Estrogen Replacement Therapy in Endometrial Cancer Patients: A Matched Control Study

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***Objective*: To determine if estrogen replacement therapy, in women with a history of endometrial cancer, increases the risk of recurrence or death from that disease.**

***Methods*: Two hundred forty-nine women with surgical stage I, II, and III endometrial cancer were treated between 1984 and 1998; 130 received estrogen replacement after their primary cancer treatments and 49% received progesterone in addition to estrogen. Among this cohort, 75 matched treatment-control pairs were identified. The two groups were matched by using decade of age at diagnosis and stage of disease. Both groups were comparable in terms of parity, grade of tumor, depth of invasion, histology, surgical treatment, lymph node status, postoperative radiation, and concurrent diseases. The outcome events included the number of recurrences and deaths from disease.**

***Results*: The hormone users were followed for a mean interval of 83 months (95% confidence interval [CI] 71.0, 91.4) and the nonhormone users were followed for a comparable mean interval of 69 months (CI 59.1, 78.7). There were two recurrences (1%) among the 75 estrogen users compared with 11 (14%) recurrences in the 75 nonhormone users. Hormone users had a statistically significant longer disease-free interval than nonestrogen users ($P = .006$).**

***Conclusion*: Estrogen replacement therapy with or without progestins does not appear to increase the rate of recurrence and death among endometrial cancer survivors. (Obstet Gynecol 2001;97:555–60. © 2001 by The American College of Obstetricians and Gynecologists.)**

Estrogen replacement therapy for women diagnosed with and treated for endometrial cancer is still controversial. With approximately 37,400 new cases diagnosed in 1999, endometrial cancer constitutes the fourth most common malignancy in American women, with an overall cure rate in excess of 70%.[1] Subsequently, these survivors may experience the negative long-term sequelae of estrogen deprivation for many years. It is important that these issues are made clear because recent data have suggested that estrogen replacement therapy in postmenopausal women may provide protection from cardiovascular disease, osteoporosis, colon cancer, and Alzheimer disease. In addition, quality of life is improved by relief from symptoms such as irritability, insomnia, urogenital atrophy, and vasomotor symptoms.[2–6]

Historically, clinicians have withheld hormone replacement therapy (HRT) for endometrial cancer patients based on the theoretic risk that occult or quiescent foci of disease may be stimulated by estrogen administration (ie, the "fuel on the fire" theory). This hypothesis has not been supported by data. In fact, three retrospective series, containing a total of 153 patients, have failed to document an increased incidence of recurrent disease among patients exposed to exogenous estrogen.[7–9] However, lack of a satisfactory control group in these past studies and the absence of a completed prospective trial has not helped to clarify this issue.

The purpose of this study was to evaluate the risk of recurrence and the death rate in a retrospective cohort study of patients with a history of endometrial cancer, International Federation of Gynecology and Obstetrics (FIGO) surgical stages I–III, treated with HRT.

Materials and Methods

The Institutional Review Boards of the University of California, Irvine Medical Center and Long Beach Memorial Medical Center approved the study design, which included a retrospective office and hospital chart review. From a cohort of 130 women with endometrial cancer who elected to receive posttherapy estrogens, 75 pairings with endometrial cancer patients not treated with estrogen were identified, using decade of age and

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stage of tumor as selection criteria. Thirty of the 75 estrogen users were included in our previous case series report with short-term follow-up.[9]

Demographic and clinical data included age at diagnosis, parity, presence of intercurrent disease at the time of diagnosis, method of surgical treatment, postoperative adjuvant therapy (chemotherapy or radiotherapy), FIGO surgical stage, grade, depth of invasion, lymph node status, and preoperative use of estrogen. The postoperative use of HRT was evaluated as a function of the interval between primary cancer therapy and initiation of estrogen replacement, type of hormone used, dosage, and duration of use. Oral, transdermal, and vaginal estrogen were considered to represent systemic use.

One hundred thirty women with endometrial cancer treated with estrogen replacement therapy at the University of California, Irvine Medical Center and Long Beach Memorial Medical Center between 1984 and 1998 were identified through procurement of Tumor Registry abstracts and cross-referencing of files to the Gynecologic Oncology Division. FIGO surgical stage was assigned retroactively to those cases treated before 1989. Exclusion criteria included FIGO surgical stage IV disease, sarcomatous histology, follow-up interval under 12 months, inability to confirm posttherapy hormone use, concurrent tamoxifen use, and absence of appropriate surgical-pathologic staging procedures performed at the time of primary tumor resection. A member of the Gynecologic Oncology Division performed all the surgical staging procedures. The control group of 75 endometrial cancer patients who did not use HRT was identified in a similar manner during the study period from a group of 119 patients.

The outcome variables included the number of disease recurrences, deaths from disease, and deaths from intercurrent illness. Thus, recurrence rate, disease-free interval, and disease-free survival constituted the outcome measures. The patients treated with hormones were compared with their control counterparts by means of χ^2 analysis or Fisher exact test for discrete variables and with two-tailed t tests for the continuous variables except for the time measurements. The Wilcoxon rank-sum test was used for comparison of follow-up time in the two groups. The product-limit method was used to estimate the survival function and disease-free interval function for each group. The log-rank test was applied to test for the equality of survival and disease-free interval functions of the two groups. Multivariable analyses were performed on the data set from 249 women using Cox proportional hazards model with time to recurrence as the outcome variable, hormone use as the main predictor, and adjustment for potential confounders (Tables 1–3). The best fitting and most parsimonious models were selected using multivariable stepwise, forward- and backward-selection procedures. Similar multivariable analyses were also performed on data from the matched pairs of 75 patients treated with hormones and 75 controls. To account for possible survival bias, these analyses were repeated, but restricted to women who began hormone therapy within the first 6 months of therapy. $P < .05$ was considered to be statistically significant. All analyses were conducted using the SAS system statistical program (SAS Institute Inc., Cary, NC).

Table 1. Demographic Characteristics

	HRT (%) (n = 75)	No HRT (%) (n = 75)	P
Age at diagnosis (y) (mean ± SD)	59.7 ± 9.4	61.1 ± 9.7	.37
Parity			.46
0	11 (15)	10 (13)	
1	5 (7)	12 (16)	
2	16 (21)	17 (23)	
>2	23 (31)	20 (27)	
Unknown	20 (27)	16 (21)	
Intercurrent diseases			.21
None	47 (63)	37 (49)	
1	12 (16)	9 (12)	
2	7 (9)	17 (23)	
>2	3 (4)	2 (3)	
Other cancers	4 (5)	6 (8)	
Unknown	2 (3)	4 (5)	
Preoperative HRT			.001
No	35 (47)	57 (76)	
Yes	37 (49)	13 (17)	
Unknown	3 (4)	5 (7)	

HRT = hormone replacement therapy.
Values presented as n (%).
t test was used for continuous variables. χ^2 was used for discrete variables and the Fisher's exact test (two-tailed) was applied when sparse data within cells were encountered.

Table 2. Treatment

Treatment	HRT (%) (n = 75)	No HRT (%) (n = 75)	P
Surgery			.24
Hysterectomy	33 (44)	26 (35)	
With lymphadenectomy	42 (56)	49 (65)	
Radiation therapy			
No	55 (73)	55 (73)	1.00
Yes	20 (27)	20 (27)	
Chemotherapy			.68
No	73 (97)	71 (95)	
Yes	2 (3)	4 (5)	

HRT = hormone replacement therapy.
Values presented as n (%).

Table 3. Tumor Characteristics

	HRT (%) (n = 75)	No HRT (%) (n = 75)	P
Stage			1.00
Ia	14 (19)	14 (19)	
Ib	44 (59)	43 (57)	
Ic	6 (8)	7 (9)	
IIa	4 (5)	5 (7)	
IIb	3 (4)	2 (3)	
IIIa	3 (4)	3 (4)	
IIIc	1 (1)	1 (1)	
Histology			.80
Adenocarcinoma	69 (92)	70 (93)	
Papillary serous	2 (3)	3 (4)	
Clear cell	4 (5)	2 (3)	
Grade			.47
1	31 (41)	24 (32)	
2	29 (39)	32 (43)	
3	15 (20)	19 (25)	
Myometrial invasion			.37
Endometrium only	16 (21)	12 (16)	
Inner ½	49 (65)	47 (63)	
Outer ½	10 (13)	16 (21)	
Lymph nodes			.30
Negative	39 (52)	48 (64)	
Positive	1 (1)	1 (1)	
Unknown	35 (47)	26 (35)	
Peritoneal washing			.78
Negative	47 (63)	43 (57)	
Positive	3 (4)	4 (5)	
Unknown	25 (33)	28 (37)	

HRT = hormone replacement therapy.
Values presented as n (%).

Results

This study was based on data from 249 women with endometrial cancer, of whom 130 were treated with HRT and 119 were not. Seventy-five matched pairs of women were selected. The mean age at diagnosis and parity did not differ statistically between the two groups. There was also no significant difference between the presence and number of intercurrent illnesses, with chronic hypertension being most common; diabetes mellitus, coronary artery disease, and morbid obesity, however, were also observed. Fewer than 10% of the subjects in each group had been diagnosed and treated for antecedent malignancies. Nearly 50% of the estrogen users had received previous HRT (ie, before the diagnosis of endometrial cancer) as compared with 17% of the nonhormone users (P = .001) (see Table 1).

The treatment of the two groups did not differ significantly (Table 2). All 150 subjects initially underwent total abdominal hysterectomies and bilateral salpingo-oophorectomies. The uterine contents were examined intraoperatively by frozen section. High-risk tumor profiles (ie, nuclear grade III, at least 50% myometrial penetration, and cervical extension of the disease) were identified in 56% of the controls versus 43% of the treatment group. In these cases, a dissection of the pelvic lymph node chains was undertaken to further delineate the extent of disease dissemination. Following acute convalescence, 27% of patients in each group were treated with postoperative adjunctive radiotherapy for high-risk prognostic factors. Less than 5% of women in each group were treated with systemic hormonal or chemotherapy secondary to widespread tumor metastases.

The two groups did not differ significantly with respect to surgical-pathologic features (Table 3). Most patients (57% of the controls and 59% of the treatment group) were diagnosed with FIGO surgical stage IB tumors. Nearly 15% of subjects in each group presented with locally advanced disease (FIGO surgical stages IIA–IIIA) or upper abdominal metastases (FIGO surgical stage IIIB). Adenocarcinoma represented the predominant cell type in more than 90% of cases. Moderately to well-differentiated lesions were encountered in 75% of the controls and 80% of the treatment group. Approximately 65% of the tumors were restricted to the inner half of the myometrium. For those patients who underwent pelvic lymphadenectomy, positive nodes were discovered in only one patient from either group. Finally, cytologic analysis disclosed the presence of free-floating tumor cells within pelvic washings from approximately 5% of patients from each group.

Details of the temporal relationship between tumor resection and the initiation of HRT are given in Table 4. For the 75 women who received estrogen replacement, 57% initiated hormonal supplementation within 6 months of primary surgery (mean interval, 2.2 months). Within 1 year of follow-up, an additional 16% of the subjects were taking HRT; the remaining 27% were started on HRT later (range, 1.1–5.0 years). Most patients used a daily dose of 0.625 mg oral conjugated equine estrogens (Ayerst Organics Ltd., Brandon, Manitoba, Canada). We routinely offered 2.5 mg medroxyprogesterone acetate (Upjohn Co., Kalamazoo, MI) and 49% of the subjects elected to include this medication in their daily regimen.

The surveillance program for all patients consisted of pelvic examinations and vaginal Papanicolaou test every 3 months for the first 2 years, after which the screening interval was increased to 6 months. The

Table 4. Interval From Surgery to Start of HRT

Interval (mo)	Mean	SD	Range	n	%
0–6	2.2	2.0	0–6	43	57
7–12	9.1	1.9	7–12	12	16
>12	38.3	25.3	13–108	20	27

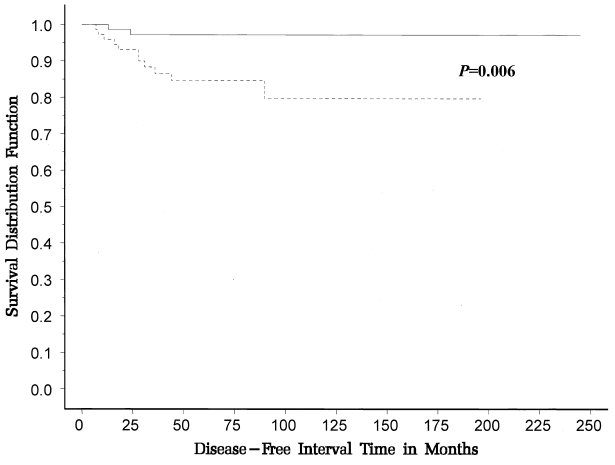

Figure 1. Kaplan–Meier survival curve comparing disease-free interval of estrogen users and nonestrogen users ($N = 150$). *Solid line* = estrogen users; *dotted line* = nonestrogen users.

follow-up status was determined by date of the last physical examination, vaginal cytology, or tumor registry data. At a mean follow-up of 83 months (95% confidence interval [CI] 71.0, 91.4), two recurrences limited to the pelvis have been documented among the 75 estrogen users. Eleven patients from the nonestrogen-user group had recurrences either locally ($n = 8$) or at distant sites ($n = 3$) at a mean follow-up of 69 months (CI 59.1, 78.7). The log rank test was used to compare the disease-free interval and disease-free survival for the two groups. The analysis demonstrated statistical significance favoring a longer disease-free interval among the hormone replacement group ($P = .006$). A Kaplan–Meier time-to-event analysis was performed to graphically display this relationship (Figure 1). No conclusions could be made from the survival analysis because there were too few events (eg, one death from disease in each group).

Multivariable analyses were performed on the data set from 249 women. Cox proportional hazards model was used with time to recurrence as the outcome variable and hormone use as the main predictor adjusted for potential confounders. In 229 women for whom the pretherapy HRT use was known, the risk ratio for posttherapy HRT was 0.52 (95% CI 0.17, 1.62) with age and preoperative use of hormone therapy. Thus, comparing patients of similar age and pretherapy hormone use, those patients who received HRT after treatment for endometrial cancer were not more likely to suffer a disease recurrence than those who did not receive posttherapy HRT (likelihood ratio test, $P = .250$). No other variables added information to the model. It should be noted that for these women, there was a strong association between pre- and posttherapy HRT use (Fisher exact test $P < .001$). Including associated variables in a multivariable model may cause instability in the parameter estimates for the predictor variables. When analyses were restricted to 173 women who began hormone therapy within the first 6 months of therapy and for whom the pretherapy HRT use was known, the risk ratio for posttherapy HRT was 0.13 (95% CI 0.02, 1.62) adjusted for preoperative use of hormone therapy and age. This analysis was performed to control for the potential of confounding due to survival bias, that is, women who survive longer may be more likely to be started on hormone therapy. Results showed that among patients of similar pretherapy hormone use and age, those patients who received HRT after treatment for endometrial cancer were not more likely to suffer a disease recurrence than those who did not receive posttherapy HRT (likelihood ratio test $P = .067$).

Similar multivariable analyses were also performed in 67 matched pairs for whom pretherapy HRT was known. The risk ratio for posttherapy HRT was 0.14 (95% CI 0.02, 1.09) adjusted for preoperative use of hormone therapy. Thus, comparing patients with similar pretherapy hormone use, those patients who received HRT after treatment for endometrial cancer were not more likely to suffer a disease recurrence than those who did not receive posttherapy HRT (likelihood ratio test $P = .016$). No other variables added information to the model. In this group of patients, there were no recurrences of disease in women who began HRT within the first 6 months of treatment for endometrial cancer. Thus, it was not possible to accurately model statistically the effect of posttherapy HRT while controlling for the potential of confounding due to survival bias.

One death from disease occurred in both the hormone replacement and the control groups. The remaining deaths resulted from intercurrent diseases: three deaths in the hormone group and four deaths in the control group. Of the two recurrences among the estrogen users, one patient died of disease and the other patient is currently alive with no evidence of disease. Within the control group, one patient died of disease after recurrence at a distant site. Eight women experienced recurrent disease in the pelvis; five are currently without disease and three are alive with disease. The remaining two women with recurrent disease at a distant site underwent salvage therapy and are currently without disease.

Finally, because the number of recurrences among the current hormone users was small ($n = 2$), the data are insufficient to address any protective effects conferred by progesterone administration with respect to disease-free interval and disease-free survival.

Discussion

A sharp increase in the incidence of endometrial cancer occurred in the United States following the introduction and resultant widespread use of HRT in the 1960s and 1970s. In 1995, Grady and colleagues[10] performed a meta-analysis on 30 studies published between 1970 and 1994 and calculated a relative risk for endometrial cancer of 2.3 for unopposed estrogen users compared with nonestrogen users (95% CI 2.1, 2.5). This risk escalated with prolonged duration of estrogen administration. Consequently, the safety of implementing HRT among endometrial cancer patients has been debated.

At first glance, it appears reasonable that if unopposed estrogen use increases the risk of primary endometrial cancer, then the administration of HRT to endometrial cancer patients should have a negative impact on recurrence rate and survival. However, the available laboratory data suggest that estrogen exposure is associated with increased cell division of normal endometrial cells, thus placing them in a particular molecular configuration susceptible to DNA damage.[11,12] If this assumption is correct, then estrogen could act as a tumor promoter to already genetically altered cells. Therefore, estrogen may not have any further deleterious effects once neoplastic transformation has already occurred. Stated differently, when the source of endometrial tissue has been removed through hysterectomy as part of primary cancer therapy, disease recurrence then becomes a function of occult residual tumor cells and not the result of de novo hormonal stimulation and neoplastic transformation.

In 1986, Creasman and co-workers[7] reported outcomes of 221 patients with stage I endometrial cancer, 47 (21%) of whom received estrogen after their cancer therapy. Of note, the estrogen group had a statistically significant longer disease-free survival. Lee and colleagues[8] described 144 women with clinical stage I endometrial cancer treated over an 11-year period, of whom 44 (31%) had low risk factors for recurrence. Although no recurrences or intercurrent deaths manifested in the estrogen-receiving group, there was an 8% incidence of both recurrent disease and intercurrent death in the 99 patients who did not receive estrogen.

In 1996, Chapman and co-workers[9] identified 123 surgical stage I and II endometrial cancer patients, of whom 62 (50.5%) received estrogen replacement after cancer therapy. After controlling for risk factors for recurrence, the investigators were unable to detect a difference in recurrence rate or time to recurrence between those patients who had received HRT and those who had not.

Although these studies have concluded that estrogen replacement does not increase the rate of recurrence, they were limited by the lack of a control group, the retrospective type of analysis, and the lengthy time interval between cancer treatment and initiation of estrogen therapy. The present study overcomes some of these shortcomings via the generation of matched controls for 75 subjects from our original cohort of 130 estrogen users. Most patients were treated with the standard oral dose of estrogen, initiating the therapy within 1 year from the primary cancer treatment when most of the recurrences are likely to occur. Our mean follow-up of nearly 7 years is substantially long for detecting recurrent disease. In addition, approximately 15% of the patients in each group had advanced disease, FIGO stage III.

Nearly 50% of the patients received progesterone in addition to estrogen. The rationale for offering progesterone is based on data that progesterone inhibits the stimulatory effects of estrogen on normal and hyperplastic endometrium. Whether progesterone truly inhibits any stimulatory effects of estrogen on nascent tumor cells is unknown. Nevertheless, whether to include progesterone in the replacement regimen deserves an informed discussion.

We found that women who had received HRT before diagnosis were more likely to have received HRT after treatment. In addition, our analysis demonstrates a protective effect incurred by pretreatment HRT exposure. Currently, the explanation for this finding is unknown. One can only speculate that pretherapy HRT may be related to more favorable tumor biology.

We also noted that the estrogen users were less likely to have recurrences and experienced a longer disease-free interval compared with their matched control counterparts. Furthermore, the recurrence rate of the estrogen users not included in the matched cohort was three of 55 women (6%). This rate is comparable to the remaining nonmatched control patients (data not shown). Importantly, the overall recurrence rate in our study is favorable and is slightly lower than that generally expected for endometrial cancer. One explanation is that this study was carried out in a single institution with many years of experience in the treatment of this malignancy. Patients are routinely treated with an aggressive surgical approach followed by radiation therapy when appropriate.

Conclusions that are more definitive would require a randomized clinical trial of sufficient power. Nevertheless, the present study constitutes the largest controlled experience to date with a follow-up period that is adequate to detect recurrent disease. The results are certainly thought provoking and should prompt further investigation into this clinical problem, especially with respect to biomarkers such as estrogen receptor status

and DNA ploidy. Recently, the Gynecologic Oncology Group initiated accrual for a randomized, matched clinical trial of estrogen replacement therapy and placebo in women with stage I and occult IIa endometrial adenocarcinoma. However, with a large target sample size of more than 1000 patients in each arm and a long follow-up period, peer review data will not be available for many years. Furthermore, this trial will not answer the question of whether estrogen replacement therapy is contraindicated for patients with advanced stage disease.

This study provides the most current and reliable data to assist patients in making informed decisions regarding HRT. The established long-term health benefits of estrogen replacement, as well as the positive impact on the quality of life, seem to outweigh the unfounded suggestion of increased risk of disease recurrence. Appropriate counseling should include a discussion of the available nonestrogen preparations through which some of the benefits of estrogen replacement may be gained.

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