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Adjuvant Hormone Therapy May Improve Survival in Epithelial Ovarian Cancer: Results of the AHT Randomized Trial

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ABSTRACT

Purpose
To assess the effects of adjuvant hormone therapy (AHT) on survival and disease outcome in women with epithelial ovarian cancer.

Patients and Methods
Participants were premenopausal and postmenopausal women who had been diagnosed with epithelial ovarian cancer (any International Federation of Gynecology and Obstetrics stage) 9 or fewer months previously. Ineligible patients included those with deliberately preserved ovarian function, with a history of a hormone-dependent malignancy, or with any contraindications to hormone-replacement therapy. Patients were centrally randomly assigned in a 1:1 ratio to either AHT for 5 years after random assignment or no AHT (control). Main outcome measures were overall survival (OS), defined as time from random assignment to death (any cause), and relapse-free survival, defined as time from random assignment to relapse or death (any cause). Patients who continued, alive and relapse free, were censored at their last known follow-up.

Results
A total of 150 patients (n = 75, AHT; n = 75, control) were randomly assigned from 1990 to 1995 from 19 centers in the United Kingdom, Spain, and Hungary; all patients were included in intention-to-treat analyses. The median follow-up in alive patients is currently 19.1 years. Of the 75 patients with AHT, 53 (71%) have died compared with 68 (91%) of 75 patients in the control group. OS was significantly improved in patients who were receiving AHT (hazard ratio, 0.63; 95% CI, 0.44 to 0.90; $P = .011$). A similar effect was seen for relapse-free survival (hazard ratio, 0.67; 95% CI, 0.47 to 0.97; $P = .032$). Effects remained after adjustment for known prognostic factors.

Conclusion
These results show that women who have severe menopausal symptoms after ovarian cancer treatment can safely take hormone-replacement therapy, and this may, in fact, infer benefits in terms of OS in addition to known advantages in terms of quality of life.

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INTRODUCTION

Ovarian cancer is the seventh most common cancer in women worldwide; greater than 140,000 deaths were reported in 2008.[1] Many women diagnosed with ovarian cancer will be postmenopausal, whereas the surgical treatment of premenopausal patients will, by necessity, induce a premature menopause. This can cause vasomotor symptoms, such as hot flushes, and also carries the more serious risks of coronary heart disease and osteoporotic fractures.[2,3] By the early 1990s, it was widely established that these adverse effects could be reduced through the use of hormone-replacement therapy (HRT).[3-5] However, uncertainty existed over the administration of HRT to this patient group as a result of concerns over an increase in the chance of disease relapse, because some ovarian cancer cells have estrogen and progesterone receptors within the cytosol.[6] Despite several advances in the treatment of patients with ovarian cancer since then, this uncertainty about the use of HRT remains.

Previous case-control and cohort studies have suggested that women diagnosed with ovarian cancer are more likely to have previously used HRT, although this increased risk is small (relative risk [RR] of ovarian cancer in HRT users, 1.3 to 1.7 fold).[7-11] An additional study showed no increase in risk of ovarian cancer (RR, 1.0) but some evidence of an increase in the risk of endometrial cancer.[12,13]

Analysis of retrospective data on the administration of HRT in patients with a previous diagnosis of ovarian cancer, in fact, suggested an improvement in survival for those who received HRT, although a statistically significant benefit was not seen (RR of death in patients with HRT, 0.73; 95% CI, 0.44 to 1.20).[14] These analyses were adjusted for other prognostic factors and for HRT receipt at different times after diagnosis.

If, as this retrospective analysis suggested, HRT does have a beneficial effect on patient survival, this would be a major advance in treatment of these patients. Even if no relationship is seen between HRT and survival, patients who receive HRT are likely to have improved quality of life (QOL) through the relief of their menopausal symptoms; thus, a null effect on survival would still be clinically important. The AHT (Adjuvant Hormone Therapy) trial, therefore, was initiated in 1990 to assess the effect of hormone therapy on outcome in patients with a previous diagnosis of epithelial ovarian cancer in a randomized, controlled trial setting. Recruitment was challenging, and the trial did not reach its original recruitment target. Publication, therefore, has awaited mature clinical follow-up to maximize the clinical utility of the trial results. Despite the long period since the trial began, considerable uncertainty still remains about the use of HRT in patients with ovarian cancer, which makes the results of this trial as relevant as ever.

PATIENTS AND METHODS

Population

Eligible patients were women who had been diagnosed with epithelial ovarian cancer (any International Federation of Gynecology and Obstetrics [FIGO] stage) fewer than 9 months previously. Both premenopausal and postmenopausal women were eligible. Ineligible patients included those for whom ovarian function was deliberately preserved and women with a history of hormone-dependent malignancy or with any contraindications to HRT.

Study Design

The AHT trial was an international, nonblinded, parallel, phase III randomized, controlled trial to assess whether administration of adjuvant hormone therapy (AHT) to women with ovarian cancer affects overall survival (OS) or relapse-free survival (RFS).

Patients were centrally randomly assigned in a 1:1 ratio to receive either AHT or no AHT (control). Independent random assignment was performed via telephone (or fax for international sites) at the Clinical Trials and Statistics Unit at The Institute of Cancer Research. Computer-generated random permuted blocks were used; stratification was by treating center, menopausal status (pre *v* post), and FIGO stage (I and II *v* III and IV).

Treatment

Within the overall context of HRT, the choice of AHT for individual patients was pragmatic and was determined according to consultant preference, with guidelines to recommend that premenopausal women receive higher doses than perimenopausal/postmenopausal women (see Data Supplement for protocol). Patients were due to start treatment within 2 weeks of random assignment and to continue their treatment for a minimum of 5 years if tolerated. Treatment was nonblinded, and no placebo was given to control-group patients. Patients otherwise were treated for their ovarian cancer according to local policies.

Assessments

Patients were observed at 6 and 12 months and then annually thereafter for a maximum of 15 years. Information was collected on current status, adverse events (AEs), and hormone treatment patterns. After this routine follow-up had been completed, when possible, patients from the United Kingdom were traced by using the Health and Social Care Information Centre (HSCIC) tracing system, so death notifications were received long after hospital-based follow-up ceased. For patients who were outside of the United Kingdom and for those who could not be traced, no additional follow-up was received after the end of routine follow-up.

Statistical Considerations

End points. The primary end point of the study was OS, defined as time from random assignment to death (any cause). The main secondary end point was RFS, defined as time from random assignment to disease relapse or death (any cause). Patients continuing alive and disease free were censored at the last known follow-up. Other secondary end points included compliance to hormone treatment and recording of selected AEs (myocardial infarction, fracture, transient ischemic attack, cerebrovascular accident, and second cancer) collected annually through the follow-up period.

Sample size. Because of the uncertainty of the benefits of AHT, the trial aimed to recruit as many patients as possible in a short amount of time. Original sample size calculations were based on estimates obtained from a study of patients at The Royal Marsden who had ovarian cancer of all stages (1970 to 1989), which observed a 5-year OS rate of 37%.[14] With 80% power and a two-sided significance level of .05, 570 patients (322 events) would be required to detect a change in relative risk of 27% (absolute improvement in 5-year OS from 37% to 48%; hazard ratio [HR], 0.73).

Analysis

Analyses were based on a data snapshot taken on September 18, 2012. For the primary end point of OS and other survival-related end points, Kaplan-Meier curves were plotted and treatment groups were compared by using the log-rank test. HRs and associated 95% CIs were obtained from unstratified Cox proportional hazards models, and an HR less than 1 favored the AHT group. For patients in the United Kingdom who were traced by the HSCIC and were still thought to be alive, a date of last follow-up of June 18, 2012, was used to allow for a possible 3-month lag in death notifications. For patients not in the United Kingdom, survival end points were calculated by using date last seen/died as a result of data on the most recent standard follow-up form. Patients not known to have had a disease relapse and without ovarian cancer as a stated cause on their death certificate were classed as other-cause deaths. All other deaths were classified as ovarian cancer deaths. Patients with a first event date equal to the random assignment date were said to have had their event 1 day after random assignment.

Multivariable analysis was performed to assess any differences in survival between treatment groups after adjustment for known prognostic factors that were statistically significant in univariable analyses, including histologic type (serous, mucinous, endometrial, clear cell, undifferentiated, and other/unknown), previous chemotherapy (yes/no), disease stage (I, II, III, and IV/recurred), tumor differentiation (poor, intermediate, well, and unknown), residual tumor bulk (none, $\leq$ 2 cm, $>$ 2 cm, and unknown), and age at random assignment (considered as a continuous variable), each of which was also statistically significant in univariable analyses. The proportional hazards assumption of the Cox model was assessed for OS and RFS by using Schoenfeld residuals. In the presence of nonproportional hazards, the difference in survival estimates between treatment groups was plotted against time, and estimates of the difference in restricted mean survival at 20 years were calculated in each treatment group. The restricted mean is an estimate of the area under the survival curve up to a certain time point.[15]

Centers were asked at each follow-up visit whether the patient was continuing AHT, and if applicable, the date AHT was stopped. The time spent on hormone treatment by patients allocated to the AHT group was estimated by calculating for each patient the time from random assignment to the date they were said to have stopped hormone treatment. In patients for whom no stopping date was given, a halfway point between the last follow-up appointment they were still said to be receiving treatment and the first where they were said to no longer be receiving treatment was used.

The proportions of patients who experienced certain AEs at any point during their follow-up were compared by using Fisher exact tests. No specific

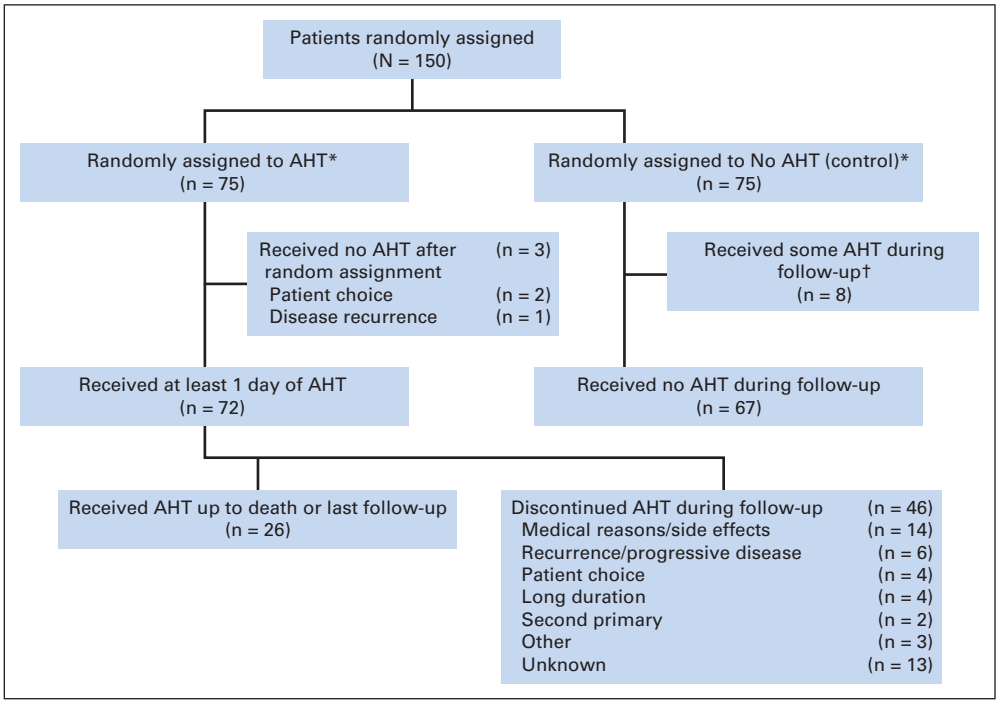

Fig 1. Patient flow through the AHT (Adjuvant Hormone Therapy) trial. (*) All subsequent analysis was by intent to treat, so all 150 patients were included. (†) Reasons for control patients taking adjuvant hormone therapy (AHT) are not known. In the AHT group, median time receiving AHT was 1.14 years (interquartile range, 0.46 to 5.08 years).

grades were given for AEs in this trial, and there was no provision for the collection of AEs other than those prespecified in the protocol.

All analyses were performed on an intention-to-treat basis, and a two-sided significance level of 5% and corresponding 95% CIs were used throughout. All analyses were performed with Stata13 (StataCorp, College Station, TX).

Trial Governance and Ethics

The Clinical Trials and Statistics Unit at The Institute of Cancer Research had overall responsibility for trial coordination, data collation, central statistical monitoring, and all final analyses. The trial management group was responsible for the day-to-day running of the trial. The trial was sponsored by The Royal Marsden NHS Foundation Trust and was conducted in accordance with the principles of good clinical practice. The recruitment and treatment period of the trial predated the widespread use of independent data monitoring committees and the current clinical trials legislation. This study was registered retrospectively in 2002 as an International Standard Randomized Controlled Trial (ISRCTN71318684).

The AHT trial was approved by the local ethics committees of all participating centers. All patients provided written informed consent.

RESULTS

Between February 1990 and November 1995, 150 patients (Fig 1) were randomly assigned. A total of 124 (83%) of patients were recruited from 17 United Kingdom centers, with the remaining 26 recruited from single centers in Spain (n = 14, 9%) and Hungary (n = 12, 8%; Appendix Table A1, online only).

Median follow-up in patients not confirmed to have died at time of analysis was 19.1 years (interquartile range [IQR], 18.2 to 20.3 years): 19.0 years (IQR, 18.2 to 20.2 years) in the AHT group compared with 19.1 years (IQR, 18.4 to 20.2 years) in the control group.

Treatment groups were comparable with respect to baseline characteristics (Table 1); 77% of patients were postmenopausal, and 63% were FIGO disease stage III or IV. Median age at random assignment was 58.7 years (range, 29.3 to 89.6 years).

Compliance

Of the 75 patients allocated to receive AHT, 72 (96%) received at least 1 day of treatment after random assignment; 3 (4%) of patients received no AHT after random assignment. Breakdown of AHT type was as follows: conjugated estrogens (Premarin; Pfizer, New York, NY; n = 38), conjugated estrogens and norgestrel (Prempak; Pfizer; n = 19), estradiol patch (n = 14), and estradiol implant (n = 1). Patients discontinued AHT for various reasons (Fig 1), with some patients seeming to have continued receiving AHT throughout trial follow-up. The median estimated time receiving AHT for patients allocated to the AHT group was 1.14 years (IQR, 0.46 to 5.08 years). Of the 75 patients allocated to the control group, 8 (11%) received some hormone therapy during their follow-up.

OS

At the time of data extraction, 121 (81%) of patients had died: 53 (71%) in the AHT group and 68 (91%) in the control group (Table 2). Of these 121 deaths, 106 (71%) were classified as a result of ovarian cancer: 50 (67%) in the AHT group and 56 (75%) in the control group. Of the 29 patients still thought to be alive as of September 18, 2012, 22 are still recorded as alive by the HSCIC tracing service. Of the remaining seven patients, one from Hungary was confirmed still alive in 2010, one patient from the United Kingdom moved to Cyprus and can no longer be traced, and five were from Spain and cannot be traced.

Long-term OS was superior in the AHT group (HR, 0.63; 95% CI, 0.44 to 0.90; $P = .011$; Fig 2). After adjustment for stratification factors of treating center, menopausal status (pre *v* post), and FIGO stage (I and II *v* III and IV), the HR was 0.51 (95% CI, 0.34 to 0.76).

Table 1. Baseline Characteristics

Characteristic	AHT* (n = 75)		Control (n = 75)		Total (N = 150)	
	No.	%	No.	%	No.	%
Country						
United Kingdom	64	85.3	60	80.0	124	82.7
Spain	6	8.0	8	10.7	14	9.3
Hungary	5	6.7	7	9.3	12	8.0
Menopausal status						
Premenopausal	16	21.3	18	24.0	34	22.7
Postmenopausal	59	78.7	57	76.0	116	77.3
Epithelial histology						
Yes	75	100.0	74	98.7	149	99.3
No	0	—	1	1.3	1	0.7
Histologic type						
Serous	29	38.7	30	40.0	59	39.3
Mucinous	8	10.7	14	18.7	22	14.7
Endometrial	11	14.7	4	5.3	15	10.0
Clear cell	9	12.0	7	9.3	16	10.7
Undifferentiated	7	9.3	5	6.7	12	8.0
Other	11	14.7	14	18.7	25	16.7
Unknown	0	—	1	1.3	1	0.7
Chemotherapy before random assignment						
Yes	65	86.7	61	81.3	126	84.0
No	10	13.3	14	18.7	24	16.0
Chemotherapy type specified (if received)†						
Single-agent platinum	39	52.0	32	42.7	71	47.3
Platinum-based doublet or triplet regimen	21	28.0	23	30.7	44	29.3
Other‡	5	6.7	6	8.0	11	7.3
FIGO disease stage						
I	17	22.7	21	28.0	38	25.3
II	8	10.7	9	12.0	17	11.3
III	46	61.3	36	48.0	82	54.7
IV	4	5.3	8	10.7	12	8.0
Recurred	0	—	1	1.3	1	0.7
Tumor differentiation						
Poor	29	38.7	28	37.3	57	38.0
Intermediate (BRO 2/3)	26	34.7	27	36.0	53	35.3
Well	15	20.0	13	17.3	28	18.7
Unknown	5	6.7	7	9.3	12	8.0
Residual bulk of disease						
None	29	38.7	33	44.0	62	41.3
≤ 2 cm	15	20.0	20	26.7	35	23.3
> 2 cm	28	37.3	20	26.7	48	32.0
Unknown	3	4.0	2	2.7	5	3.3
Family history of ovarian or breast cancer						
Yes	6	8.0	10	13.3	16	10.7
No	65	86.7	59	78.7	124	82.7
Unknown	4	5.3	6	8.0	10	6.7
Age at random assignment, years						
< 50	12	16.0	19	25.3	31	20.7
50-59	31	41.3	19	25.3	50	33.3
60-69	22	29.3	27	36.0	49	32.7
≥ 70	10	13.3	10	13.3	20	13.3
Time from diagnosis to random assignment, months§						
Median	4.2		4		4.1	
IQR	1.6-6.9		1.5-5.4		1.6-6.3	

Abbreviations: AHT, adjuvant hormone therapy; BRO, Broder classification; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range.
*Breakdown of AHT type is as follows: Premarin, n = 38; Prempak, n = 19; estradiol patch, n = 14; estradiol implant, n = 1; and not given, n = 3.
†Percentages reported are calculated from the whole cohort rather than just those who received chemotherapy.
‡Other chemotherapies given were treosulfan (AHT group, n = 4; control group, n = 6) and mitoxantrone (AHT group, n = 1).
§Date of diagnosis not known for three patients in the control group.

Table 2. Causes of Death in Patients

Cause of Death	AHT		Control		Total	
	No.	%	No.	%	No.	%
Ovarian cancer*	50	66.7	56	74.7	106	70.7
Non–ovarian cancer causes						
Other cancer	1	1.3	4	5.3	5	3.3
Respiratory	2	2.7	2	2.7	4	2.7
Cardiovascular	0	0.0	2	2.7	2	1.3
Cerebrovascular	0	0.0	2	2.7	2	1.3
Neurologic	0	0.0	1	1.3	1	0.7
Unknown	0	0.0	1	1.3	1	0.7
Total non–ovarian cancer causes	3	4.0	12	16.0	15	10.0
Total	53	70.7	68	90.7	121	80.7

Abbreviation: AHT, adjuvant hormone therapy.
*Includes four patients reported as having other causes of death but who had previous disease recurrence.

After adjustment for additional known prognostic factors, the HR for OS was 0.45 (95% CI, 0.30 to 0.69; $P < .001$).

Analysis of Schoenfeld residuals suggested some evidence that the proportional hazards assumption may be violated for OS ($P = .048$). The Data Supplement shows that the difference in the Kaplan-Meier estimates of OS between AHT and control increases over time. The restricted mean OS at 20 years was 8.5 years in the AHT group and 5.7 years in the control group, with an absolute difference of 2.8 years (95% CI, 0.3 to 5.2 years).

RFS

A total of 122 (81%) patients experienced an RFS event (disease relapse or death as a result of any cause): 54 (72%) were in the AHT group, and 68 (91%) were in the control group (Table 3). RFS again seemed better for the AHT group than the control group (HR, 0.67; 95% CI, 0.47 to 0.97; $P = .032$; Fig 3) when analysis that was adjusted for known prognostic factors as before increased the magnitude of the apparent RFS benefit (HR, 0.53; 95% CI, 0.34 to 0.81; $P = .004$). For OS, the difference in the Kaplan-Meier estimates of RFS between AHT and control is not constant over time (Data Supplement). The restricted mean RFS at 20 years was 7.5 years in the AHT group and was 4.7 years in the control group, and the absolute difference was 2.9 years (95% CI, 0.4 to 5.3 years).

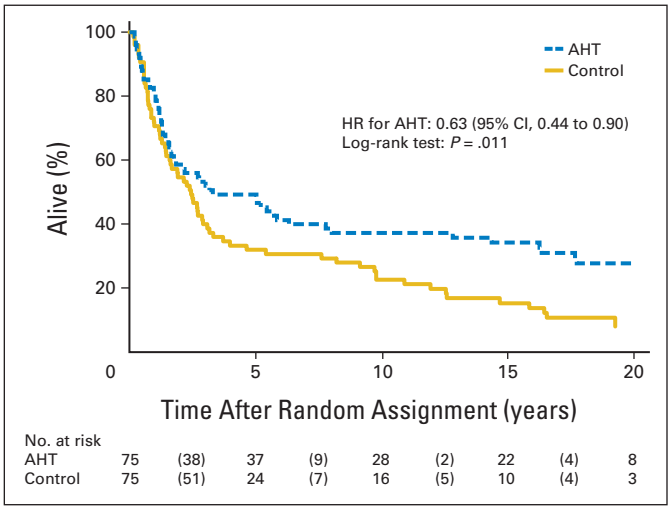

Fig 2. Kaplan-Meier estimate of overall survival, by treatment group. Numbers in parentheses indicate overall survival events reported in period. One additional death was reported in a control patient after 20 years. AHT, adjuvant hormone therapy; HR, hazard ratio.

AEs

Within the selected events recorded, AE rates were low. No statistically significant differences were seen between treatment groups (Table 4).

DISCUSSION

Despite the fact that this trial terminated accrual early because of challenges in recruitment, it remains, to our knowledge, the largest random assignment trial to investigate whether AHT has an adverse (or beneficial) effect on survival after ovarian cancer treatment. With mature follow-up, we observed statistically significant improvements in both OS and RFS for patients randomly assigned to receive AHT compared with the control group (HR, 0.63 and 0.67, respectively).

The advantage of the AHT trial is that it was pragmatic and randomized; therefore, the trial was unbiased in informing practice for all types of epithelial ovarian cancer. The median follow-up of greater than 19 years allows observance of the effects of AHT on long-term outcomes, such as OS. Of 72 patients who started AHT, 46 discontinued prematurely (Fig 1), and the median estimated time of AHT treatment was 1.14 years, yet the efficacy benefits were substantial. Given the small size of the trial and the large CIs around HRs observed, a larger trial would be needed to give more accurate estimates of the true benefit of HRT. Given this uncertainty, clinical guidance on the basis of these results could include the administration of HRT for at least 1 year after surgical treatment for ovarian cancer. The survival of those in the control group is similar to that in the literature and of the patient series used to calculate the trial sample size.[14,16,17]

The study was initiated greater than 20 years ago, and data collection was pragmatic and based on known prognostic and therapeutic options at the time. As such, there are several potentially relevant factors that cannot be assessed in these analyses, such as the use of post-relapse treatment. However, there is no reason to suggest that

Table 3. Patient Status at Time of Data Snapshot

Status	AHT		Control		Total	
	No.	%	No.	%	No.	%
Alive, disease free	21	28.0	7	9.3	28	18.7
Alive, recurrence	1	1.3	0	0.0	1	0.7
OC death, recurrence	31	41.3	34	45.3	65	43.3
OC death	16	21.3	19	25.3	35	23.3
OC death, nonovary second primary	1	1.3	0	0.0	1	0.7
OC death, recurrence, nonovary second primary	1	1.3	0	0.0	1	0.7
Other cause of death	2	2.7	9	12.0	11	7.3
Other cause of death, nonovary second primary	1	1.3	3	4.0	4	2.7
Other cause of death, recurrence*	0	0.0	3	4.0	3	2.0
Other cause of death, recurrence, nonovary second primary*	1	1.3	0	0.0	1	0.7
Total	75	100	75	100	150	100

Abbreviations: AHT, adjuvant hormone therapy; OC, ovarian cancer.
*These patients are assumed to have died as a result of OC in all subsequent analyses.

treatment after relapse would differ between randomly assigned treatment groups, because hormone treatment is not a contraindication to certain treatment types.

The only previous randomly assigned evidence in this area was published in 1999 by Guidozzi and Daponte.[18] They reported no statistically significant difference in either OS or disease-free survival between patients randomly assigned to receive or not receive oral continuous conjugated equine estrogen (ERT). The authors reported a median OS of 44 months (95% CI, 10 to 112 months) and 34 months (95% CI, 8 to 111 months) in patients with ERT and without ERT, respectively, from which an estimated HR of 0.77 (95% CI, 0.49 to 1.23) can be calculated.[19] By combining this with the AHT trial HR for OS presented here, the fixed-effects meta-analysis methods give an overall HR of 0.68 (95% CI, 0.51 to 0.90) in favor of HRT. Several single-group and comparative observational studies have also been conducted,[20-22] and estimates of the effect of HRT have ranged widely, albeit in heterogeneous patient populations. No previous study of HRT after ovarian cancer diagnosis has observed a statistically significant benefit or harm from HRT. One retrospective study from Hein et al[23] indicated that patients who received HRT before diagnosis of ovarian cancer had improved prognoses compared with those who did not if the ovarian tumor had been optimally debulked.

The use of hormone therapy in patients with ovarian cancer remains an important clinical question, because most women are treated for ovarian cancer with surgery before other modalities, particularly chemotherapy, and the surgery involves bilateral oophorectomy, which suddenly renders a previously premenopausal woman postmenopausal. For women who experience surgical menopause, it is estimated that approximately 40% believe this has a negative effect on their QOL, and approximately 96% actually take HRT after menopause.[24] However, a recent Greek survey indicated that only approximately 50% of clinicians would administer HRT after ovarian cancer[25] because of current uncertainty about whether this could compromise cancer survival.

Some women do not feel comfortable about taking HRT. This is a subject of controversy in the medical literature, particularly because there is evidence that HRT increases the risk of breast cancer in the general population, a cancer that can be estrogen receptor positive, and some ovarian cancers have the same receptors on their cell surface.[26] One study in patients with breast cancer has reported an

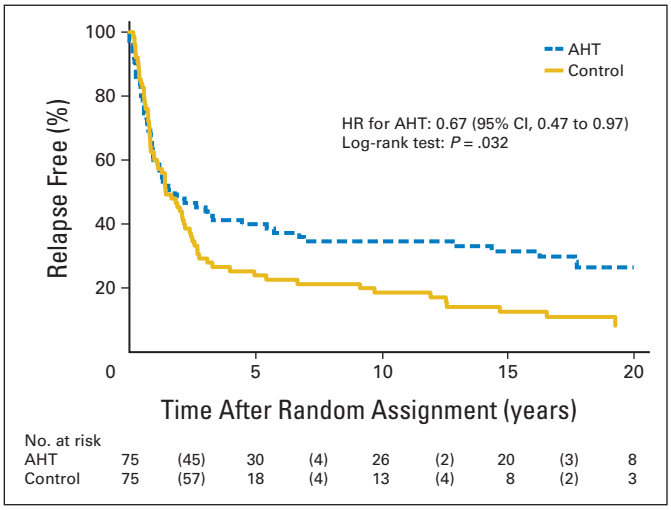

Fig 3. Kaplan-Meier estimate of relapse-free survival, by treatment group. Numbers in parentheses indicate relapse-free survival events reported in period. One additional relapse-free survival event reported in a control patient after 20 years. AHT, adjuvant hormone therapy; HR, hazard ratio.

Table 4. AEs During Follow-Up

AE	AHT (n = 75)		Control (n = 75)		Total (N = 150)		
	No.	%	No.	%	No.	%	*P* (exact)
Transient ischemic attack	2	2.7	0	—	2	1.3	.50
Cerebrovascular accident	2	2.7	3	4.0	5	3.3	.50
Myocardial infarction	0	—	2	2.7	2	1.3	.50
Fracture	2	2.7	4	5.3	6	4.0	.68
Second primary*†	4	5.3	3	4.0	7	4.7	.50
At least one of the above AEs	9	12.0	12	16.0	21	14.0	.64

Abbreviations: AE, adverse event; AHT, adjuvant hormone therapy.
*Sites of second primaries were as follows: breast (n = 2), colon (n = 1), and jejunum (n = 1) in the AHT group, and breast (n = 1), acute myeloid leukemia (n = 1), and pulmonary and mediastinum (n = 1) in the control group.
†Of the three patients with breast second primary cancer, one (in the control group) had a previous family history of breast/ovarian cancer.

increased risk of relapse of breast cancer after HRT use,[27] but another study with longer follow-up did not support this finding.[28]

It is interesting that the effect of AHT on OS, seen as early as 4 to 5 years after random assignment, seems to persist for 20 years. A similar effect of post-treatment duration has been observed in breast cancer prevention trials with hormonal treatments, in which the preventive effect persisted 7 years after termination of the hormone treatment.[29]

Most deaths are caused by ovarian cancer; numbers of deaths in the absence of relapse are small, but there are no cardiovascular or neurologic deaths in the AHT group. This trial has shown that women who have severe menopausal symptoms after ovarian cancer treatment can safely take HRT without compromising their survival by doing so. Indeed, the survival advantage reported in a retrospective study has been confirmed in the randomized AHT trial, so administration of HRT for QOL and survival benefit should be considered in patients with ovarian cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Adjuvant Hormone Therapy May Improve Survival in Epithelial Ovarian Cancer: Results of the AHT Randomized Trial

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This article is dedicated to the late Eve Wiltshaw, principal investigator of the AHT trial.

Appendix

Table A1. AHT Trial Recruitment by Center

Institution	Recruiting Clinician(s)	No. of Patients Recruited
Royal Marsden Hospital London, United Kingdom	P. Blake, E. Wiltshaw, and M. Gore	33
St George's Hospital, London, United Kingdom	J. Mansi	15
Hospital Universitari de Girona, Girona, Spain	R. Fuentes and E. Canals	14
St Thomas's Hospital, London, United Kingdom	K.S. Raju	13
Epsom General Hospital, Epsom, United Kingdom	J. Glees	12
Markusovszky Teaching Hospital, Szombathely, Hungary	M. Wenczl	12
Royal South Hants Hospital, Southampton, United Kingdom	C. Williams	8
Churchill Hospital, Oxford, United Kingdom	T. Ganesan and C.J. Alcock	8
Birmingham City Hospital, Birmingham, United Kingdom	D. Spooner	7
Aberdeen Royal Infirmary, Aberdeen, United Kingdom	H. Kitchener	6
Barts and Homerton, London, United Kingdom	M. Slevin	5
Royal Free Hospital, London, United Kingdom	A. Jones and E. Boesen	4
Addenbrookes Hospital, Cambridge, United Kingdom	R.J. Osborne	3
Royal Marsden Hospital, Sutton, United Kingdom	P. Blake and J. Glees	2
Derbyshire Royal Infirmary, Derby, United Kingdom	D. Guthrie	2
Guy's Hospital, London, United Kingdom	P. Harper	2
Southend Hospital, Southend, United Kingdom	C.W. Trask	2
Cheltenham General Hospital, Cheltenham, United Kingdom	R. Kerr-Wilson	1
Royal Sussex County Hospital, Brighton, United Kingdom	D.S. Murrell	1

Abbreviation: AHT, Adjuvant Hormone Therapy.