ARTICLES

Estrogen–Progestin Replacement Therapy and Endometrial Cancer

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Background: **It has been known for more than 20 years that estrogen replacement therapy substantially increases a woman's risk of developing endometrial cancer. To reduce this increased risk, progestins have been added to estrogen replacement therapy for between 5 and 15 days (usually 7 or 10 days) per "month" in a sequential fashion (sequential estrogen–progestin replacement therapy) or with each dose of estrogen replacement therapy (continuous combined replacement therapy). At the present time, however, little is known about the effects of varying the number of days that progestin is used in sequential estrogen–progestin replacement therapy.** ***Purpose:*** **We sought to determine the effects of sequential estrogen–progestin replacement therapy and continuous combined replacement therapy on a woman's risk of developing endometrial cancer.** ***Methods:*** **A population-based, case–control study of 833 case subjects and 791 control subjects was conducted. Women were postmenopausal, white, and aged 50-74 years when first diagnosed with invasive endometrial cancer or were aged 50-74 years at the matching date for control subjects. All subjects were interviewed in person with the aid of a month-by-month calendar. Relative risks were estimated by odds ratios (ORs); ORs were adjusted simultaneously for the different forms of hormone replacement therapy and for the known endometrial cancer risk factors.** ***Results:*** **The adjusted OR was 2.17 (95% confidence interval [CI] = 1.91-2.47) per 5 years of estrogen replacement therapy use (based on 422 users among the case subjects and 262 users among the control subjects). For women who received sequential estrogen–progestin replacement therapy with the progestin given for less than 10 days (effectively 7 days) per month, the adjusted OR was only slightly reduced to 1.87 (95% CI = 1.32-2.65) per 5 years of use (74 case subjects and 47 control subjects). However, when progestin was given for 10 or more days (effectively 10 days), there was essentially no increased risk (adjusted OR = 1.07 per 5 years of use; 95% CI = 0.82-1.41) (79 case subjects and 88 control subjects). Continuous combined replacement therapy was also associated with essentially no increased risk (adjusted OR = 1.07 per 5 years of use; 95% CI = 0.80-1.43) (94 case subjects and 81 control subjects).** ***Conclusions:*** **The progestin in sequential estrogen–progestin replacement therapy needs to be given for at least 10 days to block effectively any increased risk of endometrial cancer. Continuous combined estrogen–progestin therapy is similarly effective. Neither regimen reduces a woman's underlying risk of endometrial cancer. The sharp distinction between the effects of less than 10 days (effectively 7 days) and 10 or more days (effectively 10 days) of progestin use in sequential estrogen–progestin replacement therapy suggests that the extent of endometrial sloughing may play a critical role in determining endometrial cancer risk. [J Natl Cancer Inst 1997;89:1110-6]**

In the mid-1970s, estrogen replacement therapy was shown to substantially increase the risk of endometrial cancer (*1-4*). To counteract this risk, progestins were added to estrogen replacement therapy for between 5 and 15 days (usually 7 or 10 days) per "month"—sequential estrogen–progestin replacement therapy. Sequential estrogen–progestin replacement therapy causes regular bleeding in many women and is associated with other negative side effects (*5*). Subsequently, continuous combined replacement therapy regimens were developed in which estrogen and a lower dose of progestin are always taken together. Continuous combined replacement therapy is not associated with regular bleeding, but there is substantial spotting.

A number of case–control studies of endometrial cancer and sequential estrogen–progestin replacement therapy have been reported (*6-11*). All but one of these studies (*11*) involved very few case subjects; all found a lower risk with sequential estrogen–progestin replacement therapy than with estrogen replacement therapy, but they were inconsistent in detail. In particular, it is not clear what the effects are of different numbers of days of progestin use. To our knowledge, no studies have been reported on the effects of continuous combined replacement therapy.

We report here results from a large population-based, case–

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See "Notes" following "References."

control study of postmenopausal endometrial cancer. Our purpose was to determine the effects of sequential estrogen–progestin replacement therapy and continuous combined replacement therapy on a woman's risk of developing endometrial cancer.

Subjects and Methods

Selection of Case and Control Subjects

Case subjects were English-speaking white women who had received a first diagnosis of invasive histologically confirmed endometrial cancer with no prior invasive cancer (except non-melanoma skin cancer) at ages 50 through 74 years during the period from July 1987 through July 1993. They were identified by the Cancer Surveillance Program, the tumor registry covering all residents of Los Angeles County.

One thousand five hundred seventy-five eligible case subjects were identified. Six hundred seventy-five case subjects were excluded from the study for the following reasons: 209 had died or were too ill to be interviewed by the time we had contacted their physicians, the patients' physicians refused permission to contact an additional 103 of them, 101 patients could not be located, and 262 patients declined to be interviewed. Interviews with the remaining 900 case subjects were completed (57% of those identified and 77% of those approached) (Table 1).

Control subjects were English-speaking, nonhysterectomized white women who were individually matched to interviewed case subjects on date of birth (±5 years). Control subjects must not have had a diagnosis of any invasive cancer (excluding non-melanoma skin cancer). Initially, a neighborhood control subject was sought by use of a systematic algorithm based on the address of the case subject. If the first eligible matched control subject refused to participate, the second eligible one in the sequence was asked, and so on. If no matched control subject willing to participate could be found for a case subject older than age 65, a control subject was sought from a random sample of white female residents of Los Angeles County who were older than age 65; this sample was provided to us by the Health Care Financing Administration, Baltimore, MD. The Health Care Financing Administration control subject was matched on the case subject's socioeconomic status (five categories, based on mean income and median education of census tract of residence) (*12*) and had the closest birth date to that of the case subject. Eligible control subjects were interviewed for 864 case subjects (802 neighborhood control subjects and 62 Health Care Financing Administration control subjects). The first eligible matched control subject was interviewed for 519 (60%) of the case subjects and the second match for 193 (22%; Table 1).

During the analysis of the results, we also excluded an additional 67 case subjects and 73 control subjects for a variety of reasons, as described below.

The study was approved by the Institutional Review Board of the University of Southern California School of Medicine, and written informed consent was obtained from each case and control subject before interview.

Interview Method

Both the case subject and the matching control subject were interviewed in person by the same interviewer using the same structured questionnaire. It was impossible to blind the interviewers to case or control status, but study hypotheses were not discussed with the interviewers. A reference date was defined as 4 months before the date of diagnosis of the case subject; the same reference date was used for the case subject and her matching control subject. To facilitate recall, a month-by-month calendar was constructed from menarche to the reference date. Use of oral contraceptives and hormone replacement therapy were linked to pregnancies and other important life events, which were noted on the calendar. Questions were asked about medications used to control menstrual problems and hormones used for any purpose. A photograph album of all oral contraceptives and most hormone pills ever sold in the United States was used to aid in recall of brands and dose.

At analysis, three case subjects and four control subjects were excluded because of incomplete information on certain essential variables, and six additional case subjects were excluded because their ages at diagnosis were outside the eligible age range.

Age at Menopause

Age at menopause is an important risk factor for endometrial cancer; it is most commonly equated with age at last menstrual period. However, age at last menstrual period cannot be used uniformly to estimate age at menopause, since women who use sequential estrogen–progestin replacement therapy usually continue to have monthly menstrual periods, irrespective of their ovarian function, and women on estrogen replacement therapy and continuous combined replacement therapy can rarely distinguish breakthrough bleeding from ovarian function-determined menses. We adopted the following schema to approximate age at menopause:

"Age at menopause" (recorded to the month) is taken as the last natural menstrual period. Menstruating "naturally" is taken to mean menstruating and not using oral contraceptives or hormone replacement therapy at the time or during the previous 3 months. The only exception is for women who went on oral contraceptives within 3 months of that time, when age at menopause is taken to occur at the end of the period of oral contraceptive use. A woman was classified as postmenopausal if her age at menopause was before her reference date.

Eight case subjects and 11 control subjects had their last natural menstrual period before age 35, one control subject as early as 28, and many started hormone replacement therapy in their early 30s; these women were excluded from the analysis, since the risk associated with their hormone replacement therapy use does not appear relevant to evaluating regular postmenopausal hormone replacement therapy use and there is no truly satisfactory way to adjust for their age at menopause.

Stage and Grade at Diagnosis

Tumor stage and grade at diagnosis were determined by a review of all original pathology reports. We classified the tumors into four extent-of-invasion

Table 1. Summary of case subjects and control subjects sought, interviewed, and excluded from final analyses: Endometrial Cancer Study, Los Angeles (1987-1993)

Case subjects		Control subjects	
Eligible case subjects	1575	Control subjects sought	900
Died/too ill	209	None found	36
Physician refusal	103		
Unable to locate	101	Interviewed	
Case subjects approached	1162	1st eligible match	519
Declined to be interviewed	262	2nd eligible match	193
		⩾3rd eligible match	152
Total interviewed	900	Total interviewed	864
Excluded from final analyses		Excluded from final analyses	
Missing values in key variables	3	Missing values in key variables	4
Last natural menstrual period before age 35 y	8	Last natural menstrual period before age 35 y	11
Age at diagnosis outside eligible range	6	Age <50 or ⩾75 y	24
Premenopausal at reference date	50	Premenopausal at reference date	34
Total in final analyses*	833	Total in final analyses*	791

*Analyses stratified on single years of age (*see* text).

categories, following the International Federation of Gynecology and Obstetrics (FIGO) system (*13*): stage IA = no invasion beyond the endometrium; stage IB = invasion up to the first half of the myometrium; stage IC = invasion past the first half of the myometrium; and stages II-IV = more extensive disease, including local extension outside the myometrium and distant metastases. Stage IC+ denotes stages IC or II-IV. Stage IB+ denotes stages IB or IC or II-IV. For 11 case subjects, we could not determine the extent of tumor invasion. The tumor grades were recorded as well, moderately, or poorly differentiated. For 21 case subjects, we could not determine the tumor grade.

Pathology Review

We obtained the diagnostic pathology slides for 137 (90%) of the 152 case subjects with stage IA tumors for review. They were reviewed by the late Dr. G. d'Ablaing, M.D., professor of gynecologic pathology at our institution, and by one of us (J. C. Felix). On review, only six tumors were considered to be hyperplasia without atypia (three simple and three complex hyperplasias); 40 tumors were considered to be hyperplasia with atypia.

Statistical Methods

Statistical analyses were undertaken in two ways: 1) maintaining the original matched-pair design and 2) stratifying on age at reference date (in single years) and socioeconomic status. Both approaches involved the loss of some data; the matched-pair approach loses pairs in which either the case or control subject has been excluded for some reason, and the stratified approach loses control subjects who are outside the age range of the case subjects. Essentially the same results were obtained with both methods. Only the stratified analyses with exact matching on age in years are presented here.

With this stratified analysis, 24 control subjects with age at reference date of less than 50 years or 75 years or older were in age strata with no case subjects and were thus excluded. Premenopausal women (50 case subjects and 34 control subjects) were also excluded because they provide no useful information on postmenopausal hormone replacement therapy in a stratified analysis. This left 833 case subjects and 791 control subjects.

Standard conditional logistic methods for the analysis of stratified case–control studies were used (*14*). Relative risks were estimated by odds ratios (ORs); 95% confidence intervals are abbreviated 95% CIs. All reported statistical significance values (*P*) are from the use of two-sided tests.

Tests for trend in OR by duration of hormone replacement therapy use were made with duration as a continuous variable. We adjusted the ORs for the accepted or suggested risk factors of age at menarche, time to regular cycles, nulliparity, number of full-term pregnancies, total duration of incomplete pregnancies, weight, duration of breast feeding, total duration of premenopausal periods of amenorrhea, smoking, total duration of oral contraceptive use, and age at menopause. Adjustments were made by use of categories except where a continuous variable provided the same degree of fit to the data.

Results

The age distributions of the 833 case subjects and 791 control subjects are shown in Table 2. A total of 509 case subjects and 381 control subjects had used some form of hormone replacement therapy.

The unadjusted and adjusted ORs for estrogen replacement therapy are given in Table 3. Estrogen replacement therapy had been used by 422 case subjects and 262 control subjects. The adjusted OR per 5 years of estrogen replacement therapy was 2.17 (95% CI = 1.91-2.47; $P<.0001$).

Table 2. Postmenopausal case and control subjects 50-74 years of age: Endometrial Cancer Study, Los Angeles (1987-1993)

Age group, y	No. of case subjects	No. of control subjects
50-54	54	64
55-59	171	144
60-64	237	236
65-69	292	254
70-74	79	93
Total	833	791

Progestin in sequential estrogen–progestin replacement therapy was commonly given for 7 or 10 days per ''month.'' The relation of cyclical sequential estrogen–progestin replacement therapy to endometrial cancer risk was strongly affected by the number of days of progestin administration. Table 3 shows the ORs for sequential estrogen–progestin replacement therapy with the progestin administration divided into short progestin use (<10 days per month; 74 case subjects and 47 control subjects) and long progestin use (≥10 days per month; 79 case subjects and 88 control subjects). Sequential estrogen–progestin replacement therapy (short progestin use) was associated with a significantly increased risk of endometrial cancer, with an adjusted OR of 1.87 (95% CI = 1.32-2.65; $P = .0004$) per 5 years of use. Sequential estrogen–progestin replacement therapy (long progestin use) showed little evidence of any increased risk, with an adjusted OR of 1.07 (95% CI = 0.82-1.41; $P = .62$) per 5 years of use.

Continuous combined replacement therapy had been used by 94 case subjects and 81 control subjects and showed little evidence of any increased risk, with an OR of 1.07 (95% CI = 0.80-1.43; $P = .64$) per 5 years of use.

Stage and Grade at Diagnosis

The effect of hormone replacement therapy differed markedly, depending on the stage at diagnosis. The first column of results in Table 4 repeats the adjusted results shown in Table 3. A similar pattern was observed with all forms of hormone replacement therapy (i.e., a steadily decreasing OR with increasing stage of disease at diagnosis). There was no difference in effect for any of the hormone replacement therapy regimens between stage IC and stage II-IV tumors, and separate results are not given here.

For women who received estrogen replacement therapy, the overall OR per 5 years of use was 2.17 (95% CI = 1.91-2.47); it declined from 3.20 (95% CI = 2.49-4.12) for stage IA tumors to 2.28 (95% CI = 1.96-2.66) for stage IB tumors and to 1.73 (95% CI = 1.45-2.08) for stage IC+ tumors. For all cancers that invaded the myometrium (stage IB+), it was 2.01 (95% CI = 1.76-2.29).

The ORs per 5 years of use for sequential estrogen–progestin replacement therapy (short progestin use) showed increased risk of disease at all stages of diagnosis. Overall, the added risk of sequential estrogen–progestin replacement therapy (short progestin use), i.e., 1.87 − 1.00 = 0.87, was estimated to be some 74% of the added risk of estrogen replacement therapy, i.e., 2.17 − 1.00 = 1.17; it was 94% for stage IA tumors, 63% for stage IB tumors, and 7% for stage IC+ tumors.

For sequential estrogen–progestin replacement therapy (long progestin use), there was an increased risk for stage IA tumors—OR per 5 years of use of 1.54, decreasing to 1.10 for stage IB tumors and then to 0.90 for stage IC+ tumors. The OR for all myometrial invasive disease (stage IB+) was essentially 1 (OR = 1.02).

The results observed with continuous combined replacement therapy were very similar to those observed with sequential estrogen–progestin replacement therapy (long progestin use). There was a slightly increased risk for stage IA tumors (OR =

Table 3. Odds ratios for hormone replacement therapy: Endometrial Cancer Study, Los Angeles (1987-1993)

Hormone replacement therapy*	Months of use	No. of case subjects	No. of control subjects	Odds ratios		*P*
				Unadjusted	Adjusted†	
ERT	0	411	529	1.00	1.00	
	1-24	94	126	1.09	1.30	
	25-60	69	53	1.87	2.22	
	61-120	83	40	2.97	4.49	
	121-180	69	29	3.44	5.33	
	⩾181	107	14	12.41	24.22	
	Per 5 y			1.83	2.17 (1.91-2.47)	<.0001
SEPRT-SP	0	759	744	1.00	1.00	
	1-24	35	22	1.35	1.35	
	25-60	12	12	1.04	1.47	
	⩾61	27	13	1.92	3.49	
	Per 5 y			1.40	1.87 (1.32-2.65)	.0004
SEPRT-LP	0	754	703	1.00	1.00	
	1-24	37	30	1.03	1.00	
	25-60	19	25	0.78	0.73	
	⩾61	23	33	0.69	1.09	
	Per 5 y			0.88	1.07 (0.82-1.41)	.62
CCRT	0	739	710	1.00	1.00	
	1-24	45	41	1.08	1.05	
	25-60	25	15	1.54	1.44	
	⩾61	24	25	0.97	1.34	
	Per 5 y			0.94	1.07 (0.80-1.43)	.64

*ERT = estrogen replacement therapy; SEPRT-SP = sequential estrogen–progestin replacement therapy (short progestin use, i.e., <10 days per ''month''); SEPRT-LP = sequential estrogen–progestin replacement therapy (long progestin use, i.e., ⩾10 days per ''month''); CCRT = continuous combined replacement therapy.

†Adjusted for age at menarche, time to regular cycles, nulliparity, number of full-term pregnancies, total duration of incomplete pregnancies, weight, duration of breast feeding, total duration of premenopausal periods of amenorrhea, smoking, total duration of oral contraceptive use, and age at menopause. Values in parentheses = 95% confidence intervals.

1.26), which decreased to an OR of 1.16 for stage IB tumors and then to an OR of 0.80 for stage IC+ tumors. The OR for stage IB+ disease was again essentially 1 (OR = 1.03).

The ORs for stage IA tumors confirmed as cancers on review of pathology were very close to those given in Table 4.

The case subjects who were interviewed had less extensive disease than the eligible case subjects who were not interviewed: 18% versus 14% for stage IA disease, 51% versus 40% for stage IB disease, and 31% versus 46% for more advanced disease. The overall ORs reported here are therefore biased upward by the inclusion of a greater proportion of stage IA or IB disease. The conclusions drawn here are not affected.

The results by stage shown in Table 4 were modified by the grade of tumor for estrogen replacement therapy and estrogen–

Table 4. Adjusted odds ratios* for subjects who received hormone replacement therapy by pathologic stage at diagnosis: Endometrial Cancer Study, Los Angeles (1987-1993)

Hormone replacement therapy†	Odds ratio (95% confidence interval)‡				
	All stages (n = 833)	Stage IA (n = 152)	Stage IB (n = 419)	Stage IC+ (n = 251)	Stage IB+ (n = 670)
ERT	2.17 (1.91-2.47)	3.20 (2.49-4.12)	2.28 (1.96-2.66)	1.73 (1.45-2.08)	2.01 (1.76-2.29)
SEPRT-SP	1.87 (1.32-2.65)	3.07 (1.93-4.89)	1.81 (1.20-2.72)	1.05 (0.43-2.58)	1.62 (1.08-2.41)
SEPRT-LP	1.07 (0.82-1.41)	1.54 (0.86-2.74)	1.10 (0.80-1.52)	0.90 (0.54-1.50)	1.02 (0.76-1.37)
CCRT	1.07 (0.80-1.43)	1.26 (0.72-2.20)	1.16 (0.82-1.64)	0.80 (0.47-1.35)	1.03 (0.76-1.41)

*Per 5 years of use. Adjusted for age at menarche, time to regular cycles, nulliparity, number of full-term pregnancies, total duration of incomplete pregnancies, weight, duration of breast feeding, total duration of premenopausal periods of amenorrhea, smoking, total duration of oral contraceptive use, and age at menopause.

†ERT = estrogen replacement therapy; SEPRT-SP = sequential estrogen–progestin replacement therapy (short progestin use, i.e., <10 days per ''month''); SEPRT-LP = sequential estrogen–progestin replacement therapy (long progestin use, i.e., ⩾10 days per ''month''); CCRT = continuous combined replacement therapy.

‡Stage IA = no invasion beyond endometrium; stage IB = invasion up to first half of myometrium; stage IC+ = invasion past first half of myometrium and/or metastases and/or invasion to cervix; stage IB+ = stage IB plus stage IC+ = invasion of myometrium and/or metastases and/or invasion to cervix.

progestin replacement therapy (short progestin use) but not for estrogen–progestin replacement therapy (long progestin use) or continuous combined replacement therapy. For estrogen replacement therapy and estrogen–progestin replacement therapy (short progestin use), the ORs were considerably higher for well-differentiated tumors, but they were still significantly elevated for tumors of higher grade (results not shown).

Time Since Last Use of Estrogen Replacement Therapy

Table 5 shows the ORs for estrogen replacement therapy by time since last use of estrogen replacement therapy if no other hormone replacement therapy was used and, otherwise, by type of subsequent hormone replacement therapy. Current or recent use of estrogen replacement therapy was associated with higher ORs than last use 2-9 years before, and the risk decreased slightly further with last use 10 or more years before. If the estrogen replacement therapy use was followed (usually immediately) by sequential estrogen–progestin replacement therapy or continuous combined replacement therapy use, similar reductions in risk were found. There were too few data to look at intervals since the last use of sequential estrogen–progestin replacement therapy or continuous combined replacement therapy.

Type and Dose of Estrogen and Progestin

Conjugated estrogens and medroxyprogesterone acetate were used much more frequently than other estrogens or progestins (79% and 88%, respectively, of all estrogen and progestin use). There was little difference in risk between estrogen replacement therapy given as conjugated estrogens, other oral estrogens, "patch," or injection. Estrogen replacement therapy given as 1.25 mg conjugated estrogen was associated with a slightly higher risk (OR = 2.32; 95% CI = 1.81-2.96) than estrogen replacement therapy given as conjugated estrogen at 0.625 mg (OR = 2.05; 95% CI = 1.73-2.44).

There was evidence of an estrogen and a progestin dose effect in both sequential estrogen–progestin replacement therapy (short progestin use) and sequential estrogen–progestin replacement therapy (long progestin use) regimens. Sequential estrogen–progestin replacement therapy (short progestin use) with conjugated estrogens given at 0.625 mg (low dose) had an OR of 1.68 (95% CI = 1.07-2.65), which is somewhat lower than the overall OR of 1.87 (95% CI = 1.32-2.65); when given with medroxyprogesterone acetate at 10 mg (high dose), the OR was reduced to 1.33 (95% CI = 0.80-2.21). Sequential estrogen–progestin replacement therapy (long progestin use) regimens with conjugated estrogens at 0.625 mg had an OR of 0.90 (95% CI = 0.66-1.23), which is somewhat lower than the overall OR of 1.07 (95% CI = 0.82-1.41); when given with medroxyprogesterone acetate at 10 mg, the OR was reduced to 0.76 (95% CI = 0.49-1.17).

While none of these differences was statistically significant, the pattern was suggestive of a true effect.

Discussion

In this study, the addition of a progestin to estrogen replacement therapy for less than 10 days (effectively 7 days) reduced the increased risk of endometrial cancer associated with unopposed estrogen replacement therapy by only 26%, while the use of a progestin for 10 or more days (effectively 10 days) essentially abolished the increased risk, as did continuous combined replacement therapy. The overall adjusted ORs per 5 years of use of unopposed estrogen replacement therapy and sequential estrogen–progestin replacement therapy (short progestin use, i.e., effectively 7 days) were 2.17 and 1.87, respectively, while the comparable ORs for sequential estrogen–progestin replacement therapy (long progestin use, i.e., effectively 10 days) and continuous combined replacement therapy were both 1.07. The risks were much greater for disease confined to the endometrium, but they were clearly evident for disease involving the myometrium for both estrogen replacement therapy and sequential estrogen–progestin replacement therapy (short progestin use). The high risk for early disease may simply be a mark of increased surveillance; it was not a mark of overdiagnosis, since our pathology review found no evidence that simple hyperplasia

Table 5. Adjusted odds ratios* for subjects who received estrogen replacement therapy by time since last use and subsequent estrogen–progestin replacement therapy use: Endometrial Cancer Study, Los Angeles (1987-1993)

Last hormone replacement therapy use†	Odds ratio (95% confidence interval)‡				
	All stages	Stage IA	Stage IB	Stage IC+	Stage IB+
ERT within last 2 y	2.53 (2.13-2.99)	3.63 (2.71-4.86)	2.66 (2.20-3.22)	1.82 (1.43-2.31)	2.29 (1.94-2.71)
ERT 2-9 y before	1.86 (1.26-2.75)	0.39§ (0.04-4.14)	2.13 (1.29-3.54)	1.73 (1.12-2.66)	1.91 (1.28-2.85)
ERT ⩾10 y before	1.63 (1.04-2.53)	—	1.49 (0.79-2.82)	1.69 (0.97-2.94)	1.61 (1.02-2.53)
SEPRT-SP	1.87 (1.11-3.17)	2.14 (1.16-3.96)	1.86 (1.06-3.26)	1.42 (0.61-3.30)	1.82 (1.03-3.21)
SEPRT-LP or CCRT	1.59 (1.26-2.00)	2.58 (1.69-3.93)	1.41 (1.04-1.93)	1.64 (1.21-2.21)	1.45 (1.14-1.84)

*Per 5 years of use. Adjusted for age at menarche, time to regular cycles, nulliparity, number of full-term pregnancies, total duration of incomplete pregnancies, weight, duration of breast feeding, total duration of premenopausal periods of amenorrhea, smoking, total duration of oral contraceptive use, and age at menopause.

†ERT = estrogen replacement therapy; SEPRT-SP = sequential estrogen–progestin replacement therapy (short progestin use, i.e., <10 days per ''month''); SEPRT-LP = sequential estrogen–progestin replacement therapy (long progestin use, i.e., ⩾10 days per ''month''); CCRT = continuous combined replacement therapy.

‡Stage IA = no invasion beyond endometrium; stage IB = invasion up to first half of myometrium; stage IC+ = invasion past first half of myometrium and/or metastases and/or invasion to cervix; stage IB+ = stage IB plus stage IC+ = invasion of myometrium and/or metastases and/or invasion to cervix.

§Estrogen replacement therapy ⩾2 years before.

was frequently being misdiagnosed as cancer and the results for stage IA tumors were not affected when we restricted attention to cases confirmed by pathology review. Distinguishing hyperplasias with atypia from cancers is clearly difficult, but it is not an important factor in the results presented here.

Of the 833 cases analyzed, 801 were simple adenocarcinomas and 32 had other histologies (i.e., 23 adenosquamous carcinomas, seven papillary serous crystadenocarcinomas, and one each of clear-cell adenocarcinoma and villous adenocarcinoma). As one would expect, excluding the 32 other histology cases from the analysis made little difference to the results because they constitute so few of the total cases. When the 23 case subjects with adenosquamous carcinomas were considered separately, the unadjusted OR for 5 years of estrogen replacement therapy use was only 1.16 ($P = .54$) compared with the overall figure of 1.83 (Table 3), but the difference was not statistically significant.

There have been a few previous reports on the effects of sequential estrogen–progestin replacement therapy, usually with very small numbers of users, but, to our knowledge, there have been no reports on continuous combined replacement therapy. Persson et al. (*6*) found an OR for sequential estrogen–progestin replacement therapy of 0.9 (average use, 2.5 years; 95% CI = 0.4-2.0, based on seven case subjects). Voigt et al. (*7*) found for sequential estrogen–progestin replacement therapy use with less than 10 days of progestin use per month an OR of 2.0 (average use unclear; 95% CI = 0.7-5.3, based on 11 case subjects), while use of progestins for 10 days or more had an OR of 0.9 (average use unclear; 95% CI = 0.3-2.4, based on seven case subjects). Brinton and Hoover (*8*) found an OR of 1.8 for sequential estrogen–progestin replacement therapy use (average use unclear; 95% CI = 0.6-4.9, based on 11 case subjects). In contrast to the results obtained by Voigt et al. (*7*), they found that "Risk did not vary substantially by the number of days per month that progestogens were used." Jick et al. (*9,10*) found an OR for sequential estrogen–progestin replacement therapy use of 1.4 (average use unclear; based on 28 case subjects). Finally, Beresford et al. (*11*) recently added to the study results reported by Voigt et al. (*7*). They again found that short progestin use was associated with an increased risk (OR = 3.1; average use approximately 5 years; 95% CI = 1.7-5.7, based on 25 case subjects), while use of progestins for 10 or more days had an OR of 1.3 (average use approximately 5 years; 95% CI = 0.8-2.2, based on 25 case subjects). These results are in general agreement with those presented here.

What do these results suggest with regard to the mechanism of the protective effect of progestins?

Conjugated estrogens at 0.625 and 1.25 mg/day, unopposed by a progestin, produce endometrial cell proliferation to a degree that approximates that found during the follicular phase of the menstrual cycle (*15*). Medroxyprogesterone acetate at 5 and 10 mg/day reduces such cell proliferation to effectively zero within 6 days (despite continued estrogen) (*16*). This abolition of cell proliferation and the observation that "Seven . . . [is the] number of days that the level of progesterone is above 5 ng/mL in the normal menstrual cycle" (*17*) persuaded many that 7 days of progestin was sufficient to abolish any risk.

However, progestin use for 7 days does not completely remove the risk of hyperplasia. Paterson et al. (*18*) found that with conjugated estrogens at 1.25 mg/day given for 21 days per 28-day cycle the incidence of hyperplasia was 21.0 (per 1000 woman-months), but it declined to 4.0 when a progestin was used for the last 5-7 days, to 1.3 when it was used for 10 days, and to zero when it was used for 13 days. It has been suggested that this variability in response occurs because there is considerable inter-individual variability of uptake and metabolism of medroxyprogesterone acetate (*16*) and because it takes longer than 6 days of progestin treatment to change the morphology of the endometrial cells to a secretory pattern (*19*), although why changing the morphology should be important is not clear.

Key and Pike (*20*) argued that, if endometrial cell proliferation in the basalis (stem-cell) layer was the key to increased risk from estrogen replacement therapy (*21*), then there would still be an increased risk even with 12 or 13 days of progestin use, since there would still be unopposed estrogen for 14 or 15 days per treatment cycle.

If the protection is due to the reduction in cell proliferation, then the effects on endometrial cancer can be estimated on the basis of a mathematical model of endometrial cancer (*22*). In a standard regimen with conjugated estrogens given for 25 days in a 28-day cycle, the total cell proliferation is reduced by 16% (from 25 days to 21 days) with 7 days of progestin and by 28% with 10 days of progestin, based on the time taken by progestin to reduce endometrial cell proliferation to zero. These results translate into reductions in the endometrial cancer risk relative to unopposed estrogen replacement therapy of 11% and 19%—much lower than the 26% and 94% observed (Table 3). If the model parameters are adjusted to fit the 24% reduction observed with sequential estrogen–progestin replacement therapy (short progestin use), then the predicted reduction with sequential estrogen–progestin replacement therapy (long progestin use) is 62%—still much less of a reduction than is observed (Table 3). A simple cell proliferation model (*20*) for endometrial cancer does not appear tenable.

If the protection is due to the reduction in hyperplasia, then the risk of estrogen replacement therapy compared with that of sequential estrogen–progestin replacement therapy may be estimated from the reduction in the incidence of hyperplasia according to the number of days of progestin use. Paterson et al. (*18*) found an 81% reduction in hyperplasia between estrogen replacement therapy (conjugated estrogens at 1.25 mg/day) and sequential estrogen–progestin replacement therapy (short progestin use) and a 94%-100% reduction with sequential estrogen–progestin replacement therapy (long progestin use). We found a much smaller reduction in the risk of endometrial cancer between sequential estrogen–progestin replacement therapy (short progestin use) and estrogen replacement therapy than these results would suggest.

In their studies of endometrial tissue after 7 days of progestin therapy, Flowers et al. (*17*) found that sequential estrogen–progestin replacement therapy (short progestin use) did "not cause all the endometrium to desquamate to the basalis layer . . . [only] 40 to 50% of the functional layer . . . was lost." If these functionalis cells are susceptible to cancer and if a greater proportion of such cells are lost with longer progestin therapy, this could explain the sharp distinction between estrogen–progestin replacement therapy (short progestin use) and estrogen–progestin replacement therapy (long progestin use). It

would also be consistent with the observation of pathologists that stage IA tumors often appear to arise in the functionalis. This possibility could be studied directly and might lead to a deeper understanding of the origin and prevention of endometrial cancer. It would certainly help to predict the effects of proposed regimens in which progestin is added for 13 days every 3 months (*23*).

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Notes

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