Estrogen Replacement Therapy for Ovarian Carcinoma Survivors

A Randomized Controlled Trial

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BACKGROUND. Surgery for premenopausal and perimenopausal patients with epithelial ovarian carcinoma may often result in significant menopausal symptoms. Physicians may well be reluctant to prescribe, and patients loathe to take, postoperative estrogen replacement therapy because they fear that supplementation may lead to ovarian carcinoma relapse. This randomized prospective study was undertaken to determine whether postoperative estrogen replacement therapy had a negative influence on the disease free interval and overall survival of ovarian carcinoma survivors.

METHODS. Between January 1987 and June 1994, at the time of a routine consultation held 6–8 weeks postoperatively, 130 patients younger than 59 years with invasive epithelial ovarian carcinoma were randomized to continuous oral conjugated equine estrogen (ERT) or to no supplementation (non-ERT). All patients were followed prospectively for a minimum of 48 months.

RESULTS. Three patients in the ERT group and 2 in the non-ERT group were lost to follow-up, so 59 and 66 were finally analyzed in their respective groups. Nine patients originally randomized to ERT refused or stopped their supplementation, whereas 5 in the non-ERT commenced taking estrogens. A total of 32 recurrences occurred in the ERT group and 41 in the non-ERT group. The median disease free interval was 34 versus 27 months, respectively, whereas overall survival was 44 versus 34 months, respectively, for the two groups. The differences in disease free interval ($P = 0.785$) and overall survival ($P = 0.354$) between the two groups were not statistically significant.

CONCLUSIONS. Postoperative estrogen replacement therapy did not have a negative influence on the disease free interval and overall survival of ovarian carcinoma survivors. ***Cancer* 1999;86:1013–8.** © *1999 American Cancer Society.*

KEYWORDS: estrogen replacement therapy, ovarian carcinoma survivors, outcome, randomized controlled trial.

Ovarian carcinoma still results in more deaths than any other gynecologic malignancy. In the vast majority of cases it presents as advanced disease that is widespread in the abdominal cavity. Even though the incidence increases with age, a significant proportion of cases will occur in premenopausal and perimenopausal women. Surgical management will, by necessity, induce a premature menopause that may result in annoying and often debilitating symptoms, including hot flushes, mood swings, emotional disorders, sleep disturbances, dyspareunia, and atrophic vaginitis with its attendant urinary tract symptoms.

Nevertheless, be it due to lack of definitive data and the fact that there is only one study that has retrospectively addressed the topic,

Data from this report was presented at the 25th South African Obstetric and Gynecology Congress, Stellenbosch, Cape Town, South Africa, March 1998.

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Received September 18, 1998; revisions received January 4, 1999, and April 6, 1999; accepted April 6, 1999.

physicians have been, and still are, reluctant to give ovarian carcinoma survivors estrogen replacement therapy (ERT) because they fear that it will decrease survival by increasing the chances of relapse.

Since the mid-1970s, a plethora of literature has been published pertaining to estrogen and progesterone receptors and their activity in patients with ovarian carcinoma. Even though receptors are present in a high proportion of ovarian carcinomas,[1] there are as many studies claiming that expression of receptors are associated with improved survival as there are studies claiming that receptors are not significant predictors of survival.[2–4] The data provide no obvious guidelines as to the safety of estrogen in these patients.

We therefore conducted a study of women with invasive epithelial ovarian carcinoma who were prospectively randomized to either estrogen or no estrogen replacement postoperatively. The aim of the study was primarily to determine whether estrogen had an adverse effect on the disease free interval and overall survival of these patients.

MATERIALS AND METHODS

All patients younger than 59 years with invasive epithelial ovarian carcinoma who had their primary management at our hospital were included in the study. Patients with ovarian carcinoma of low malignant potential and those who had ever taken conjugated estrogens were excluded from the study. Recruitment was from January 1987 to June 1994. Ever having taken the oral contraceptive pill was not an exclusion criteria. Primary management consisted of radical cytoreductive surgery, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and tumor debulking, followed in all cases by 6 cycles of cisplatin 100 mg/m^2 and cyclophosphamide 500 mg/m^2 and then 2 cycles of cisplatin only. Oral chlorambucil was administered for 1 year thereafter. The surgery was performed by one surgeon in all cases (F.G.). All patients were randomized at the routine assessment consultation held 6–8 weeks postoperatively; randomization involved patient choice of a sealed opaque envelope from a predetermined equal number of similarly sealed opaque envelopes that contained directions for the randomization to either continuous conjugated equine estrogen replacement (ERT), consisting of Premarin 0.625 mg daily (Wyeth-Ayerst, Philadelphia, PA), or no supplementation (non-ERT). Placebo tablets were not used, and prior to randomization all patients were fully counseled about the risks and benefits of estrogen replacement as well as the aims and limitations of the study. Medication such as clonidine, multivitamins, beta blockers, antidepressants, and hypnotics were permissible in both groups of patients for control or adjuvant control of symptomatology, but progestogens and "homeopathic hormonal" medication were not permissible. Informed consent was obtained from all patients. The patients were seen every 3–6 months, and ultrasonography and/or computed tomography was performed every 6 months or when clinically indicated. Tumor marker CA125 was analyzed at monthly intervals for the first year and every 3 months thereafter. Mammograms were performed every 18–24 months.

Regarding sample size, it was calculated that a 20% difference in disease free interval between the 2 groups randomly allocated to estrogen supplementation or no supplementation would require a sample of at least 118 patients (a minimum of 59 patients in each group) to demonstrate statistical difference at the 5% level with an 80% power of the test.

The main outcome measures of the two groups were disease free interval and overall survival. Statistical analysis using a BMDP statistical software package (BMDP, Los Angeles, CA) was performed on an intention-to-treat basis, regardless of whether patients stopped/refused or commenced taking estrogens within each group, despite the randomization. Median follow-up time was calculated as time from date of entry to the date of death for patients who died of disease and from date of entry to date last confirmed alive for living patients.

Survival and disease free survival curves were calculated for each treatment group using Kaplan–Meier life table analysis. Differences between the groups were tested according to the generalized Wilcoxon test, and multivariate analysis was performed using Cox proportional hazards regression analysis.

RESULTS

One hundred thirty patients met the criteria and were randomized into their respective groups: 62 to postoperative ERT and 68 to non-ERT. Three patients in the ERT group and 2 in the non-ERT group were lost to follow-up, so that the final analysis involved 59 patients in the ERT group and 66 in the non-ERT group. Nine patients originally randomized to the ERT arm either refused or stopped taking estrogen supplementation (3 refused ERT and 6 stopped taking their ERT 2–9 months after commencing ingestion), whereas 5 in the non-ERT arm ultimately started taking estrogens because of debilitating symptoms. For the purposes of analysis, the patients remained in the treatment group to which they were originally allocated, irrespective of whether they elected to commence, stop taking, or refuse ERT, i.e., intention-to-treat analyses are reported. From the outset of the study, we expected some patients to deviate from their random-

TABLE 1
Characteristics of Patients

	ERT	Non-ERT
Age (yrs)		
27–35	5 (8%)	2 (3%)
36–45	11 (19%)	9 (14%)
46–55	19 (32%)	24 (36%)
56–59	24 (41%)	31 (47%)
Stage		
I	7 (12%)	9 (13.5%)
II	9 (15%)	4 (6%)
III	38 (65%)	46 (70%)
IV	5 (8%)	7 (10.5%)
Histology		
Serous	39 (66%)	46 (70%)
Mucinous	16 (27%)	11 (16.5%)
Endometrioid	2 (3.5%)	7 (10.5%)
Clear cell	2 (3.5%)	2 (3%)
Differentiation		
Well differentiated	25 (42%)	28 (42.5%)
Moderately	15 (25%)	11 (16.5%)
Poorly	19 (33%)	27 (41%)
Surgical		
Optimal	44 (74.5%)	46 (69.5%)
Suboptimal	15 (25.5%)	20 (30.5%)
Bowel surgery	17 (29%)	25 (38%)
Splenectomy	1	
Total no. of recurrences	32 (54%)	41 (62%)
Survival		
No. alive	27 (46%)	25 (38%)
Disease free	26	24
With disease	1	1
D.O.D.	32 (54%)	41 (62%)

ERT: estrogen replacement therapy; D.O.D.: died of disease.

ization and cross over between groups. By analyzing our results on an intention-to-treat basis, we anticipated that these problems would be overcome. The ages of the patients, stages of disease, histologic subtypes and differentiation of the tumors, surgical outcomes, recurrences, and overall survival are shown in Table 1. Nine patients in the ERT arm and 7 in the non-ERT arm had a hysterectomy prior to their diagnosis, and no patient had a first-degree relative with a diagnosis of ovarian carcinoma. Thirty-nine patients gave a history of having used the oral contraceptive pill, of whom 17 were finally randomized to ERT and 22 to non-ERT. Further data pertaining to duration and age of initiation were not available. A total of 32 recurrences occurred in the ERT group (54%) and 41 in the non-ERT group (62%). Recurrences, as expected, occurred most often in patients who had poorly differentiated tumors or advanced stage disease, or who had had suboptimal primary cytoreductive surgery (Table 2).

All patients with recurrences were given a second course of chemotherapy aiming at 6 cycles (the number achieved was 1–6). Most patients received cisplatin 100 mg/m^2 or carboplatin 350 mg/m^2. In the ERT group, 11 of 32 patients with recurrence and 13 of 41 in the non-ERT group had secondary surgery, respectively. Secondary intervention prolonged survival in the ERT group by a median of 7 months (range, 1–39 months) and in the non-ERT group by 5.5 months (range, 3–43 months). Despite recurrence, 10 of 32 patients in the ERT group continued ERT. The cumulative disease free interval and overall survival are shown in Figure 1. The median disease free interval for patients taking ERT was 34 months versus 27 months in patients not taking ERT, whereas the median overall survival for the ERT and non-ERT groups was 44 and 34 months, respectively. The differences in outcome for disease free interval ($P = 0.785$) and overall survival ($P = 0.354$) were not statistically significant (Table 3). Prognostic factors, such as stage ($P = 0.785$), differentiation ($P = 0.53$), and suboptimal cytoreductive surgery ($P = 0.369$), did not have an adverse impact when the disease free intervals of the two groups were compared, as they did not have an effect on overall survival (stage, $P = 0.354$; differentiation; $P = 0.418$; suboptimal cytoreductive surgery, $P = 0.588$). However, stage ($P < 0.005$), differentiation ($P < 0.005$), and suboptimal debulking surgery ($P < 0.001$) were significant prognostic factors within each group.

TABLE 2
Occurrence of Relapses According to Stage, Differentiation, and Debulking Surgery

	No. (%) of patients		
	ERT	Non-ERT	*P* value
Stage			
I	1 (14%)	2 (22%)	
II	2 (22%)	1 (25%)	
III	25 (66%)	33 (72%)	N.S.
IV	4 (80%)	5 (71%)	N.S.
Differentiation			
Well differentiated	7 (22%)	8 (19.5%)	N.S.
Moderately	9 (28%)	8 (19.5%)	N.S.
Poorly	16 (50%)	25 (61%)	N.S.
Surgery			
Optimal	19 (43%)	22 (48%)	N.S.
Suboptimal	13 (86%)	19 (95%)	N.S.

ERT: estrogen replacement therapy; N.S.: not significant.

DISCUSSION

The side effects that may occur as a result of premature menopause induced by surgery in patients with

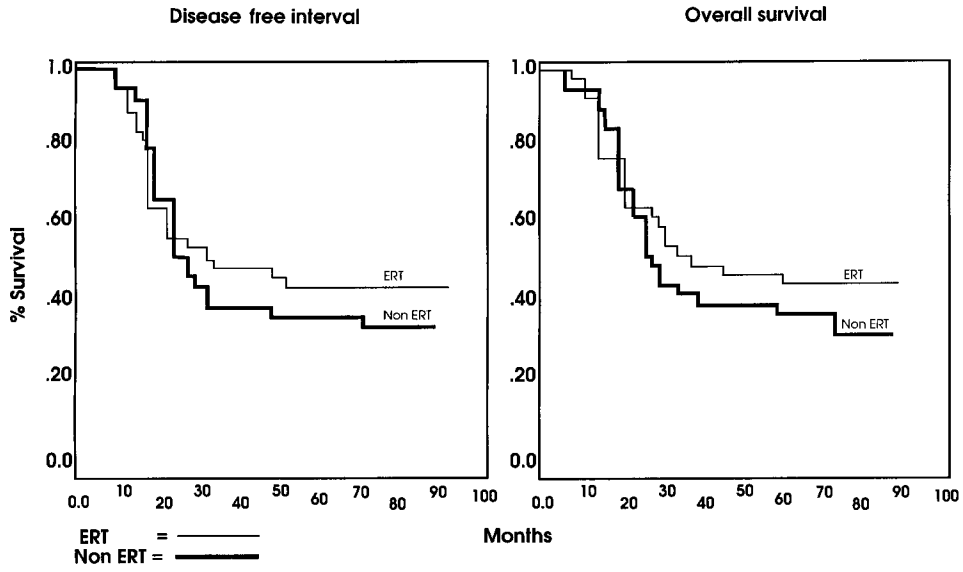

FIGURE 1. The percentage of survival, depicted as disease free interval and overall survival, is shown for patients who received estrogen replacement therapy and patients who did not receive estrogen supplementation.

TABLE 3
Median Disease Free Interval and Overall Survival (Months)

	Median in mos (range)		
	ERT	Non-ERT	*P* value
Disease free survival			
All stages	34 (10–64)	27 (9–49)	0.785
Stage III only	25 (11–40)	23 (9–32)	0.816
Overall survival			
All stages	44 (10–112)	34 (8–111)	0.354
Stage III only	32 (11–94)	29 (9–110)	0.395

ERT: estrogen replacement therapy.

ovarian carcinoma will be alleviated by estrogen supplementation in the vast majority of cases. Estrogen is being advocated not only for the short term treatment of menopausal symptoms, but also as long term prophylactic therapy against coronary artery disease, osteoporosis, and Alzheimer disease.[5–11]

However, the relation between ERT and ovarian carcinoma still remains controversial. The only retrospective study of women with ovarian carcinoma who received ERT postoperatively showed that ERT did not have a negative influence on disease free interval or overall survival in a group of 78 women treated for ovarian carcinoma. There was a correction in this study between the degree of differentiation and the stage of disease.[12] Yet, despite this, ERT is still not freely advocated or routinely administered to improve the quality of life of ovarian carcinoma survivors, particularly those who prove to be long term survivors.

Epidemiologic studies have also not made an obvious clarification of the association between past users or ever-users of ERT and occurrences of ovarian carcinoma. Of 15 published studies, 1 showed a significantly lower risk of ovarian carcinoma for ever-users of ERT,[13] 7 found risks close to unity,[14–20] and 5 found nonsignificantly elevated risks.[21–25] A collaborative analysis of U.S. case–control studies did not find any alteration in ovarian carcinoma risk for women who had ever used ERT.[26] The overall relative risk of epithelial ovarian carcinoma for ever-users of ERT determined from the data of 10 studies was 1.06 (95% CI, 0.96–1.17). This represented a weighted average of the individual study relative risks and showed no significant elevation in risk.[27] It is the more recently published prospective study of Rodriguez et al.[28] that again has questioned the role of ERT in the evolution of ovarian carcinoma. Those authors analyzed 434 deaths from all types of ovarian carcinoma in a large prospective mortality study of 240,073 peri- and postmenopausal women. Having ever used ERT was associated with a rate ratio for fatal ovarian carcinoma of 1.15 (95% CI, 0.94–1.42), whereas the mortality rate ratio increased with duration of use from 1.40 (95% CI, 0.92–2.11) at 6–10 years to 1.71 (95% CI, 1.06–2.77) at or beyond 11 years of usage; their data suggested that long term use of ERT may increase the risk of fatal ovarian carcinoma.

The primary aim of our study was to determine whether ERT had a detrimental influence on the disease free interval and overall survival of patients with ovarian carcinoma who were randomized to either postoperative ERT or no ERT and were followed up for a minimum of 48 months. Our major concern at the outset of the study was not only to counsel our patients to consider ERT but also to ensure long term

compliance. Of the 62 patients originally randomized to the ERT arm, 3 were lost to follow-up, 3 refused to commence ERT, and 6 stopped taking ERT during the study period. Rates of commencement and maintenance of ERT at 1 and 4 years revealed that 95% of patients commenced ERT and at 4 years 84.7% of the patients who had not developed a recurrence were still taking ERT. We felt that this compliance among the patients may have been attributed to the fact that the primary management of all patients was conducted by one physician who was then also responsible for their counseling. Particular emphasis was placed on ensuring that patients were fully aware of all potential risks and benefits of ERT, as well as the importance of immediate treatment of complications or side effects.

To give patients a degree of confidence and ensure the continuity of visits, one physician (F.G.) was responsible for the majority of follow-up consultations.

Advice and management strategies were also continuously offered to the non-ERT patients. These results are not confined to our study; recently, in a study that evaluated the compliance, following oophorectomy, of women who had a family history of ovarian carcinoma, a similar outcome was achieved.[29] However, in our study, significant attrition in compliance and usage was achieved following the development of recurrences, as the majority of these patients voiced their concern that ERT may have had a detrimental effect on their outcome and associated ERT with their recurrence. Nevertheless, despite these concerns, 10 of 32 patients still persisted with their ERT. Equally surprising was the fact that 5 patients randomized to the non-ERT group elected to commence ERT because of debilitating symptoms.

As stated previously, the primary aim of this study was essentially to conduct a comparative analysis of the median disease free interval and overall survival of the two groups of patients and determine whether estrogen supplementation had a negative influence. These proved to be 34 months versus 27 months and 44 months versus 34 months, respectively, for the ERT and non-ERT groups. These differences were not significant in either group.

In conclusion, even though this was a small study, it did reveal that not only is ERT compliance feasible for ovarian carcinoma survivors, but it is also not obviously detrimental to disease free interval and overall survival. Studies pertaining to quality of life for ovarian carcinoma survivors have not been published extensively.[30] Following the preliminary analysis of our study, we have for the last 2 years been routinely offering all our patients with ovarian carcinoma postoperative ERT. Until larger studies contradict our findings, we feel that this is the appropriate policy, the primary intention being to improve quality of life.

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