Effects of Estrogen Plus Progestin on Gynecologic Cancers and Associated Diagnostic Procedures

The Women's Health Initiative Randomized Trial

Garnet L. Anderson, PhD
Howard L. Judd, MD
Andrew M. Kaunitz, MD
David H. Barad, MD, MS
Shirley A. A. Beresford, PhD
Mary Pettinger, MS
James Liu, MD
S. Gene McNeeley, MD
Ana Maria Lopez, MD
for the Women's Health Initiative Investigators

Context The effects of continuous combined hormone therapy on gynecologic cancers have not been investigated previously in a randomized trial setting.

Objective To determine the possible associations of estrogen plus progestin on gynecologic cancers and related diagnostic procedures.

Design, Setting, and Participants Randomized, double-blind, placebo-controlled trial of 16608 postmenopausal women, who had not had a hysterectomy at baseline and who had been recruited from 40 US clinical centers between September 1993 and October 1998 (average follow-up, 5.6 years).

Intervention One tablet per day containing 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate (n=8506) or placebo (n=8102).

Main Outcome Measure Incident invasive cancer of the ovary and endometrium.

Results In 5.6 years of follow-up, there were 32 cases of invasive ovarian cancer, 58 cases of endometrial cancer, 1 case of nonendometrial uterine cancer, 13 cases of cervical cancer, and 7 cases of other gynecologic cancers. The hazard ratio (HR) for invasive ovarian cancer in women assigned to estrogen plus progestin compared with placebo was 1.58 (95% confidence interval [CI], 0.77-3.24). The HR for endometrial cancer was 0.81 (95% CI, 0.48-1.36). No appreciable differences were found in the distributions of tumor histology, stage, or grade for either cancer site. The incidence of other gynecologic cancers was low and did not differ by randomization assignment. More women taking estrogen plus progestin required endometrial biopsies (33% vs 6%; $P<.001$).

Conclusions This randomized trial suggests that continuous combined estrogen plus progestin therapy may increase the risk of ovarian cancer while producing endometrial cancer rates similar to placebo. The increased burden of endometrial biopsies required to assess vaginal bleeding further limits the acceptability of this regimen. These data provide additional support for caution in the use of continuous combined hormones.

JAMA. 2003;290:1739-1748 www.jama.com

For years, there has been concern about possible associations of gynecologic malignancies with postmenopausal hormone therapy. The development of endometrial hyperplasia and endometrial cancer with unopposed estrogen is well recognized. To reduce or avoid this complication, progestin has been added,[1-3] although results from randomized trials are extremely limited. These concerns have created a need for reasonable monitoring guidelines to follow-up women who experience vaginal bleeding while taking estrogen plus progestin.

The Women's Health Initiative (WHI) trial of estrogen plus progestin provides the first opportunity to examine possible associations of gynecologic malignancies with continuous combined postmenopausal hormone therapy in a large, randomized, double-blind, placebo-controlled setting. The trial was stopped early at the recommendation of the independent data and safety monitoring board on the basis of an increased risk of breast cancer supported by a summary measure of effects indicating risks exceeded

See also p 1729.

Author Affiliations: Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Wash (Drs Anderson and Beresford and Ms Pettinger); Department of Epidemiology, University of Washington, Seattle (Dr Beresford); Department of Obstetrics and Gynecology, University of California, Los Angeles (Dr Judd); Department of Obstetrics and Gynecology, University of Florida Health Science Center, Jacksonville (Dr Kaunitz); Department of Obstetrics and Gynecology and Women's Health, Albert Einstein College of Medicine, Bronx, NY (Dr Barad); Department of Reproductive Biology, Case Western Reserve University, Cleveland, Ohio (Dr Liu); Department of Obstetrics and Gynecology, Wayne State University, Detroit, Mich (Dr McNeeley); and Department of Internal Medicine, University of Arizona Cancer Center, Tucson (Dr Lopez).
WHI Investigators, Centers, and Financial Disclosures are listed at the end of this article.
Corresponding Author and Reprints: Garnet L. Anderson, PhD, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, MP-1002, Seattle, WA 98109 (e-mail: garnet@whi.org).

©2003 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 11/28/2015

benefits over an average of 5.2 years of follow-up. The initial report provided interim, locally adjudicated outcomes for endometrial cancer reported through April 30, 2002. This article summarizes centrally coded gynecologic cancer outcomes and related diagnostic procedures occurring prior to the announcement of the trial closure and participant unblinding (July 8, 2002).

METHODS

Study Population, Randomization, and Intervention

Women were recruited at 40 clinical centers in the United States between September 1993 and October 1998, largely through direct mail. Eligibility required women to be between age 50 and 79 years, to be postmenopausal, and to provide written informed consent. Women were excluded if they had preexisting conditions that contraindicated use of hormones, had health conditions that suggested a predicted survival of less than 3 years, or were considered likely to be poor adherers to the study protocol. Only women who had not had a hysterectomy were considered for this trial. Eligible women were randomized in equal proportions using a stratified permuted block algorithm to either placebo or to 0.625 mg/d of conjugated equine estrogens plus 2.5 mg/d of medroxyprogesterone acetate, which was administered in a single tablet (Prempro, Wyeth, St Davids, Pa). Women who had a prior hysterectomy were randomized to a parallel trial of estrogen alone and are not included in these results. Study design details have been published.[4,5]

Data Collection

All WHI participants provided demographic, medical, reproductive, and family history information using self-administered questionnaires at baseline. Prior postmenopausal hormone use was ascertained through a structured interview asking women to describe the strength, schedule, and duration of each hormone preparation.

Endometrial Evaluation. For safety, endometrial biopsies were performed on every woman interested in the estrogen plus progestin trial prior to randomization. A 5% cohort of women was randomly selected at enrollment to undergo routine biopsies at follow-up years 3, 6, and 9. This cohort was intended to provide a valid comparison of the rates of endometrial pathological findings.

The WHI procedures called for endometrial biopsies to be performed by WHI trained and certified staff, who were licensed physicians, nurse practitioners, or physician assistants, using plastic endometrial suction curettes.[6,7] Readings were obtained from local pathologists blinded to randomization assignment.

During follow-up, women with persistent or heavy bleeding were evaluated by the clinic gynecologist. If a nonroutine biopsy was indicated, study guidelines permitted the clinic gynecologist to then be unblinded to assist in further safety evaluation. Women selected for routine biopsies who had a biopsy in the last 12 months to evaluate bleeding problems were not required to repeat the procedure. When biopsies could not be accomplished, vaginal ultrasounds of the endometrium were performed.

At baseline, biopsy evidence of endometrial cancer, complex or adenomatous hyperplasia, or atypia disqualified women from participating, whereas findings of simple hyperplasia resulted in temporary exclusion pending resolution. During study follow-up, evidence of endometrial cancer, complex or adenomatous hyperplasia, or atypia required permanent discontinuation of study medicines. Simple hyperplasia identified during follow-up led to unblinding of the consulting gynecologist. Those participants assigned to placebo had study medications discontinued and were referred to their health care clinicians for further management. Those assigned to active therapy continued study medications supplemented with 20 mg/d of medroxyprogesterone acetate. In such women, the biopsy was repeated in 3 to 6 months.

An endometrial wall thickness of greater than 0.5 cm on vaginal ultrasound was considered evidence of an endometrial pathological finding[8] and resulted in exclusion (at baseline) or discontinuation of study pills unless further evaluation ruled out malignancy.

Cervical Cytology. In all participants, Papanicolaou tests were performed at 3-year intervals in conjunction with routine pelvic examinations. Absent an a priori hypothesis of association between estrogen plus progestin and cervical cancer, these tests were performed by WHI staff as a courtesy, in conjunction with a required pelvic examination. Pathological analysis was obtained locally. During follow-up, the protocol was modified to accept Papanicolaou test results from a participant's health care clinician.

Abnormal test results were referred to the participant's health care clinician for further diagnostic evaluation and treatment, except when a change in use of study medicines was required.

Outcomes

Outcome ascertainment procedures have been described.[5] Briefly, semiannual self-reports of new diagnoses were recorded and all associated medical records were obtained from local health care clinicians and classified by blinded physician adjudicators at each clinical center. The documents from all gynecologic cancer cases were forwarded to the WHI clinical coordinating center for centralized review by cancer coding specialists who were also blinded to randomization assignment and reported symptoms. Histological codes were based on the *International Classification of Diseases for Oncology, 2nd Edition*.[9] Histological analysis was available from pathology reports for all ovarian and endometrial cancers. Stage and grade were coded using Surveillance, Epidemiology, and End Results guidelines.[10] In this system, local-stage ovarian cancer refers to a tumor confined to the ovary with no tumor on the ovarian surface. A regional stage ovarian cancer represents a tumor that is present on the ovarian surface, or has evidence of spread to ascites, peritoneal washings, or other locations within the pelvis. Tumors that spread beyond the pelvis are considered distant stage. For endometrial cancers, local stage refers to cancers

 ©2003 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 11/28/2015

confined to the endometrium or myometrium/serosa. Regional-stage tumors have spread only to the pelvis, vagina, and/or the wall of the rectum or bladder. Information could not be obtained for ovarian cancer stage in 1 woman and ovarian cancer grade in 9 women. Because the number of primary peritoneal and fallopian tube cancers was small, these are reported together as other gynecologic cancers.

Statistical Analyses

Tests for differences between groups in the distribution of pathological features of diseases, and rates and results of endometrial biopsies and Papanicolaou tests are based on Fisher exact tests. When a diagnostic procedure was performed multiple times for a woman, her most severe result is reported.

Cancer incidence rate comparisons are presented as hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox proportional hazards models, stratified by age and randomization to the WHI dietary trial. Kaplan-Meier estimates of cumulative hazards are shown as 1 minus the disease-specific failure time estimates. For the primary results, adjusted 95% CIs are corrected for the 7 outcomes that contributed to the global index, which is consistent with our initial report.[5] This adjustment may not completely account for the variability in these estimates, given the multiple outcomes that will be examined in this trial. No adjustments were made for multiple tests over time because these outcomes make only a minor contribution to early stopping considerations under WHI monitoring guidelines.[11]

The primary analyses are based on the intent-to-treat principle. In the original design, women who had not had a hysterectomy were randomized to either unopposed estrogen, estrogen plus progestin, or placebo. After information from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial[12] indicated that it was not feasible to include an unopposed estrogen group in a long-term prevention study in women who had not had a hysterectomy, the estrogen group was closed and the 331 women

Table 1. Baseline Risk Factors for Gynecologic Cancers by Randomization Assignment

	No. (%) of Women	
	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)
Age at screening, y		
50-59	2839 (33.4)	2683 (33.1)
60-69	3853 (45.3)	3657 (45.1)
70-79	1814 (21.3)	1762 (21.8)
Ethnicity		
White	7140 (83.9)	6805 (84.0)
Black	549 (6.5)	575 (7.1)
Hispanic	472 (5.5)	416 (5.1)
American Indian	26 (0.3)	30 (0.4)
Asian/Pacific Islander	194 (2.3)	169 (2.1)
Unknown	125 (1.5)	107 (1.3)
Body mass index, kg/m^2		
<25	2579 (30.3)	2479 (30.6)
25-29	2992 (35.2)	2834 (35.0)
≥30	2899 (34.1)	2737 (33.8)
Unknown	36 (0.4)	52 (0.6)
Smoking		
Never	4178 (49.1)	3999 (49.3)
Past	3362 (39.5)	3157 (39.0)
Current	880 (10.3)	838 (10.3)
Unknown	86 (1.0)	108 (1.3)
Hypertension*		
Never	5332 (62.7)	5277 (65.1)
Not treated	635 (7.5)	631 (7.8)
Treated	1640 (19.3)	1631 (20.1)
Unknown	899 (10.6)	563 (6.9)
History of ovarian cancer		
No	8428 (99.1)	8034 (99.2)
Yes	6 (0.1)	2 (<0.1)
Unknown	72 (0.8)	66 (0.8)
Female relatives with breast cancer		
None	6770 (79.6)	6486 (80.1)
1	927 (10.9)	816 (10.1)
2	75 (0.9)	69 (0.9)
≥3	7 (0.1)	10 (0.1)
Unknown	727 (8.5)	721 (8.9)
Female relatives with ovarian cancer		
None	7704 (90.6)	7332 (90.5)
≥1	186 (2.2)	172 (2.1)
Unknown	616 (7.2)	598 (7.4)
First-degree relative with breast/ovarian cancer		
None	6937 (81.6)	6679 (82.4)
1	1054 (12.4)	949 (11.7)
2	101 (1.2)	83 (1.0)
≥3	11 (0.1)	15 (0.2)
Unknown	403 (4.7)	376 (4.6)
Relatives with colorectal cancer		
None	6631 (78.0)	6183 (76.3)
1	832 (9.8)	891 (11.0)
2	88 (1.0)	105 (1.3)
≥3	18 (0.2)	23 (0.3)
Unknown	937 (11.0)	900 (11.1)

(continued)

©2003 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 11/28/2015

Table 1. Baseline Risk Factors for Gynecologic Cancers by Randomization Assignment (cont)

	No. (%) of Women	
	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)
Age at menopause, y		
<40	195 (2.3)	189 (2.3)
40-44	677 (8.0)	632 (7.8)
45-49	1943 (22.8)	1996 (24.6)
50-54	3629 (42.7)	3506 (43.3)
≥55	1235 (14.5)	1186 (14.6)
Unknown	827 (9.7)	593 (7.3)
Age at menarche, y		
≤11	1725 (20.3)	1670 (20.6)
12	2141 (25.2)	2095 (25.9)
13	2437 (28.7)	2239 (27.6)
≥14	2182 (25.7)	2061 (25.4)
Unknown	21 (0.2)	37 (0.5)
Parity		
Never pregnant	856 (10.1)	832 (10.3)
1	690 (8.1)	661 (8.2)
2	1908 (22.4)	1708 (21.1)
3	2020 (23.7)	1952 (24.1)
4	1416 (16.6)	1412 (17.4)
≥5	1575 (18.5)	1500 (18.5)
Unknown	41 (0.5)	37 (0.5)
Oral contraceptive use		
Never	4811 (56.6)	4655 (57.5)
Ever	3695 (43.4)	3447 (42.5)
Duration, y		
<5	1982 (23.3)	1781 (22.0)
5 to <10	825 (9.7)	808 (10.0)
10 to <15	598 (7.0)	585 (7.2)
≥15	288 (3.4)	270 (3.3)
Unknown	2 (<0.1)	3 (<0.1)
Recency of use		
<20 y ago	748 (8.8)	705 (8.7)
20 to <30 y ago	2133 (25.1)	2013 (24.8)
≥30 y ago	807 (9.5)	718 (8.9)
Unknown	7 (0.1)	11 (0.1)
Infertility†		
No	7123 (83.7)	6897 (85.1)
Yes	1301 (15.3)	1145 (14.1)
Unknown	82 (1.0)	60 (0.7)
Oopherectomy status		
None	8083 (95.0)	7705 (95.1)
Partial	347 (4.1)	339 (4.2)
Bilateral	29 (0.3)	24 (0.3)
Unknown	47 (0.6)	34 (0.4)
Unopposed estrogen use		
Never	7603 (89.4)	7237 (89.3)
Ever	903 (10.6)	865 (10.7)
Duration, y		
<5	677 (8.0)	659 (8.1)
5 to <10	134 (1.6)	109 (1.4)
≥10	92 (1.0)	97 (1.2)
Recency of use		
Within past 5 y	204 (2.4)	194 (2.4)
5 to <10 y ago	141 (1.7)	154 (1.9)
≥10 y ago	555 (6.5)	513 (6.3)
Unknown	3 (<0.1)	4 (<0.1)

(continued)

previously randomized to unopposed estrogen were unblinded and switched to combined hormone therapy. Mean (SD) duration of exposure to unopposed estrogen in these women was 5.4 (3.1) months. When appropriate, analyses were performed separating out the women randomized during this phase to account for the exposure to unopposed estrogen. Several other sensitivity analyses were conducted. In per protocol analyses, events and follow-up time occurring more than 6 months after the participant became nonadherent to study medicines or initiated use of nonstudy hormones were censored. This analysis preserves the randomization assignment and attempts to limit the dilution of effects that nonadherence may entail. As treated analyses (attributing events to the woman's use of hormones, either study pills or those provided by her health care clinician, 6 months prior to the event) were also performed. Analyses censoring women at the time of surgical removal of the organs of interest (total hysterectomy for endometrial cancer and bilateral oophorectomy for ovarian cancer) were also conducted.

Potential effect modification with known gynecologic cancer risk factors was assessed in expanded proportional hazards models that included the designated risk factor and randomization assignment as main effects and the interaction between these. Participants with missing values were excluded only from the analyses using the relevant variables.

Throughout this article, we report unadjusted 2-sided P values to indicate the relative strength of evidence in these secondary analyses. Seventeen tests for interactions with selected baseline characteristics were examined and accordingly 1 test would be expected to be significant at the $P = .05$ level by chance alone. All analyses were performed using SAS statistical software (version 8.2, SAS Institute Inc, Cary, NC).

RESULTS

Many subject characteristics have been presented.[5] Use of unopposed estrogen prior to enrollment was limited

©2003 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 11/28/2015

(11%), was generally of short duration (<5 years), and had not taken place recently (TABLE 1). Prior use of combined hormones was more common (18%) and also more recent.

The average follow-up time for this report is 5.6 years. At the time of our interim report, 42% of women randomized to estrogen plus progestin and 38% of women randomized to placebo had stopped taking their study medications.[5] A total of 485 deaths (3%) occurred before July 8, 2002 (FIGURE 1).

The observed annual incidence rate of ovarian cancer was 34 per 100 000 person-years, somewhat lower than the population-based rate of 45 per 100 000 person-years reported by the Surveillance, Epidemiology, and End Results for women of this age distribution.[13] The rate in the estrogen plus progestin group was elevated (20 vs 12; HR, 1.58; 95% CI, 0.77-3.24 [adjusted 95% CI, 0.59-4.23]), but not statistically significant. Limiting the analyses to invasive epithelial cancers did not change the results substantially (HR, 1.64; 95% CI, 0.78-3.45). The possibility of an increasing effect over time is suggested by the Kaplan-Meier estimates of cumulative hazards (FIGURE 2A) but likewise did not reach statistical significance. Controlling for family history of colorectal cancer, the only baseline risk factor exhibiting a noticeable degree of imbalance, produced a modest increase in the estimated effect (HR, 2.11; 95% CI, 0.96-4.60). No substantial changes were found in analyses conducted per protocol (HR, 1.51; 95% CI, 0.64-3.55), as treated (HR, 1.76; 95% CI, 0.87-3.55), or censoring at the time of bilateral oophorectomy (HR, 1.59; 95% CI, 0.78-3.25).

There was no evidence of a difference between treatment groups in the distribution of histological classes, morphological grade, or stage of disease at diagnosis (TABLE 2). No significant interactions were found with age, race/ethnicity, body mass index, family history of breast or ovarian cancer, family history of colorectal cancer, prior use of oral contraceptives, prior exposure to unopposed estrogen, or prior use of combined hormones. However, power for these tests was limited because the number of events was small. None of the women reporting a history of ovarian cancer at baseline experienced a new diagnosis of ovarian cancer. Ovarian cancer was the reported cause of death in 9 women taking estrogen plus progestin and 3 women taking placebo (HR, 2.70; 95% CI, 0.73-10.0).

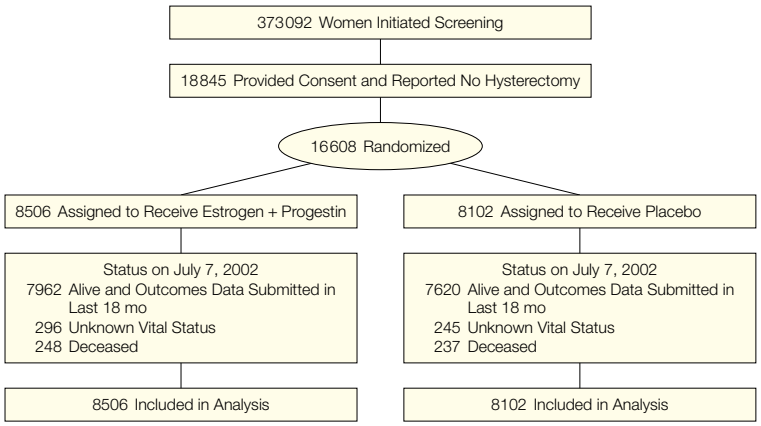
The observed incidence rate of endometrial cancer was 62 per 100 000 person-years, which was also lower than the Surveillance, Epidemiology, and End Results rate of 83 per 100 000 person-years.[13] A small, nonsignificant reduction in endometrial cancer risk was observed with estrogen plus progestin use (27 vs 31; HR, 0.81; 95% CI, 0.48-1.36 [adjusted 95% CI, 0.40-1.64]). A similar reduction was observed in cancers arising from the epithelium (all reported histological classes except stromal sarcoma and mixed mullerian) (23 vs 30; HR, 0.71; 95% CI, 0.41-1.22). Kaplan Meier estimates of the cumulative hazards reveal no differences in rates throughout follow-up beyond what could be readily explained by chance alone

Table 1. Baseline Risk Factors for Gynecologic Cancers by Randomization Assignment (cont)

	No. (%) of Women	
	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)
Estrogen + progestin use		
Never	6990 (82.2)	6706 (82.8)
Ever	1516 (17.8)	1396 (17.2)
Duration, y		
<5	1050 (12.3)	997 (12.3)
5 to <10	315 (3.7)	258 (3.2)
≥10	151 (1.8)	141 (1.7)
Recency of use		
Within past 5 y	1129 (13.3)	1019 (12.6)
5 to <10 y ago	247 (2.9)	225 (2.8)
≥10 y ago	138 (1.6)	151 (1.9)
Unknown	2 (<0.1)	1 (<0.1)
Abnormal Papanicolaou test result in last 3 y		
Never had test	101 (1.2)	115 (1.4)
No abnormal result	6748 (79.3)	6674 (82.4)
Abnormal result	341 (4.0)	328 (4.0)
Unknown	1316 (15.5)	985 (12.2)

*Defined as self-report of physician diagnosis.
†Defined as unable to conceive after a year of unprotected intercourse.

Figure 1. Profile of the Estrogen Plus Progestin Component of the Women's Health Initiative as of July 7, 2002



©2003 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 11/28/2015

(Figure 2B). Three (0.9%) endometrial cancers were diagnosed among the 331 women originally randomized to estrogen alone compared with 3 (0.5%) cases among the 573 women randomized to combined hormones and 2 (0.4%) cases among the 522 women randomized to placebo during this same period. Removing these cases had a limited impact on the results (21 vs 29; HR, 0.72; 95% CI, 0.41-1.26). The per protocol and as treated analyses for endometrial cancer also did not yield important differences in overall findings (HR, 0.83; 95% CI, 0.42-1.64 and HR, 0.80; 95% CI, 0.45-1.43, respectively). Censoring at the time of hysterectomy provided a similar result (HR, 0.81; 95% CI, 0.49-1.36).

There was no evidence of a difference in the distributions of histological class, morphological grade, or stage at diagnosis of endometrial cancer by randomization assignment. No significant interactions were found with age, race/ethnicity, body mass index, hypertension, smoking status, pack-years of smoking, prior use of unopposed estrogen, or prior use of estrogen plus progestin. The possibility of an interaction with diabetes could not be tested because of the sparseness of these data. One death in the placebo group was attributed to endometrial cancer.

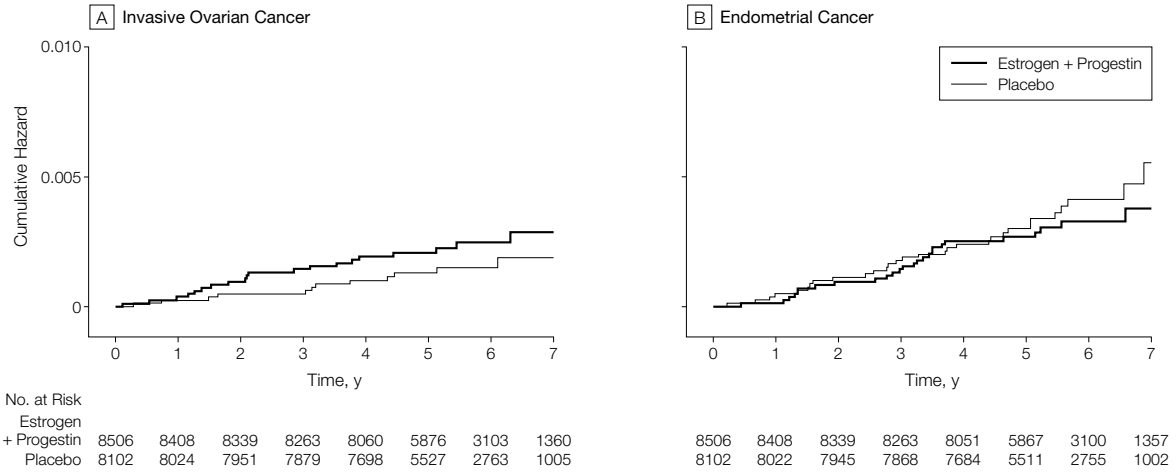
The numbers of borderline ovarian tumors (1 vs 3) and other gynecologic cancers (6 vs 1) were too small to provide meaningful comparisons. Using a combined outcome of invasive ovarian, primary peritoneal, and fallopian tube cancers resulted in an estimated HR that was slightly higher than invasive ovarian cancer alone (26 vs 13; HR, 1.92; 95% CI, 0.99-3.74). We note that one primary peritoneal cancer in the estrogen plus progestin group was detected by an ultrasound performed to evaluate the endometrium. One leiomyosarcoma of the uterus was also reported. No difference was detected in cervical cancer incidence (8 vs 5; HR, 1.44; 95% CI, 0.47-4.42).

Estrogen plus progestin reduced the percentage of unsuccessful biopsies relative to placebo in the cohort randomly selected for routine surveillance (21% vs 36%, $P<.001$), but no difference was observed in the distribution of findings among women with results available ($P=.28$) (TABLE 3). This comparison may be confounded by a higher proportion of women having multiple biopsies in the estrogen plus progestin group (47% vs 27%; $P<.001$) because it is impossible to accurately attribute biopsies in these women to those conducted in response to reports of bleeding vs those done routinely.

Among women selected for usual care, the fraction of women taking combined hormones and requiring diagnostic biopsies increased more than 5-fold over placebo (33% vs 6%; $P<.001$) and twice as many women required multiple biopsies (38% vs 17%; $P<.001$). Among women having successful biopsies, a higher proportion taking estrogen plus progestin had normal findings (85% vs 68%), reflecting increased bleeding not arising from malignant or premalignant lesions. While the proportion of biopsies yielding abnormal findings in women taking estrogen plus progestin was low, the proportion of women having these abnormalities in the estrogen plus progestin group was not reduced relative to placebo. More simple and adenomatous hyperplasias and atypias were found in the estrogen plus progestin group, although this increase may be an artifact of the higher biopsy rate.

More women in the estrogen plus progestin group were examined with ultrasound; the fraction with repeat ultrasounds was also elevated (TABLE 4). No significant differences were found in the endometrial findings of these examinations, but some small differences were noted in the proportion with other pelvic abnormalities.

Figure 2. Kaplan-Meier Estimates of Cumulative Hazards by Randomization Assignment



A, The hazard ratio is 1.58 (95% confidence interval, 0.77-3.24; adjusted 95% confidence interval, 0.59-4.23). B, The hazard ratio is 0.81 (95% confidence interval, 0.48-1.36; adjusted 95% confidence interval, 0.40-1.64).

©2003 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 11/28/2015

Follow-up Papanicolaou test results were available for 94% of trial participants (TABLE 5). The distribution of findings varied significantly ($P<.001$) with the estrogen plus progestin group yielding slightly more mild dysplasia, low grade squamous intraepithelial lesions, or atypia than the placebo group (7.8% vs 5.5%) and fewer normal results (92% vs 94%).

COMMENT

During 5.6 years of follow-up, 111 women were diagnosed as having invasive gynecologic cancers (invasive ovarian, 32; endometrial, 58; nonendometrial uterine, 1; cervical, 13; and other gynecologic, 7). In women randomized to estrogen plus progestin, a nonsignificant 1.58-fold increase in ovarian cancer and a nonsignificant 19% reduction in endometrial cancer were observed, relative to placebo. Data for other gynecologic malignancies were too sparse to provide meaningful comparisons but were included for completeness. Women randomized to continuous combined hormones were subjected to more endometrial biopsies and vaginal ultrasounds and were more frequently found to have mild abnormalities in routine Papanicolaou tests.

Ovarian Cancer

In this trial, women taking estrogen plus progestin were diagnosed as having invasive ovarian cancer at a rate of 42 per 100 000 person-years, 15 per 100 000 person-years more than the placebo group rate. The possibility of an increase in ovarian cancer mortality was also noted. Many, but not all, observational studies have found a modest increased risk of ovarian cancer or ovarian cancer mortality associated with postmenopausal estrogen use,[14-19] but few studies have reported results specifically on combined hormones. In a recently reported US cohort study,[20] an association was found with estrogen alone (odds ratio [OR], 1.6; 95% CI, 1.2-2.0) but not with combined hormones (OR, 1.1; 95% CI, 0.64-1.7), except possibly in women previously exposed to estrogen alone (OR, 1.5; 95% CI, 0.91-2.4). That study did not address the schedule of progestin use. A recent Swedish case-control study[21] (the only currently available study known to distinguish between continuous combined

Table 2. Gynecologic Cancer Incidence and Distribution of Tumor Characteristics by Randomization Assignment*

Type of Cancer	No. (%) of Cancers: Estrogen + Progestin (n = 8506)	No. (%) of Cancers: Placebo (n = 8102)	HR (95% CI)
Invasive ovarian (annualized %)†	20 (0.04)	12 (0.03)	1.58 (0.77-3.24)
Histology			
Serous papillary	11 (55.0)	7 (58.3)	1.64 (0.78-3.45)‡
Adenocarcinoma (not otherwise specified carcinoma)	4 (20.0)	3 (25.0)	
Clear cell	2 (10.0)	1 (8.3)	
Endometroid	2 (10.0)	0 (0)	
Embryonal	1 (5.0)	0 (0)	
Mixed mullerian	0 (0)	1 (8.3)	
Tumor stage			
Localized§	3 (15.0)	0 (0)	
Regional‖	4 (20.0)	3 (25.0)	
Distant¶	12 (60.0)	9 (75.0)	
Missing	1 (5.0)	0 (0)	
Tumor grade			
Moderately differentiated	5 (25.0)	1 (8.3)	
Poorly differentiated	6 (30.0)	8 (66.7)	
Undifferentiated	1 (5.0)	2 (16.7)	
Missing	8 (40.0)	1 (8.3)	
Borderline ovarian (annualized %)†	1 (<0.01)	3 (<0.01)	
Endometrial (annualized %)†	27 (0.06)	31 (0.07)	0.81 (0.48-1.36)
Histology			
Endometroid	14 (51.9)	17 (54.8)	0.71 (0.41-1.22)‡
Adenocarcinoma (not otherwise specified carcinoma)	8 (29.6)	9 (29.0)	
Mucinous	1 (3.7)	1 (3.2)	
Squamous cell	0 (0)	1 (3.2)	
Clear cell	0 (0)	1 (3.2)	
Serous papillary	0 (0)	1 (3.2)	
Stromal sarcoma	2 (7.4)	0 (0)	
Mixed mullerian	2 (7.4)	1 (3.2)	
Tumor stage			
Localized#	23 (85.2)	26 (83.9)	
Regional**	4 (14.8)	5 (16.1)	
Tumor grade			
Well differentiated	9 (33.3)	6 (19.4)	
Moderately differentiated	10 (37.0)	15 (48.4)	
Poorly differentiated	5 (18.5)	7 (22.6)	
Undifferentiated	3 (11.1)	3 (9.7)	
Nonendometrial uterine (annualized %)†	1 (<0.01)	0 (0)	
Cervical (annualized %)†	8 (0.02)	5 (0.01)	1.44 (0.47-4.42)
Other gynecologic (annualized %)††	6 (<0.01)	1 (<0.01)	

Abbreviations: CI, confidence interval; HR, hazard ratio.
*The mean (SD) follow-up time was 67.8 (16.2) for the estrogen plus progestin group and 66.8 (15.2) for the placebo group.
†Reflects rate per person-year.
‡Among epithelial histologies.
§Confined to ovary with no tumor on the surface of ovary.
‖Confined to the pelvis.
¶Implants beyond the pelvis.
#Confined to endometrium, myometrium/serosa.
**Confined to pelvis, vagina, or wall of rectum or bladder.
††Includes fallopian tube and primary peritoneum cancers.

©2003 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 11/28/2015

Table 3. Proportion With Follow-up Endometrial Biopsies and Distribution of Findings by Randomization Assignment*

	No. (%) of Women Selected for Routine Biopsy			No. (%) of Women Selected for Usual Care		
	Estrogen + Progestin (n = 482)	Placebo (n = 453)	*P* Value†	Estrogen + Progestin (n = 7693)	Placebo (n = 7649)	*P* Value†
No. of women with biopsies	412 (85.5)	368 (81.2)	.09	2569 (33.4)	439 (5.7)	<.001
No. of women with multiple biopsies	194 (40.2)	98 (21.6)	<.001	979 (12.7)	72 (0.9)	<.001
Findings‡						
No endometrial tissue/insufficient specimen	74 (18.0)	105 (28.5)	<.001	270 (10.5)	98 (22.3)	<.001
Normal	264 (64.1)	180 (48.9)	.28§	2004 (78.0)	267 (60.8)	<.001§
Simple hyperplasia	3 (0.7)	0 (0)		53 (2.1)	12 (2.7)	
Adenomatous hyperplasia	1 (0.2)	1 (0.3)		10 (0.4)	3 (0.7)	
Atypia	3 (0.7)	5 (1.4)		16 (0.6)	6 (1.4)	
Cancer	0 (0)	0 (0)		7 (0.3)	7 (1.6)	
Unknown	67 (16.3)	77 (20.9)		259 (10.1)	46 (10.5)	

*Excludes the 331 women switched from estrogen alone to estrogen plus progestin.
†Fisher exact test.
‡Most severe result for women with multiple biopsies.
§Among women with a sufficient specimen sample.

Table 4. Proportion With Transvaginal Uterine Ultrasound Examinations and Findings by Randomization Assignment

	No. (%) of Women		
	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	*P* Value*
No. of women with ultrasound examinations	1089 (12.8)	331 (4.1)	<.001
No. of women with multiple ultrasound examinations	299 (3.5)	60 (0.7)	<.001
Findings†			
Unable to evaluate thickness/perform examination	31 (2.8)	8 (2.4)	.85
Endometrial thickness			
≤5 mm	771 (70.8)	248 (75.0)	.16‡
>5 mm	277 (25.4)	72 (22.0)	
Unknown	10 (0.9)	3 (0.9)	
Pelvic pathological result (ever)§			
Polyps	97 (9.1)	17 (5.1)	.03
Uterine mass	229 (21.0)	52 (15.7)	.04
Pelvic fluid	11 (1.0)	3 (0.9)	>.99
Ovarian mass	77 (7.1)	29 (8.8)	.28
Other	65 (6.0)	14 (4.2)	.27

*Fisher exact test.
†Most severe result for women with multiple ultrasound examinations.
‡Among women with evaluable thickness.
§Data for other pelvic pathologies available on 98% of women with ultrasound.

hormone therapy and sequential progestin treatment) found an increased risk associated with use of unopposed estrogen (OR, 1.43; 95% CI, 1.02-2.00) and sequential preparations (OR, 1.54; 95% CI, 1.15-2.05), but not with use of continuous progestin regimens (OR, 1.02; 95% CI, 0.73-1.43). However, the majority of women in this latter study used a progestin derived from 19-nortestosterone rather than the 17-hydroxyprogesterone derivative medroxyprogesterone acetate used in the current trial.

While the etiologies of ovarian cancer are poorly understood, a role for estrogen and progestin is biologically plausible.[22] For example, the gonadotropin hypothesis asserts that the many reproductive history risk factors having a modest association with ovarian cancer risk act indirectly by increasing exposure of the ovarian epithelium to estrogen[23,24] and consequently to proliferation and malignant transformation.[25] Other hypotheses regarding inflammation of the ovarian epithelium[26] and retrograde bleeding[27] have been introduced and allow for an increased risk with hormones through an indirect pathway. The WHI data do not relate directly to the incessant ovulation hypothesis[28] because all participants were menopausal at entry.

Progestins have been hypothesized to have a favorable effect on ovarian cancer incidence[22] based on generally consistent findings of lower risk associated with increasing parity and the use of oral contraceptives,[29] and on animal data describing a role for progestins in promoting apoptosis.[30] The current WHI trial cannot address this question directly, but the eventual comparison with the parallel trial of estrogen alone in women with prior hysterectomy may provide some insight. The WHI data suggest that the continuous combined estrogen and progestin preparation examined in the trial will have no role in ovarian cancer prevention.

Endometrial Cancer

In women taking estrogen plus progestin, the incidence of endometrial cancer during the 5.6 years of follow-up was 56 per 100 000 person-years or 13 fewer cases per 100 000 person-years than observed in women taking placebo. This difference cannot be distinguished from chance.

This is the first randomized, double-blind, placebo-controlled trial to demonstrate that endometrial cancer rates for women taking continuous combined

©2003 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 11/28/2015

hormones are similar to placebo group rates, indicating that progestin protects against the increased risk of endometrial cancer associated with unopposed estrogen. Several reasonably sized, randomized, placebo-controlled trials of combined hormones have reported a substantial reduction in the formation of endometrial hyperplasia, the presumed precursor to many endometrial carcinomas compared with women given estrogen-only therapy.[12,31,32] The results of the present study are also consistent with one smaller randomized trial[33] and 3 observational studies reporting no increase in endometrial cancer risk associated with continuous combined estrogen plus progestin therapy of at least 3 years' duration.[1-3]

Uterine bleeding was a frequent adverse effect of this regimen, leading to much more frequent biopsies and ultrasounds in women taking combined hormones than taking placebo. This increase in bleeding and the gynecologic procedures needed to diagnose and resolve the ensuing concerns (including hysterectomy) continue to be a major drawback of combined hormone therapy, including continuous progestins.

Table 5. Proportion With Follow-up Papanicolaou Tests and Findings by Randomization Assignment

	No. (%) of Women		
	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	*P* Value*
No. of women with Papanicolaou test	7950 (93.5)	7599 (93.8)	.39
No. of women with multiple Papanicolaou tests	6072 (71.4)	5671 (70.0)	.05
Findings†			
Insufficient specimen or slide damaged	1 (<0.1)	5 (0.1)	.12
Normal result	7300 (91.8)	7135 (93.9)	<.001
Mild dysplasia/LGSIL, atypia‡	619 (7.8)	420 (5.5)	
Moderate to severe dysplasia/HGSIL	25 (0.3)	29 (0.4)	
Cancer	2 (<0.1)	3 (<0.1)	
Unknown	3 (<0.1)	7 (<0.1)	

Abbreviations: HGSIL, high-grade squamous intraepithelial lesion; LGSIL, low-grade squamous intraepithelial lesion.
*Fisher exact test.
†Most severe result for women with multiple Papanicolaou tests.
‡Includes atypical squamous cells of undetermined significance and atypical glandular cells of uncertain significance/atypical glandular cells of undetermined significance.

Cervical Cancer

The WHI data on cervical cancer are too limited to suggest there is any association between incidence and estrogen plus progestin therapy. The statistically significant increase in mild abnormalities detected on Papanicolaou tests is interesting and warrants further investigation.

Limitations

The WHI estrogen plus progestin trial is the largest, randomized, double-blind, placebo-controlled trial of continuous combined hormones that has been conducted, yet some limitations must be acknowledged. The number of gynecologic cancers observed was small, yielding wide CIs for the overall effects and limited power to examine possible differential effects in disease subtypes or in subgroups of women. Use of community-based diagnoses rather than central reading of pathological specimens constrains our ability to provide detailed subclassification of disease. As gynecologic cancers were secondary end points of the trial, issues of multiple testing apply. Adjusted CIs are provided to suggest the additional conservatism needed in interpreting these results. The trial was stopped early, which limited the precision of these results and precluded the examination of longer-term exposure. Finally, this trial tested one means of administering a single hormone regimen. We do not know the extent to which these results apply to other postmenopausal hormones. The effects of estrogen alone will be examined in the parallel trial that is ongoing.

Implications

In assessing the overall merit of estrogen plus progestin therapy, the low rates of gynecologic cancers in the population and the limited precision in the estimated effects from this trial suggest that these results should not have an appreciable influence on most women's decision making when seeking relief for moderate to severe vasomotor symptoms, nor can they resolve questions of etiology. The possibility of an increased risk of ovarian cancer incidence and mortality remains worrisome, however, and needs confirmation. The increased need for diagnostic procedures in response to bleeding is an added burden and could reasonably affect a woman's decision to use these medicines. These data provide further support for the recently revised guidelines for the use of continuous combined estrogen plus progestin therapy.[34,35]

Author Contributions: Dr Anderson, as co-principle investigator of the Women's Health Initiative Clinical Coordinating Center, had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analyses.
Study concept and design: Anderson, Judd, Barad, Beresford.
Acquisition of data: Anderson, Barad, Beresford, McNeeley.
Analysis and interpretation of data: Anderson, Judd, Kaunitz, Barad, Pettinger, Liu, Lopez.
Drafting of the manuscript: Anderson, Judd, Barad.
Critical revision of the manuscript for important intellectual content: Anderson, Judd, Kaunitz, Barad, Beresford, Pettinger, Liu, McNeeley, Lopez.
Statistical expertise: Anderson, Pettinger.
Obtained funding: Anderson.
Administrative, technical, or material support: Judd, Beresford, Liu, McNeeley, Lopez.
Study supervision: Anderson, Judd, Liu.
WHI Investigators and Clinical Centers: *Alabama*: University of Alabama at Birmingham, Cora E. Lewis, Albert Oberman, Mona N. Fouad, James M. Shikany, Delia Smith West. *Arizona:* Tucson/Phoenix: University of Arizona, Tamsen Bassford, John Mattox, Marcia Ko, Timothy Lohman. *California:* University of California at Los Angeles, Howard Judd, David Heber, Robert Elashoff; Oakland: Kaiser Permanente Division of Research, Bette Caan, Stephen Sidney, Geri Bailey, Jane Hirata; Orange: University of California at Irvine, Allan Hubbell, Gail Frank, Nathan Wong, Nancy Greep, Bradley Monk; Sacramento: University of California at Davis, John Robbins, S. Yasmeen, Karen Lindfors, Judith Stern; University of California at San Diego, Robert D. Langer, Michael H. Criqui, Gregory T. Talavera, Cedric F. Garland, R. Elaine Hanson; Stanford Center for Research in Disease Prevention, Stanford University, Marcia L. Stefanick, Mark A. Hlatky, Bertha Chen, Randall S. Stafford, Linda C. Giudice; Torrance: Harbor-UCLA Research and Education Institute, Rowan Chlebowski, Robert Detrano, Anita Nelson, James Heiner, John Marshall. *District of Columbia:* Washington: MedStar Research Institute/Howard University, Barbara V. Howard, Lucile Adams-Campbell, Maureen Passaro, Monique Rainford, Tanya Agurs-Collins; George Washington University, Judith

©2003 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 11/28/2015

Hsia, Nancy Gaba, Joao Ascensao, Somchia Laowattana. *Florida:* Gainesville/Jacksonville: University of Florida, Marian Limacher, Michael Perri, Andrew Kaunitz, R. Stan Williams, Yvonne Brinson; University of Miami, Mary Jo O'Sullivan, Linda Parker, R. Estape, Diann Fernandez. *Georgia:* Atlanta: Emory University, Lawrence Phillips, Margaret Pedersen, Ora Strickland, Margaret Huber, Vivian Porter. *Hawaii:* Honolulu: University of Hawaii, David Curb, Helen Petrovitch, Beatriz Rodriguez, Kamal Masaki, Santosh Sharma. *Illinois:* Chicago: Northwestern University, Linda Van Horn, Philip Greenland, Janardan Khandekar, Kiang Liu, Carol Rosenberg; Rush-Presbyterian-St Luke's Medical Center, Henry Black, Lynda Powell, Ellen Mason. *Iowa:* Davenport: University of Iowa, Robert Wallace, James Torner, Susan Johnson, Linda Snetselaar, Bradley VanVoorhis. *Massachusetts:* Boston: Brigham and Women's Hospital, JoAnn Manson, Julie Buring, J. Michael Gaziano, Kathryn Rexrode, Claudia Chae; Worcester: University of Massachusetts/Fallon Clinic, Judith Ockene, Milagros Rosal, Ira Ockene, Robert Yood, Patricia Aronson. *Michigan:* Detroit: Wayne State University School of Medicine/Hutzel Hospital, Susan Hendrix, Michael Simon, Gene McNeeley, Pamela Gordon, Paul Makela. *Minnesota:* Minneapolis: University of Minnesota, Richard H. Grimm, Kathleen M. Hall, Donald B. Hunninghake, June LaValleur, Karen L. Margolis. *Nevada:* Reno: University of Nevada, Robert Brunner, Sachiko St Jeor, William Graettinger, Vicki Oujevolk. *New Jersey:* Newark: University of Medicine and Dentistry of New Jersey, Norman Lasser, Norman Hymowitz, Vera Lasser, Monika Safford, John Kostis. *New York:* Bronx: Albert Einstein College of Medicine, Sylvia Wassertheil-Smoller, William Frishman, Judith Wylie-Rosett, David Barad, Ruth Freeman; State University of New York at Buffalo, Maurizio Trevisan, Jean Wactawski-Wende, Susan Graham, June Chang, Ellen Smit; State University of New York at Stony Brook, Dorothy Lane, Iris Granek, William Lawson, Gabriel San Roman, Catherine Messina. *North Carolina:* Chapel Hill: University of North Carolina, Gerardo Heiss, Pamela Haines, David Ontjes, Carla Sueta, Ellen Wells; Winston-Salem: Wake Forest University School of Medicine, Greg Burke, Robin Crouse, Lynne Parsons, Mara Vitolins. *Ohio:* University of Cincinnati, Margery Gass, Suzanne Wernke, Nelson Watts; Columbus: Ohio State University, Rebecca Jackson, Randall Harris, David Frid, W. Jerry Mysiw, Michael Blumenfeld. *Oregon:* Portland: Kaiser Permanente Center for Health Research, Cheryl Ritenbaugh, Barbara Valanis, Patricia Elmer, Victor Stevens, Njeri Karanja. *Pennsylvania:* University of Pittsburgh, Lewis Kuller, Arlene Caggiula, Jane Cauley, Sarah Berga, N. Carole Milas. *Rhode Island:* Providence: Brown University, Annlouise R. Assaf, Richard Carleton†, Carol Wheeler, Charles Eaton, Michelle Cyr. *Tennessee:* Memphis: University of Tennessee, Karen C. Johnson, Suzanne Satterfield, Raymond W. Ke, Jere Vile, Fran Tylavsky; *Texas:* Houston: Baylor College of Medicine, Jennifer Hays, Ronald Young, Jill Anderson, Sandy Lithgow, Paul Bray; San Antonio: University of Texas Health Science Center, Robert Brzyski, Robert Schenken, Jose Trabal, Mercedes Rodriguez-Sifuentes, Charles Mouton. *Washington:* Seattle: Fred Hutchinson Cancer Research Center, Shirley A. A. Beresford, Vicky M. Taylor, Nancy F. Woods, Maureen Henderson, Mark Kestin. *Wisconsin:* Madison: University of Wisconsin, Catherine Allen, Douglas Laube, Patrick McBride, Julie Mares-Perlman, Barbara Loevinger; Milwaukee: Medical College of Wisconsin, Jane Morley Kotchen, Vanessa Barnabei, Theodore A. Kotchen, Mary Ann C. Gilligan, Joan Neuner.

†Deceased.

Clinical Coordinating Center: Fred Hutchinson Cancer Research Center, Seattle, Wash: Ross Prentice, Garnet Anderson, Andrea LaCroix, Ruth Patterson, Anne McTiernan, Barbara Cochrane, Julie Hunt, Lesley Tinker, Charles Kooperberg, Martin McIntosh, C. Y. Wang, Chu Chen, Deborah Bowen, Alan Kristal, Janet Stanford, Nicole Urban, Noel Weiss, Emily White.

Coordinating Center Subcontractors: *California:* University of California at San Francisco, Steven Cummings, Michael Nevitt, Maurice Dockrell. *Kentucky:* Highland Heights: Medical Research Labs, Evan Stein, Peter Laskarzewski. *Maryland:* Rockville: McKesson BioServices, Frank Cammarata, Steve Lindenfelser. *Minnesota:* Minneapolis: University of Minnesota, Lisa Harnack. *North Carolina:* Winston-Salem: Wake Forest University School of Medicine, Sally Shumaker, Pentti Rautaharju, Ronald Prineas, Michelle Naughton. *Washington:* University of Washington, Seattle, Bruce Psaty, Susan Heckbert.

Program Office: National Heart, Lung, and Blood Institute, Bethesda, Md, Barbara Alving, Jacques Rossouw, Linda Pottern, Shari Ludlam, Joan McGowan.

Financial Disclosures: Dr Kaunitz has received funding for clinical trials from Barr Laboratories, Berlex, Galen, Johnson & Johnson, and Pharmacia (Pfizer); has continuing medical education presentations and publications funded by Aventis, Ortho-McNeil, Pharmacia (Pfizer), and Wyeth-Ayerst; has been a consultant for Aventis, Barr Laboratories, Berlex, Johnson & Johnson (Ortho-McNeil), and Pharmacia (Pfizer); and holds stock in Aventis and Johnson & Johnson. Dr Liu has been on the speakers bureau with Merck Pharmaceuticals and Wyeth; has been a consultant for Watson Pharmaceuticals, Barr Laboratories, UMD Inc, Merck Pharmaceuticals, and Solvay Pharmaceuticals; and has received research grants from Procter & Gamble Pharmaceuticals, Aventis, and Pfizer.

Funding/Support: The WHI program is funded by the National Heart, Lung, and Blood Institute, US Department of Health and Human Services. Wyeth-Ayerst Research provided the study medication (active and placebo).

Acknowledgment: We appreciate the WHI participants and staff for their efforts and in particular to Allison Weber for cancer coding and Noel Weiss for his review of this article.

REFERENCES

1. Pike MC, Peters RK, Cozen W, et al. Estrogen-progestin replacement therapy and endometrial cancer. *J Natl Cancer Inst.* 1997;89:1110-1116.

2. Weiderpass E, Adami HO, Baron JA, et al. Risk of endometrial cancer following estrogen replacement with and without progestins. *J Natl Cancer Inst.* 1999; 91:1131-1137.

3. Hill DA, Weiss NS, Beresford SAA, et al. Continuous combined hormone replacement therapy and risk of endometrial cancer. *Am J Obstet Gynecol.* 2000; 183:1456-1461.

4. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials.* 1998;19:61-109.

5. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA.* 2002;288:321-333.

6. Kaunitz AM, Masciello A, Ostrowski M, Rovira EZ. Comparison of endometrial biopsy with the endometrial pipelle and vabra aspirator. *J Reprod Med.* 1988; 33:427-430.

7. Stovall TG, Photopulos GJ, Poston WM, Ling FW, Sandles LG. Pipelle endometrial sampling in patients with known endometrial carcinoma. *Obstet Gynecol.* 1991;77:954-956.

8. Smith-Bindman R, Kerlikowske K, Feldstein VA, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abmormalites. *JAMA.* 1998; 280:1510-1517.

9. Percy C, Van Holten V, Muir C, eds. *International Classification of Diseases for Oncology, 2nd Edition.* Geneva, Switzerland: World Health Organization; 1990.

10. *The SEER Program Code Manual, Revised Edition.* Bethesda, Md: Cancer Statistics Branch, National Cancer Institute; 1992.

11. Freedman LS, Anderson GL, Kipnis V, et al. Approaches to monitoring the results of long-term disease prevention trials. *Control Clin Trials.* 1996;17: 509-525.

12. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. *JAMA.* 1996;275:370-375.

13. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER)*Stat Database (1973-2000). Available at: http://www.seer.cancer.gov. Accessed April 17, 2003.

14. Weiss NS, Lyon JL, Rishnamurthy S, Dietert SE, Liff JM, Daling J. Noncontraceptive estrogen use and the occurrence of ovarian cancer. *J Natl Cancer Inst.* 1982;68:95-98.

15. Booth M, Beral V, Smith P. Risk factors for ovarian cancer. *Br J Cancer.* 1989;60:592-598.

16. Whittemore AS. Personal characteristics relating to risk of invasive epithelial ovarian cancer in older women in the United States. *Cancer.* 1993;72:558-565.

17. Purdie D, Green A, Bain C, et al. Reproductive and other factors and risk of epithelial ovarian cancer. *Int J Cancer.* 1995;62:678-684.

18. Risch HA. Estrogen replacement therapy and risk of epithelial ovarian cancer. *Gynecol Oncol.* 1996; 63:254-257.

19. Rodriguez C, Patel AV, Calle EE, Jacobs EJ, Thun MJ. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA.* 2001;285:1460-1465.

20. Lacey JV, Mink PJ, Lubin JH, et al. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA.* 2002;288:334-341.

21. Riman T, Dickman PW, Nilsson S, et al. Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish Women. *J Natl Cancer Inst.* 2002;94:497-504.

22. Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. *J Natl Cancer Inst.* 1998; 90:1774-1786.

23. Gardner WU. Tumorigenesis in transplanted irradiated and non-irradiated ovaries. *J Natl Cancer Inst.* 1961;26:829-854.

24. Stadel BV. The etiology and prevention of ovarian cancer. *Am J Obstet Gynecol.* 1975;123:772-774.

25. Cramer DW, Welch WR. Determinants of ovarian cancer risk, II: inferences regarding pathogenesis. *J Natl Cancer Inst.* 1983;71:717-721.

26. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. *J Natl Cancer Inst.* 1999;91:1459-1467.

27. Cramer DW, Xu H. Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. *Ann Epidemiol.* 1995;5:310-314.

28. Fathalla MF. Incessant ovulation: a factor in ovarian neoplasia? *Lancet.* 1971;2:163.

29. Ness RB, Grisso JA, Klapper J, et al. Risk of ovarian cancer in relation to estrogen and progestin dose and use characteristics of oral contraceptives. *Am J Epidemiol.* 2000;152:233-241.

30. Rodriguez GC, Walmer DK, Cline M. Effect of progestin on the ovarian epithelim of macaques. *J Soc Gynecol Investig.* 1998;5:271-276.

31. Woodruff JD, Pickar JH, et al. Incidence of endometrial hyperplasia in postmenopausal women taking conjugated estrogens (Premarin) with medroxyprogesterone acetate or conjugated estrogens alone. *Am J Obstet Gynecol.* 1994;170:1213-1223.

32. Speroff L, Rowan J, Symons J, et al. The comparative effect on bone density, endometrium and lipids of continuous hormones as replacement therapy (CHART study). *JAMA.* 1996;276:1397-1403.

33. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy. *JAMA.* 2002;288:58-66.

34. American College of Obstetricians and Gynecologists. Hormone therapy: questions and answers from ACOG physicians. Available at: http://www.acog.org/from_home/publications/press_releases/nr08-30-02.cfm. Accessed March 31, 2003.

35. US Preventive Services Task Force. Postmenopausal hormone replacement therapy for primary prevention of chronic conditions: recommendations and rationale. *Ann Intern Med.* 2002;137:834-839.

 ©2003 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 11/28/2015