyclic combined estrogen-progestogen therapy.<sup>14</sup> Here both the estrogen and progestogen are prescribed according to the calendar from the 1st through the 25th of the month. In our practice estrogen is no longer stopped when breast cancer develops, but the progestogen is changed to megestrol acetate 40 mg and given from the 1st through the 25th of the month. Because carcinoma of the breast is listed as a contraindication to medroxyprogesterone acetate in the United States and megestrol acetate is used to treat metastatic breast cancer, medical oncologists can accept this latter progestogen more readily. In a cohort study by DiSaia et al,<sup>10</sup> there were 2 deaths among the 41 patients receiving HRT and 6 deaths in 82 comparison patients (relative risk, 0.67). Mean survival time was 68.9 ± 1.9 months in those patients receiving HRT compared with 46.2 ± 0.6 months in the comparison patients. The most recent, largest, and longest study to date was a cohort study of 1472 women with breast cancer, 167 of

whom were treated with estrogen, and 91% of whom also used a progestogen.<sup>25</sup> HRT was used from 4 months to 22 years, and the hazard ratio for recurrence in the estrogen-progestogen users was 0.67 (95% confidence interval, 0.38-1.16). There were 2 deaths among the hormone users (1.2%) and 167 deaths among the nonusers (12.8%).

Our data confirm the data obtained in other studies and recommendations of estrogen use in breast cancer survivors.<sup>2-10, 25</sup> They support the data of Eden et al<sup>4</sup> that moderate dosages of progestogen may even decrease recurrences and mortality when compared with untreated women with carcinoma of the breast. There were fewer deaths among our estrogen hormone users (6%) than among either the nonestrogenic hormone users (12.5%) or those not using hormones (33.3%). Women with early breast cancer should be offered HRT after full explanation of all the benefits, risks, and controversies.

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#### Discussion

**DR DONALD G. GALLUP**, Savannah, Georgia. This study from the Medical College of Georgia by Dr Natrajan and his associates addresses a problem many of us in practice occasionally encounter—can ERT be safely used in women previously treated for early breast cancer?

This retrospective study divided patients with breast cancer into 3 groups. Fifty patients with breast cancer were treated with estrogens, and 8 patients received nonestrogenic HRT, usually with testosterone with or without megestrol and tamoxifen. Eighteen patients did not receive any hormonal replacement. The mean duration of follow-up in all 3 groups was adequate, but breast cancer does recur after 10 years.

The mortality rate among the estrogen users was 6%. Of the 3 deaths, 2 patients died of breast cancer. Of the nonestrogenic HRT group, 1 patient died of breast cancer, for a mortality of 12.5%. In the group not receiving hormonal replacement, 33% have died. Five of the 6 died of breast cancer.

Unfortunately, the numbers of patients in each group were relatively small. HRT is variable in those receiving any regimen of replacement.

The advantages of ERT in postmenopausal women are well known to all of us. In the authors' review of several small series, they correctly pointed out that the mortality resulting from estrogen use in patients with breast cancer is not increased, nor are there data to indicate an

increased risk of recurrent breast cancer in postmenopausal women receiving ERT.<sup>1-3</sup> In fact, the Australian study<sup>3</sup> noted fewer recurrences in hormone users with prior breast cancer compared with nonhormone users.

None of the small studies thus far published are prospective or randomized. Furthermore, some surgeons and some gynecologic oncologists are vocal opponents of any estrogen therapy in patients with previously treated breast cancer.

The Gynecologic Oncology Group has initiated a randomized, prospective study of ERT in women with early-stage endometrial cancer. In this study, Gynecologic Oncology Group protocol 137, women are randomized into a group receiving 0.625 mg conjugated estrogen versus placebo. Eligibility criteria include all stage I and stage II occult disease and all histologic types. The estrogen or placebo must be initiated within 12 weeks after the surgical excision of the uterus and ovaries. The end points of the study are progression-free interval and survival. This study was in committee for several years before initiation, with several adverse comments from the Food and Drug Administration that had to be addressed.

The only way to answer the question of whether to use HRT in previously treated patients with breast cancer is a randomized prospective trial, a plea given by many.<sup>1, 2</sup> It seems inappropriate to continue to categorically prohibit HRT in all breast cancer survivors.

My discussion prompts my first question to the authors. How would they design such a prospective trial? For example, what 2 or 3 medication arms would they choose? What would be the eligibility criteria, such as stage, estrogen and progesterone receptor status, and ploidy? When would HRT begin?

My second question regards the "Material and Methods" section. Did patients in this study sign a special consent form approved by an institutional review board, or were they simply counseled and an extensive note written in the chart?

I congratulate the authors for their courageous approach to a complex problem.

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**DR JIM FIORICA**, Tampa, Florida. What was the study period for your patient enrollment? Did your dose of estrogen vary during that study period?

**DR JOHN HILL**, Athens, Georgia. What were the stages assigned to your patients, and what was the receptor status? Did these patients have symptoms before they started ERT? Why was the pellet therapy chosen? Was the quality of life of these women improved? Did your high dose of progestogen cause any of these patients to have adverse symptoms?

**DR NATRAJAN** (Closing). To answer Dr Gallup's questions, the study of HRT in patients with breast cancer should include 3 medication arms: (1) placebo, (2) estrogen alone if the patient has had a hysterectomy, and (3) estrogen plus progestogen if the patient has a uterus. Because the Australian study observed fewer recurrences and deaths with a moderate dose of progestogen, medroxyprogesterone acetate 50 mg continuously, it is recommended that megestrol acetate 40 mg be given for 25 days a month as used in our study. Interrupting the progestogen should prevent the endometrial cancers seen with continuous combined HRT. The eligibility criteria should limit the study to patients with stage I and early stage II cancer. Receptor status and ploidy should not matter. Therapy could begin whenever the patient seeks consultation for menopausal symptoms, or the therapy can be continued when breast cancer is diagnosed while the patient is already using estrogen. Patients were from our clinical practice, and because no therapy was changed for the purpose of this study, informed consent was not obtained. Patients were counseled in detail, and extensive notes were made in the chart.

In response to Dr Fiorica's questions, the study period was about 18 years, and some of the patients had been in our practice for longer than that. The dose of estrogen did not vary during this study period.

To answer Dr Hill's questions, the majority of occurrences of breast cancer were stage I, and a few were early stage II. Receptor status was known in 19 patients, and 12 had positive estrogen receptors, whereas 8 had positive progesterone receptors. Two of the patients with negative estrogen receptors had positive progesterone receptors, and 1 patient with negative progesterone receptors had positive estrogen receptors. Some patients had symptoms before estrogen therapy, whereas other patients continued receiving estrogen after extensive counseling. Pellet therapy has been used in our clinic for nearly 60 years, and most of the patients were using pellets before receiving the diagnosis of breast cancer. They had been doing so well that they were continued with the same treatment. Their quality of life was definitely improved. The dose of progestogen rarely had any adverse side effects, and when they occurred, these were managed with mild diuretics.