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Long-term postmenopausal hormone therapy and endometrial cancer

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Abstract

Estrogen alone therapy (ET) or estrogen and progestin (EPT) as menopausal hormone therapy (HT) has been commonly used to alleviate menopausal symptoms. Treatments containing ≥10 days/month (d/m) of progestin are considered relatively safe with respect to endometrial cancer risk. However, the endometrial safety of long-term EPT regimens is uncertain.

We conducted a case-control study of 311 invasive endometrial cancer cases and 570 controls nested within the California Teachers Study cohort. We used unconditional logistic regression to obtain odds ratios (ORs) and 95% confidence intervals (95%CIs) for the association between long term HT use and endometrial cancer risk and to assess the modifying effect of body mass index (BMI).

Long-term (≥ 10 years) use of ET, sequential EPT with < 10 d/m progestin, and continuous-combined EPT (≥ 25 d/m progestin) were all associated with an elevated risk of endometrial cancer (OR: 4.5; 95%CI: 2.5–8.1, OR: 4.4, 95%CI: 1.7–11.2, and OR: 2.1; 95%CI: 1.3–3.3, respectively; all P for trend < .0001). Risk associated with short-term use was elevated only for ET preparations. The association for continuous-combined EPT was confined to thinner women (BMI < 25 kg/m^2) (P for interaction: 0.03). Among heavier women (BMI ≥ 25 kg/m^2), use of continuous-combined EPT was associated with a statistically nonsignificant reduction in risk.

These findings confirm that long-term use of ET, sequential EPT, or, among normal weight women, continuous-combined EPT is associated with increased risk of endometrial cancer.

INTRODUCTION

Menopausal estrogen therapy (ET) increases the risk of endometrial cancer in postmenopausal women (1–3). Histologic studies, however, have reported significantly reduced endometrial hyperplasia when progestin was added to estrogen in a sequential manner (4–6). Thus, to counteract the adverse effects of ET on the endometrium, combined estrogen-progestin therapy

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(EPT) was introduced in the early 1980s. Initially several different sequential EPT regimens ranging from 5 to 15 days (mostly 7 days) of progestin per month were prescribed (7). By the late 1990s short-sequential EPT (<10 days/month [d/m] progestin) was found to be associated with an increased risk of endometrial cancer (3). Long-sequential EPT (≥10 d/m progestin) or continuous-combined EPT (estrogen and progestin daily) were not associated with such high risk (3,8,9).

More recent studies, published from 2000 onwards, provide inconsistent results on the effect of long-sequential EPT and continuous-combined EPT on endometrial cancer risk. Although two case-control studies (10,11), two randomized clinical trials (12,13), and a large cohort study (14) suggested a null or inverse association between use of continuous-combined EPT and the risk of endometrial cancer, two case-control studies (15,16) and a cohort study (17) found increased risk with long-term use of continuous-combined EPT. Thus the long term safety of these regimens with respect to the endometrium is not clear.

Another remaining question is whether body mass modifies the effect of specific regimens of postmenopausal hormone therapy (HT) on endometrial cancer risk (14,18–20). One hypothesis is that the effect of ET would be minimal among women who already have elevated endogenous estrogen levels due to obesity, while combined EPT might be beneficial against endometrial cancer in obese women. We address these questions using data from the California Teachers Study (CTS).

MATERIALS and METHODS

Study Population

The CTS has been described elsewhere in detail (21). Briefly, the CTS is an ongoing cohort study of current and former female public school teachers and administrators. The cohort was established in 1995–96 when 133,479 women completed a self-administered questionnaire related to women's health. Women were eligible for the current case-control study if they maintained California residence after joining the cohort and had not been previously diagnosed with endometrial cancer or had a hysterectomy.

Eligible cases were identified by linkage between the cohort files and the California Cancer Registry. Women were included in the case group if they were 50–85 years old when diagnosed with an incident first endometrial cancer (ICD-O-3 codes C54.1 and C54.9) between joining the cohort and December 31, 2004. Of 675 eligible cases approached for an interview and asked to provide a DNA specimen, 401 (59%) participated. We were unable to contact 48 (7%) women, 113 (17%) declined to participate, 95 (14%) had died before we were able to contact them, and 18 (3%) were not interviewed for other reasons. Of the 401 interviewed cases we excluded seven women with *in situ* carcinomas and nine women with either endometrial sarcomas or mullerian mixed tumors (ICD-O-3 morphology codes: 8930–8933, 8950, 8980).

Control selection was based on eligibility at pre-determined quarterly selection dates starting on March 31, 1996. Because a portion of the controls were identified during the case ascertainment period, controls were frequency-matched to the expected distribution of cases with respect to age (five-year age groups through 80+), race/ethnicity (white, African American, Hispanic, Asian/Pacific Islander, Native American, and other/mixed), and broad geographic region within California (corresponding to the state's 10 regional cancer registry regions) with interview dates for both cases and controls spread out over the period of case selection. Of 1329 eligible controls selected, 682 (51%) were interviewed and provided a DNA sample. We were unable to contact 170 (13%) women, 359 (27%) declined to participate, 82 (6%) died before we were able to contact them, and 36 (3%) were not interviewed for other reasons, leaving 682 controls for the analyses.

We compared the distribution of patient characteristics and established endometrial cancer risk factors (including age, race/ethnicity, birthplace, body mass index [BMI], height, history of diabetes, age at menarche, age at first full-term pregnancy, parity, oral contraceptive use, menopausal status, and HT use) as assessed on the baseline CTS questionnaire between cases participating in this nested case-control study and CTS cases not participating in the case-control study (and a similar comparison among controls). We found no evidence that cases (or controls) participating in the nested case-control study differed from non-participating cases (or women eligible to be controls) on any of these factors (data not shown).

The case-control study was approved by the Institutional Review Boards of the Northern California Cancer Center and the University of Southern California, and all participants provided signed informed consent.

Data Collection

In addition to the limited exposure data collected from mailed questionnaires from all members of the cohort at baseline, we obtained detailed menstrual, reproductive and hormone use histories from participants in this nested case-control study through interviews using a structured questionnaire. Cases and controls were interviewed in person (91%) or by telephone during the time period February 2002 – May 2007. Lifetime calendars were created during these interviews and used to facilitate the recall of important life-events including dates of HT use. The respondents were shown photographs of common HT formulations (22). For each episode of HT use we obtained detailed information on the: 1) date use started and ended; 2) brand and dosage; 3) number of days per month of usage; and 4) reasons for use. Exposure data were truncated at 12-months prior to diagnosis for cases or selection date for controls (hereafter referred to as the reference date).

Hormone Use

We categorized each episode of postmenopausal HT use based on the number of days per month that the woman used progestin. Four types of HT use were defined: 1) ET: no progestin use; 2) short-sequential EPT: progestin < 10 d/m; 3) long-sequential EPT: progestin 10–24 d/m; and 4) continuous-combined EPT: progestin ≥ 25 d/m. Because the effects of ET and short-sequential EPT were similar ($p = 0.83$), we combined ET and short-sequential EPT (ET/short-sequential) in our secondary analyses.

We calculated total lifetime duration of use of each HT type and categorized the duration of use as no use (never users and users for < 6 months), 6–59 months, 5–9 years, and ≥ 10 years of use.

Age at Menopause

Age at menopause was defined as the age at last menstrual period (LMP) for women who had not used oral contraceptives (OC) or HT within the 12 months prior to their LMP. For women who started using HT while still menstruating, age at menopause was defined as the age at which they started using HT. Eight women had used OCs through their last menstrual period, and their age at menopause was defined as their age at last OC use. Women were considered pre- and peri-menopausal if they reported their LMP within 3 months and 3–12 months of their assigned reference date, respectively.

Statistical analysis

For the present analysis, we excluded women with a prior history of breast cancer (37 cases and 59 controls); women who were pre- or peri-menopausal at reference date (28 cases and 45 controls); women with unknown menopausal status (5 cases and 4 controls) and women with

unknown age at menopause (3 cases and 2 controls). We also excluded women (1 case and 2 controls) who reported having natural menopause before age 35 because it was not clear whether this was secondary amenorrhea or actual menopause. The final data set included 311 cases and 570 controls.

We estimated odds ratios (OR) and 95% confidence intervals (95%CI) using unconditional logistic regression analysis with HT never users as the referent group. Twenty women, classified as never-users, reported using episodes of progestin-only pills in the postmenopausal period, but excluding these women from the referent group did not change the results. The regression models were adjusted for matching factors (age at reference date, race/ethnicity [White, African American, Hispanic], and geographic area of residence) and reference year. In addition, we adjusted our models for the following known or suspected confounders selected *a priori*: number of full-term pregnancies, age at the last full-term pregnancy, BMI at reference date, lifetime duration of OC use, and age at menopause. The categories for the covariates used in the statistical model are the same as the categories reported in table 1 unless otherwise noted. Additional adjustment for hypertension, other medication use, history of endometrial fibroadenoma, and number of previous dilatations and curettages (D&Cs) did not alter the results (not shown).

We defined current use as taking HT for at least six consecutive months within one year of the reference date, and then further evaluated the effect of current use of the various HT types compared to never users. To examine whether the risk of endometrial cancer associated with past ET/short-sequential use was modified if women shifted to continuous-combined regimens, we conducted an analysis restricted to women who were past ET/short-sequential users. We excluded 20 women who used a combination of ET and EPT in the past, were current long-sequential users and used ET in the past, were current ET users and used EPT in the past, or used ET in the past and current HT use was unknown. Past ET/short sequential users (reference group) were compared to women who 1) were current users of ET/short-sequential; or 2) changed formulations to continuous-combined therapy.

To evaluate the modifying effect of BMI, we performed separate analyses using 25 kg/m^2 as the cut point. Tests for trend and interaction were performed using likelihood ratio tests. The reported P-values are two-sided. SAS® 9.2 (SAS Institute, Cary, NC) was used for all analyses.

RESULTS

The characteristics of the study population are provided in table 1. The distribution of known endometrial cancer risk factors followed the expected patterns. Compared to controls, cases were more likely to have later menopausal age and higher BMI, to be nulliparous, to have had their last full-term pregnancy at a younger age and to be less likely to have used oral contraceptives.

A total of 211 cases (68%) and 347 controls (61%) reported using some type of HT (table 2). Use of both ET and short-sequential EPT were strongly associated with increased risk of endometrial cancer, with increasing risk for longer duration of use. The ORs per 5-year use of ET and short-sequential EPT were 1.63 (95%CI: 1.38–1.95) and 1.70 (95%CI: 1.28–2.31), respectively. Use of long-sequential EPT was associated with a small increased risk (OR: 1.10 per 5-year use), but this result was not statistically significant. Since the number of women who used long-sequential EPT was small we did not present the results of this category of HT use in the secondary analyses. Women who used continuous-combined EPT for ≥10 years were twice (95%CI: 1.27–3.30) as likely to develop endometrial cancer as never users and the OR per 5-year use was 1.26 (95%CI: 1.11–1.44). Restricting the analysis to women who reported using only one type of HT did not change our results (data not shown).

ET/short-sequential use was associated with an increased risk both among women with low and high BMI, and the relative risks were of almost equal magnitude (ORs per 5-year use: 1.65 and 1.51 among women with BMI < 25 kg/m^2 and ≥ 25 kg/m^2, respectively) (table 3). Among the continuous-combined EPT users, we observed increased risk with longer duration of use for women with a BMI< 25 kg/m^2 (p for trend = 0.0001) but no effect among heavier women (P for trend: 0.49) (table 3).

Because it is conceivable that specific HT regimens would have different effects whether started around the time of menopause or after menopause, we stratified the data on timing of HT initiation. Among the women who used only one type of HT, there was no difference in the effect of ET/short-sequential between women who started HT within one year of menopause and those who started HT more than a year later (p for interaction = 0.47) (table 4). Among women who had only used continuous-combined EPT, the risk was significantly elevated among women who started continuous-combined EPT within one year of menopause (OR per 5-year: 1.37; 95%CI: 1.16–1.63), but not among those who started continuous-combined EPT later (OR per 5-year: 1.08; 95%CI: 0.82–1.38).

We further addressed the question of whether risk differed for ET/short-sequential users who stopped taking hormones and ET/short-sequential users who switched to continuous-combined EPT or long-sequential EPT (table 5). Although there was some indication that both continuing ET/short-sequential use or shifting to continuous-combined EPT was worse than stopping all hormone use, this finding was no longer statistical significant after we adjusted for duration of ET/short-sequential use.

We also examined whether the increased risk associated with ET decreases with increasing time since last use. Among the past ET users, the OR per 5-year use of ET was 2.21 (95%CI: 1.36– 4.05) for the last episode of HT ending 1–4 years before the reference date and 2.59 (95%CI: 1.60 4.33) for the last HT use ending 5+ years before the reference date.

When analyses were restricted to women who underwent natural menopause, the associations with duration of ET use as well as duration of continuous combined use was even stronger (2.32 per 5 years of ET use and 1.35 per 5 years use of continuous-combined EPT use).

DISCUSSION

In this case-control study of endometrial cancer we observed a statistically significant increased risk associated with long-term use of continuous-combined EPT, which was limited to thinner (BMI < 25 kg/m^2) women. ET and long-term use of short-sequential EPT were associated with significant increased risks of endometrial cancer both in thinner and heavier women.

Sequential Estrogen-Progestin Therapy

Our findings for both short-sequential EPT and long-sequential EPT are consistent with previous studies (3,8,9). The four-fold increased risk for ≥ 10 years of short-sequential EPT use is similar to that in a recent report by Doherty et al. (OR: 5.9; 95%CI: 2.9–12.0) for > 6 years of use (11). Beral and colleagues (14) extensively reviewed the effects of long-sequential EPT (defined as progestin 10–15 d/m). Their meta-analysis, based on 456 cases from six published studies, reported a 1.14 elevation in risk (95%CI: 1.01–1.28) associated with ever-use of long-sequential EPT. We observed a similar although not statistically significant elevation in risk per five years of long-sequential EPT use.

Continuous Combined Estrogen-Progestin Therapy

Findings for the effects of continuous-combined EPT on the risk of endometrial cancer are inconsistent. In general early studies found no association, while several of the newer studies

have reported inconsistent effects. Case-control studies conducted in Seattle (10,11), and Sweden (8) reported reduced risks with continuous-combined EPT of 0.77 (95%CI: 0.45–1.3) for > 6 years of use and 0.2 (95%CI: 0.1–0.8) for ≥ 5 years of use, respectively. On the other hand, Newcomb et al. reported a significant increased risk for women who used EPT with progestin for > 21 d/m (OR: 2.6; 95%CI: 1.27–4.0) (15). A Canadian case-control study (16) and one conducted in Los Angeles (3) both found an elevated but statistically non-significant increased risk associated with ever use and ≥ 2 years of continuous-combined EPT use, respectively.

The results of two cohort studies were also inconsistent for continuous-combined EPT (defined as progestin > 15 d/m). The Million Women Study (14) reported a statistically significant reduced risk (RR: 0.71; 95%CI: 0.56–0.9) based on 73 cases who reported continuous-combined EPT as their last hormone therapy. However, in a smaller US cohort study based on 15 exposed cases, the risk for continuous-combined EPT use was significantly elevated (RR: 2.3; 95%CI: 1.3–4) (17).

Clinical trials have reported a statistically non-significant reduced risk with use of continuous-combined EPT, perhaps because case numbers have been small. The Women's Health Initiative trial, found a decreased risk of postmenopausal endometrial cancer in the continuous-combined EPT arm with a relative risk of 0.81 (95%CI: 0.41–1.22) after 5.6 years of follow-up (12). After 6.8 years of follow-up in the smaller Heart and Estrogen/Progestin Replacement Therapy (HERS II) trial, only two women in the hormone group and eight women in the placebo group developed endometrial cancer (RR: 0.25; 95%CI: 0.05–1.18) (13). However, it is possible that the duration of use in these trials was not sufficient to find the increased risks observed with long term use in several recent observational studies. In our study, continuous-combined EPT did not increase endometrial cancer risk during the first 10 years of use. However, using continuous-combined EPT ≥ 10 years was associated with a significantly increased risk of cancer (OR: 2.05; 95%CI: 1.27–3.30).

It is generally believed that daily use of low-dose progestin opposes the effect of exogenous and endogenous estrogen on the endometrium, resulting in a lower risk of endometrial cancer with the use of a continuous-combined EPT (23). Supporting this hypothesis, several histology studies and randomized trials have reported significantly lower rates of complex and atypical hyperplasia among continuous-combined EPT users when compared to HT never-users (24). However, there is some evidence for epithelial cell proliferation in the endometrium of women using continuous-combined EPT even in the absence of hyperplasia (25–29). Around 85% of continuous-combined EPT users in our study reported using 2.5 or 5 mg of medroxyprogesterone (MPA) as a separate pill. We hypothesize that on a long-term basis, this dose of MPA would not be sufficient to oppose the effect of exogenous estrogen on cell proliferation, and that this is why we observed an increased risk of endometrial cancer in women with long-term continuous-combined EPT use in our study. Consistent with this, we observed the same pattern of increased risk among women who used continuous-combined EPT for more than 10 years whether the women exclusively used MPA 2.5 mg or used MPA of 5mg (results not shown).

Similar to our findings, in the Million Women Study and the National Institutes of Health American Association of Retired Persons (NIH-AARP) Diet and Health Study the risk of endometrial cancer associated with continuous-combined EPT use was lower for obese women (14,30). Obese women have higher levels of endogenous estrogen associated with greater aromatase activity and lower levels of sex-hormone-binding-globulin (SHBG). In these women, the addition of exogenous progestin associated with EPT may work to oppose the already-elevated serum estrogen levels (23,31–33). Key and Pike have suggested that the endometrial response to estrogen has a ceiling beyond which additional estrogen exposure does

not further increase the mitotic activity of the endometrial cells in the basal layer (23). This may explain the significantly lower risks associated with continuous-combined EPT in heavier women. This hypothesis could also explain the observed increase in risk among thin women. Given the low levels of endogenous estrogen among postmenopausal women with a lower BMI, it is possible that the risk associated with long-term use of exogenous estrogen exceeds the protective effect of daily progestin use.

According to the model proposed by Pike et al (34) aging of the endometrium occurs more slowly following menopause. In our study the elevated risk associated with continuous-combined EPT use was higher among women who started HT within one year of their menopause. One could speculate that among these women, the aging of the endometrium continues at the premenopausal rate and that their hormone use postpones the time at which the endometrium goes through estrogen-deprivation and postmenopausal changes.

As in all case-control studies, there is the possibility of recall bias in our study, especially for long-term hormone therapy users and women who used several different types or preparations of HT. To evaluate the role that such bias may have played in our findings, we compared the HT exposure information for women who reported long-term HT use as reported on the case-control questionnaire to that obtained from the same women on the CTS baseline questionnaire. A few cases had discrepancies in their hormone treatment histories between the two assessments. When we redid the case-control analyses excluding these cases, our results did not change, suggesting that it is unlikely that recall bias explained our findings. Also, 4 cases and 11 controls reported using continuous-combined pills (Prempro) before these were available in the United States. However, when we either excluded these women or changed the episodes to ET alone, we found an even higher increased risk associated with combined EPT, indicating that this misclassification of exposure simply introduced a bias towards the null. In order to verify our findings for long-term continuous-combined EPT use in our study, we performed a nested case-control analysis within the CTS, based solely on the baseline questionnaire data, using an incidence-density sampling method. The HT information from self-completed baseline questionnaire was less detailed than that obtained in the nested case-control study which was able to collect information on start and stop dates of HT use and exact formulations. We restricted this analysis to women who were either HT never users or those who reported using progestin $\geq$ 25 d/m. The results of this analysis confirmed our findings (supplementary table). The participation rate for both cases and controls in our study were modest, owing in part to the request for a DNA sample. While we cannot exclude the possibility that the results could have been biased by the participation rates, our cohort analyses and the comparison of interviewed and non-interviewed cases and controls, showing little difference, suggest that this is unlikely.

Our study has several strengths. First, the percentage of postmenopausal CTS members who used HT at baseline (74%) was relatively high (21) providing additional statistical power for evaluating specific patterns of use. We observed a high proportion of continuous-combined EPT users in our population who tended to use this regimen for a longer duration than in other published studies. Second, identification of cancer diagnoses based on the high-quality and highly complete California Cancer Registry reduces the possibility of case-control misclassification in our study. Finally, all of the CTS participants have a college education; thus, they may more accurately report their past hormone-therapy use.

In summary, the results of this study confirm that estrogen alone and sequential EPT increase endometrial cancer risk. Our results also suggest that long term use of continuous-combined EPT may be less safe for the endometrium than initially assumed in normal weight women. However, whether continuous-combined EPT may be beneficial with respect to endometrial cancer risk among obese women remains to be determined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of 311 endometrial cancer cases and 570 controls (nested within the California Teachers Study)

Characteristics	Categories	Cases N (%)	Controls N (%)	P Value*
Age	<55	28 (9.0)	54 (9.5)	
	55–59	58 (18.6)	100 (17.5)	
	60–64	63 (20.3)	101 (17.7)	
	65–69	54 (17.4)	110 (19.3)	
	70–74	55 (17.7)	108 (18.9)	
	75+	53 (17.0)	97 (17.0)	
Race	White	300 (96.5)	525 (92.1)	
	African American	2 (0.6)	9 (1.6)	
	Hispanic	3 (1.0)	17 (3.0)	
	Other	6 (1.9)	19 (3.3)	
Menopause Type	Natural	205 (65.9)	391 (68.6)	
	First HT Use	100 (32.2)	167 (29.3)	
	Other	6 (1.9)	12 (2.1)	0.75
Menopause Age	<47	55 (17.7)	102 (17.9)	
	47–49	57 (18.3)	125 (21.9)	
	50–52	91 (29.3)	192 (33.7)	
	53–55	74 (23.8)	115 (20.2)	
	56+	34 (10.9)	36 (6.3)	0.033
Menarche Age	<12	64 (20.6)	99 (17.4)	
	12	78 (25.1)	162 (28.4)	
	13	104 (33.4)	180 (31.6)	
	14+	65 (20.9)	129 (22.6)	0.58
BMI	<25	142 (45.7)	336 (58.9)	
	25–29	93 (29.9)	163 (28.6)	
	30–34	48 (15.4)	51 (8.9)	
	35+	28 (9.0)	20 (3.5)	<0.001
Parity	Nulliparous	75 (24.1)	108(18.9)	
	Parous	236 (75.9)	462 (81.1)	0.092
Number of Full-Term Pregnancies	0	75 (24.1)	108 (18.9)	
	1	40 (12.9)	70 (12.3)	
	2	95 (30.5)	173 (30.4)	
	3	72 (23.2)	145 (25.4)	

Characteristics	Categories	Cases N (%)	Controls N (%)	P Value*
	4+	29 (9.3)	74 (13.0)	0.19
Age at Last full-Term Pregnancy†	<25	25 (10.6)	42 (9.1)	
	25–29	92 (39.0)	149 (32.3)	
	30–34	85 (36.0)	178 (38.5)	
	35+	34 (14.4)	93 (20.1)	0.053
OC Use	Never Use	187 (60.1)	298 (52.3)	
	<5y	69 (22.2)	120 (21.1)	
	5–9y	37 (11.9)	70 (12.3)	
	10–14y	9 (2.9)	39 (6.8)	
	15+y	9 (2.9)	43 (7.5)	<0.001

*Multivariate logistic regression models adjusted for matching factors (age, race, geographic area of residence, and reference year)

†Additionally, adjusted for total number of full-term pregnancies

Abbreviations: BMI: Body Mass Index; OC: Oral Contraceptive

Table 2

Association between duration of use of postmenopausal hormone therapy (HT) and endometrial cancer by HT type

HT Type	Duration (Years)	N Ca (Co)	OR (95% CI)*	P For Trend
Never		100 (223)	**1 (Ref)**	
ET	< 5	53 (58)	2.42 (1.56–3.77)	
	5–9	17 (21)	2.48 (1.23–5.01)	
	10+	34 (29)	4.46 (2.46–8.11)	<.0001
	Per 5 years		1.63 (1.38–1.95)†	
Short-Sequential EPT	< 5	13 (20)	1.41 (0.65–3.06)	
	5–9	10 (11)	1.87 (0.74–4.73)	
	10+	12 (9)	4.35 (1.68–11.22)	<.0001
	Per 5 years		1.70 (1.28–2.31)†	
Long-Sequential EPT	< 5	4 (12)	0.48 (0.14–1.68)	
	5–9	7 (12)	1.30 (0.46–3.68)	
	10+	4 (16)	0.91 (0.29–2.91)	0.854
	Per 5 years		1.10 (0.75–1.55)†	
Continuous-Combined EPT	< 5	44 (87)	0.86 (0.55–1.35)	
	5–9	27 (67)	0.81 (0.48–1.37)	
	10+	47 (69)	2.05 (1.27–3.30)	0.0006
	Per 5 years		1.26 (1.11–1.44)†	

*Mutually adjusted ORs: adjusted for age, race, reference year, geographic area of residence, menopause age, number of full-term pregnancies, age at the last full-term pregnancy, lifetime oral contraceptive use duration and body mass index

†OR per 5-year use

Abbreviations: ET: Estrogen Therapy; EPT: Estrogen-Progestin Therapy; OR: Odds Ratio; CI: Confidence Interval; Ca: Case; Co: Control; Ref: Reference Group; HT: Hormone Therapy

Table 3

Association between duration of postmenopausal hormone therapy and endometrial cancer by type of HT and BMI

		BMI < 25 kg/m^2		BMI ≥ 25 kg/m^2		
HT Type	**Duration (Years)**	**N Ca (Co)**	**OR (95% CI)***	**N Ca (Co)**	**OR (95% CI)***	**P for Interaction**
Never		26 (126)	**1 (Ref)**	74 (97)	**1 (Ref)**	
ET/Short-Sequential EPT	< 5	27 (45)	2.23 (1.24–3.99)	26 (29)	1.61 (0.86–3.02)	
	5–9	16 (17)	3.86 (1.77–8.42)	8 (14)	1.01 (0.39–2.65)	
	10+	30 (30)	4.86 (2.51–9.41)	18 (8)	4.66 (1.82–11.97)	
			P trend < .0001		P trend = 0.001	
	Per 5 years		1.65 (1.37–2.02)		1.51 (1.19–1.96)	0.459
Continuous-Combined EPT	< 5	19 (56)	0.80 (0.42–1.52)	25 (31)	0.81 (0.43–1.55)	
	5–9	13 (35)	1.27 (0.59–2.71)	14 (32)	0.48 (0.23–1.00)	
	10+	28 (40)	3.03 (1.60–5.73)	19 (29)	1.13 (0.56–2.30)	
			P trend = 0.0001		P trend = 0.49	
	Per 5 years		1.40 (1.18–1.67)		1.09 (0.89–1.32)	0.033

* Mutually adjusted ORs: adjusted for age, race, reference year, geographic area of residence, menopause age, number of full-term pregnancies, age at the last full-term pregnancy, lifetime oral contraceptive use duration and body mass index as a continuous variable

Abbreviations: BMI: Body Mass Index; ET: Estrogen Therapy; EPT: Estrogen-Progestin Therapy; OR: Odds Ratio; CI: Confidence Interval; Ca: Case; Co: Control; Ref: Reference Group; HT: Hormone Therapy

Table 4

Association between lifetime duration of hormone therapy use and endometrial cancer, by delay between menopause and start of hormone therapy.

	Menopause–Hormone Therapy Delay				
	< 1 year		≥ 1 year		
HT Category	**N Ca (Co)**	**OR (95%CI)* per 5-year use**	**N Ca(Co)**	**OR (95%CI)* per 5-year use**	**P for Interaction**
Never Use	100 (223)	**1 (Ref)**	100 (223)	**1 (Ref)**	
ET/Short-Sequential EPT	83 (103)	1.63 (1.38–1.95)	42 (40)	2.00 (1.46–2.79)	0.259
Continuous-Combined EPT	76 (136)	1.35 (1.16–1.58)	42 (87)	1.16 (0.93–1.44)	0.151
ET/Short-Sequential EPT (only)	53 (61)	1.85 (1.50–2.32)	26 (31)	1.86 (1.35–2.65)	0.472
Continuous-Combined EPT (only)	49 (91)	1.37 (1.16–1.63)	28 (76)	1.08 (0.82–1.38)	0.076

*Mutually adjusted ORs per 5 year of use; adjusted for age, race, reference year, geographic area of residence, menopause age, number of full-term pregnancies, age at the last full-term pregnancy, lifetime oral contraceptive use duration and body mass index

Abbreviations: ET: Estrogen Therapy; EPT: Estrogen-Progestin Therapy; OR: Odds Ratio; CI: Confidence Interval; Ca: Case; Co: Control; Ref: Reference Group; HT: Hormone Therapy

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2011 February 1.

Table 5

Association between type of current use of postmenopausal hormone therapy (HT) used and endometrial cancer among women who previously used ET/short-sequential EPT.

Current HT Type	N Ca (Co)	OR (95% CI)*	OR (95% CI)†
Not Current HT User	35 (57)	**1 (Ref)**	**1 (Ref)**
ET/ Short-Sequential EPT User	43 (35)	2.23 (1.16–4.27)	1.77 (0.87–3.61)
Continuous-Combined EPT User	27 (30)	1.65 (0.83–3.27)	1.47 (0.73–2.96)

*Adjusted for, age, menopause age, and lifetime oral contraceptive use duration

†Further adjusted for lifetime duration of ET/ Short-Sequential EPT use

Abbreviations: ET: Estrogen Therapy; EPT: Estrogen-Progestin Therapy; OR: Odds Ratio; CI: Confidence Interval; Ca: Case; Co: Control; Ref: Reference Group; HT: Hormone Therapy