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# Long-term Use of Continuous-Combined Estrogen-Progestin Hormone Therapy and Risk of Endometrial Cancer

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## Abstract

The daily administered dose of progestin in continuous-combined estrogen-progestin therapy is provided to counteract the proliferative effect of estrogen on the postmenopausal endometrium. However, there remains some uncertainty as to whether use of such a combined regimen, over the long-term, is associated with an altered risk of endometrial cancer. We pooled data from four population-based case-control studies of endometrial cancer in western Washington State. Cases, ages 45–74, were diagnosed between 1985 and 2005. Using logistic regression with adjustment for confounding factors, women who had exclusively used continuous-combined estrogen-progestin therapy (90 endometrial cancer cases, 227 controls) were compared to women who had never used any type of hormone therapy (774 cases, 1116 controls). Associations with duration and recency of use were evaluated overall and within strata defined by body mass index. Long-term use of continuous-combined estrogen-progestin therapy (≥10 years) was associated with a reduced risk of endometrial cancer (OR=0.37, 95% CI: 0.21–0.66). This association was most pronounced in women with a body mass index ≥30 kg/m$^2$ (OR=0.19, 95% CI: 0.05–0.68). Associations did not differ according to recency of use. These results suggest that long duration of use of continuous-combined estrogen-progestin therapy is associated with a reduced risk of endometrial cancer risk.

### Keywords

endometrial cancer; hormone therapy; estrogen; progestin; body mass index

## INTRODUCTION

Strong and consistent evidence of an increased risk of endometrial cancer in women using postmenopausal unopposed estrogen hormone therapy (1) led to the introduction of combined estrogen-progestin therapy (EPT). The added progestin in EPT has been observed to counteract the proliferative effect of exogenous estrogen on the postmenopausal endometrium (2–4), offering a benefit over unopposed estrogen therapy with respect to risk of both endometrial hyperplasia (5) and endometrial cancer (6–12). Even now, however,

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there remains some uncertainty as to whether long-term use of EPT results in a risk of endometrial cancer that differs from that in women who have not received hormone therapy.

One common mode of administering EPT involves a daily dose of both estrogen and progestin (i.e., continuous-combined EPT). Given the relatively recent advent of continuous-combined EPT, most studies to date have been limited in their ability to assess the effect of long-term use of this therapy (6–9, 13, 14). Two recent studies have evaluated the association between use of continuous-combined EPT for ≥10 years, with conflicting results (10, 11). In a large case-control study, Jaakkola et al. found an inverse association between continuous-combined EPT use and endometrial cancer risk, even after 10 or more years of use (11). The other recent analysis reported that, while there was no evidence of any increased risk in women who used continuous-combined EPT for <10 years, women who used this therapy exclusively for ≥10 years experienced a 2-fold increased risk of endometrial cancer relative to women who had never used any hormone therapy (10). Although the basis for a possible duration threshold is unclear, it is possible that the low doses of medroxyprogesterone in continuous-combined EPT are insufficient to counteract the proliferative effect of exogenous estrogens over such an extended duration.

We updated a previous analysis exploring the association between postmenopausal EPT use and endometrial cancer risk (8), adding data from a recently completed case-control study to evaluate the association with longer durations of continuous-combined EPT use.

## MATERIALS AND METHODS

### Study Population

We pooled data from four population-based case-control studies of endometrial cancer conducted in Washington State. Although these studies were conducted over different time periods, the protocols and questionnaires used in data collection were similar. Each study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center in Seattle, Washington, and written informed consent was obtained from all study participants.

Details of each of these studies have been published previously (15–19). Briefly, cases were identified through the Cancer Surveillance System, a population-based cancer registry affiliated with the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Eligible cases included women diagnosed with histologically confirmed endometrial adenocarcinoma who resided in King, Pierce, or Snohomish counties of Washington State, and were ages 45–74 years at the time of diagnosis. Previously, we have presented analyses pooling data from three of these four studies (8, 20), including cases diagnosed in 1985–1991, 1994–1995, and 1997–1999. Here we also include data from a more recently completed study, with cases meeting the same eligibility criteria as in the previous studies, but with dates of diagnosis ranging from 2003–2005 (18). Of a total 2,324 eligible cases, 1,716 (74%) were interviewed; 162 women died before they could be contacted for interview and 446 women either declined to be interviewed or had physicians who instructed us to not contact them. Of the 1,716 interviewed cases, one was excluded due to poor quality interview data, one interview was lost, and one was excluded because she was later discovered not to have had endometrial cancer.

Control ascertainment employed multiple sampling schemes for different subsets of the study population. Eligible controls for reference years 1985–1991 (ages 45–74), 1994–1995 (ages 50–64), and 1997–1999 (ages 50–65) were identified using random-digit dialing (RDD), and included women with an intact uterus and no previous endometrial cancer who resided in the same counties as study cases during the reference period; these control

subjects were frequency-matched to cases by five-year age group and county of residence at the reference year (8, 15, 16). The overall RDD response proportion (i.e., screening response × interview response) across these study periods was 73.0%. For the reference years 1994–1995 and 1997–1999, control subjects aged 65–69 years were identified via random selection from Health Care Financing Administration files (N=116, interview response proportion=66%) (8, 16). For the reference years 1994–1995 and 1997–1998, the control population also included a subset of cancer-free controls (with intact uteri) aged 50–64 years from a population-based case-control study of breast cancer [the Contraceptive and Reproductive Experience (CARE) study] (N=252) (17). Interview questions asked of these women with regard to hormone therapy use and the potential confounding factors considered here were similar to those included in the other studies. The overall response proportion among CARE controls ascertained through RDD was 73.8%. Lastly, controls for reference years 2003–2005 were a subset of the control population from a population-based case-control study of ovarian cancer, described in detail elsewhere (19); these controls were also identified using RDD and were originally frequency-matched to ovarian cancer cases based on age and county of residence. For the present analysis, this latter subset of controls was restricted to women aged 50–74 years with an intact uterus, who resided in the same counties and were interviewed during the same time frame as interviewed cases. The overall RDD response proportion in these controls was 69.0%. In total, interviews were completed by 2,135 controls; one control was later found to be ineligible and was excluded from the present analysis.

## Exposure Assessment

Cases and controls participating in each study completed a structured in-person interview which included questions about demographic factors, height, weight, medical and reproductive history, and medication use prior to the diagnosis date (cases) or reference date (controls). Assessment of hormone therapy use included detailed questions about the duration, timing, indication, and regimen of therapy, and allowed for separate reporting of multiple usage periods differing in formulation and/or separated in time. To aid participants in recalling details of their past medication use, particularly hormone therapy use, we used photograph books of common medications and provided a life events calendar.

Women who reported having never used hormone therapy or who reported use of hormone therapy for a cumulative duration less than six months were grouped together as never users of hormone therapy. We classified women as being exclusive users of continuous-combined EPT if they reported having used a continuous-combined EPT regimen (i.e., progestational agent received cyclically ≥25 days per month) for ≥6 months, and had not used any other hormone therapy regimen for ≥6 months. Women who used continuous-combined EPT but reported having also used some other hormone therapy regimen for ≥6 months were excluded (95 cases, 138 controls). For the present analysis, we excluded use of hormone therapy prior to age 44 years that was not for menopausal symptoms.

In addition to the above restrictions, we excluded interview data from women who reported exclusive use of any hormone regimen other than continuous-combined EPT for ≥6 months, including: unopposed estrogen therapy (360 cases, 189 controls), EPT that included <25 days of progestin per month (139 cases, 196 controls), EPT with an unknown or non-monthly cycle of progestin (29 cases, 23 controls), unopposed progestin or androgen therapy (28 cases, 33 controls), or non-oral/non-patch hormonal preparations (e.g., creams or injections) (65 cases, 74 controls). Interview data from women who used any combination of the formulations above (i.e., not continuous-combined EPT) were also excluded (101 cases, 92 controls). We excluded women who used no single regimen for 6 months but still had a total duration of hormone therapy use ≥6 months (7 cases, 5 controls), women who could not identify the type of hormone therapy they had used for ≥6 months (14 cases, 18

controls), and women who could not recall the duration of their hormone therapy use (2 cases, 4 controls). Another 9 cases and 19 controls were excluded because they had used a drug for menopausal symptoms but could not recall whether it was hormone therapy. The total exclusions correspond to 37% of the combined controls. Thus, this analysis was based on a sample of 864 cases and 1,343 controls.

### Statistical Analysis

We used unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) comparing exclusive users of continuous-combined EPT to women who had never used any type of hormone therapy. We assessed the association between duration of use (never use/0.5–<5 years/5–<10 years/≥10 years), recency of use (never use/<2 years/≥2 years since last use), and endometrial cancer risk; we also evaluated these variables in combination. In light of prior studies suggesting effect modification by body mass index (BMI) (8–10, 12, 13), age (12, 13), and smoking history (12, 13), we repeated the former two of these analyses within BMI strata (<25.0/25.0–29.9/≥30.0 kg/m$^2$), and within strata defined by age at the reference date (<60/≥60 years) and smoking status at the reference date (current smoker/not a current smoker).

We adjusted all regression models for the variables used in frequency-matching (five-year age group at the reference date, county of residence, reference year), and for other potential confounding variables that altered main effect coefficient estimates by at least 10%. Specifically, we assessed potential confounding by BMI (<25.0/25.0–29.9/≥30.0 kg/m$^2$), parity, duration of oral contraceptive use (none/≤5 years/>5 years), education (<high school/high school graduate/college graduate), race (white/non-white), age at menarche (<12/12–13/≥14 years), history of infertility (yes/no), and smoking history (never smoker/former smoker/smoker within 5 years of reference year). Among the variables assessed, only BMI met pre-specified criteria for inclusion in the multivariate model. We also assessed confounding by the variables noted above in analyses stratified by BMI and found no additional variables met our criteria for inclusion in stratum-specific models. We performed all analyses using STATA SE version 11.0 (College Station, Texas).

## RESULTS

Characteristics of the study population are presented in Table 1 by case and exposure status. Compared to women who had never used any type of hormone therapy, exclusive users of continuous-combined EPT were more likely to have graduated from college (42% versus 30%, respectively, among controls), had lower BMI (60% versus 54% with BMI <25.0 kg/m$^2$), and were more likely to have used oral contraceptives for >5 years (36% versus 21%). Within strata defined by use of hormone therapy, cases were more likely than controls to be nulliparous (19% versus 13%, respectively, in never users of hormone therapy, 21% versus 11% in users of continuous-combined EPT), more likely to have a BMI ≥30 kg/m$^2$ (50% versus 20%, 23% versus 15%), and less likely to be current or recent smokers (12% versus 20%, 11% versus 17%).

Women who had used continuous-combined EPT for ≥6 months had a lower risk of endometrial cancer than women who had never used any hormone therapy (OR=0.50, 95% CI: 0.37–0.67) (Table 2). This lower risk persisted in women with prolonged use of continuous-combined EPT; in women who had used continuous-combined EPT exclusively for ≥10 years, the odds ratio was 0.37 (95% CI: 0.21–0.66). There was no evidence of a difference in the size of the association with continuous-combined EPT use according to recency of use (OR=0.53, 95% CI: 0.38–0.74, and OR=0.41, 95% CI: 0.24–0.71, for use within the last 2 years or ≥2 years ago, respectively). When exposure to continuous-combined EPT was jointly stratified by recency and duration of use, the reduced risk

associated with long-term use (i.e., ≥10 years) persisted among recent users (OR=0.55, 95% CI: 0.30–1.00) (results not shown). For all comparisons, associations were slightly stronger when analyses were restricted to the most recent 2003–2005 study population. Controls from that study population accounted for 13% of hormone therapy never users and 40% of continuous-combined EPT ever users in the combined control population. Cases from the 2003–2005 study accounted for 31% of hormone therapy never users and 42% of continuous-combined EPT users in the overall case population.

There was a reduced risk associated with use of continuous-combined EPT regardless of BMI (Table 3); however, the risk reduction appeared to be greatest among women with a BMI ≥30 kg/m$^2$ (OR=0.26, 95% CI: 0.14–0.47). Associations for long-term use of continuous-combined EPT were limited by small numbers, but also suggested a reduced risk across BMI strata (OR=0.47, 95% CI: 0.20–1.07; OR=0.48, 95% CI: 0.17–1.33; OR=0.19, 95% CI: 0.05–0.68 for BMI <25.0, 25.0–29.9, and ≥30 kg/m$^2$, respectively). There were no differences in the associations with ever use or duration of use of continuous-combined EPT by age or smoking status (results not shown).

## DISCUSSION

In this pooled analysis of data from four case-control studies, we found evidence of a reduced risk of endometrial cancer associated with use of continuous-combined EPT, even after very long durations of use (≥10 years). This analysis builds upon the previously conducted studies pooled here (8, 15, 16). Given temporal shifts favoring continuous-combined EPT over sequential EPT (i.e., less than 25 days of administered progesterone per month) and unopposed estrogen therapy, adding data from the most recent of the four studies (2003–2005) allowed us to focus on associations with continuous-combined EPT, and to consider longer durations of use than had been possible in our earlier studies.

The results presented here should be considered in the context of study limitations. Differential recall or reporting of exposure history among cases versus controls is a possible source of bias that could have influenced results; however, we attempted to minimize such bias through the use of validated memory aides (21, 22), including life events calendars and photograph books of different hormone therapy preparations. Misclassification of BMI is also possible since this measure was based on self-reported height and weight; however, given that our analyses were adjusted for or stratified by broad categories of BMI, we expect the impact of such misclassification to be minor. Selection bias is possible if the otherwise eligible cases and controls who refused participation in these studies differed from study participants in their exposure to different hormone therapy regimens. Generalizability of our findings is also impacted by the fact that we excluded women who had used other hormone therapy regimens in addition to continuous-combined EPT. Lastly, although we grouped together all women who had exclusively used continuous-combined EPT, it is possible that associations could vary across specific formulations of this therapy according to dosage of estrogen and progestin. Assessment of specific continuous-combined EPT formulations was beyond the scope of this analysis; however, in a previous analysis within this study population, Reed et al. reported no increased risk of endometrial cancer among users of continuous-combined EPT regardless of whether the hormonal formulation provided a monthly dose of medroxyprogesterone acetate <75 mg or ≥75 mg (23).

Prior observational studies have explored the possible association between use of continuous-combined EPT and endometrial cancer, with varying results. Specifically, while several studies have reported either no increased risk (6, 9, 24) or a modest decreased risk (7, 11–13, 20) of endometrial cancer associated with use of continuous-combined EPT, three have reported an increased risk (10, 14, 25). In a prior analysis including three of the studies

pooled here, we reported a reduced risk of endometrial cancer among exclusive users of continuous-combined EPT (OR=0.59, 95% CI: 0.40–0.88; N=52 exposed cases and 138 exposed controls), with a suggestion of a reduced risk among women who had used continuous-combined EPT for ≥6 years (OR=0.77, 95% CI: 0.45–1.3; N=27 exposed cases and N=56 exposed controls) (8). In a meta-analysis of studies prior to that publication, Beral et al. reported a relative risk of 0.88 (95% CI: 0.75–1.03) associated with use of continuous-combined EPT (13). Also consistent with these findings, Jaakkola et al. recently reported a relative risk of 0.57 (95% CI: 0.37–0.88) associated with use of continuous-combined EPT for 5–10 years and a relative risk of 0.79 (95% CI: 0.61–1.02) for use ≥10 years (11). In contrast, however, a recent case-control study nested within the California Teachers Study found a 2.1-fold (95% CI: 1.3–3.3) increased risk of endometrial cancer in women who had exclusively used continuous-combined EPT for ≥10 years relative to women who had never used any hormone therapy, noting that this association was limited to women with a BMI <25.0 kg/m$^2$ (10). Reasons for the inconsistencies across studies are not entirely clear. It is likely that small numbers of exposed individuals, differences in study population demographics, and differences in definitions of what constitutes continuous-combined EPT and what constitutes long-term use are responsible for some between-study variability.

The results presented here are consistent with those of the two randomized trials to have assessed the association between continuous-combined EPT and endometrial cancer (26, 27). The Women's Health Initiative (26) and the Heart and Estrogen/Progestin Replacement Therapy (27) trials observed a reduced risk of endometrial cancer associated with use of continuous-combined EPT [hazard ratio (HR)=0.81, 95% CI: 0.41–1.22, and HR=0.25, 95% CI: 0.05–1.18, respectively]. Both trials were limited by small case numbers (N=58 and N=10, respectively) and a shorter duration of exposure than has been examined in most observational studies. However, when considered in the context of findings from observational and histologic studies, these trials are part of a collective literature that, while not entirely consistent, is more heavily weighted towards indicating that continuous-combined EPT use is not associated with an increased risk of endometrial cancer.

The progestational agent in EPT is provided to oppose the proliferative effects of estrogen on the postmenopausal endometrium: progestins are known to mediate renewal of the endometrial epithelium and reduce the concentration of estrogen receptors (28). The provision of a daily progestin dose in continuous-combined EPT is thus expected to reduce the endometrial mitotic rate compared to what would be observed in the presence of sequential EPT (where progestin is given for fewer days per month) and unopposed estrogen therapy. If the progestin component in continuous-combined EPT truly is effective in opposing the proliferative effects of the estrogen component, it is plausible that users of continuous-combined EPT would experience no increased risk of endometrial cancer compared to never users of hormone therapy, as we found. The fact that we observed continuous-combined EPT to be associated with a reduced risk of endometrial cancer suggests that the opposing effect of the daily added progestin may have further benefit beyond countering the effects of the daily estrogen component in this therapy. Specifically, it is possible that this added progestin may also oppose some of the proliferative effects of endogenous estrogens; this possibility is consistent with the fact that we found the reduced risk associated with use of continuous-combined EPT to be most pronounced among obese women, given that adipose tissue is the principal source of endogenous estrogens in postmenopausal women.

Despite some ambiguity in the literature, several studies have now suggested that long-term use of continuous-combined EPT is not associated with an increased risk of endometrial cancer and may be associated with a reduced risk. The results of this analysis further weight the collective evidence in the direction of no increased risk.

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## Table 1

Characteristics of Cases and Controls in Relation to History of Hormone Therapy Use, Seattle, Washington, 1985–2005

| | Never users of any hormone therapy | | Users of continuous-combined EPT[a] | |
|---|---|---|---|---|
| | Cases (N=774) N (%) | Controls (N=1116) N (%) | Cases (N=90) N (%) | Controls (N=227) N (%) |
| **Age (years)** | | | | |
| 45–49 | 60 (8) | 115 (10) | 0 (0) | 2 (1) |
| 50–54 | 187 (24) | 290 (26) | 20 (22) | 57 (25) |
| 55–59 | 175 (23) | 236 (21) | 33 (37) | 65 (29) |
| 60–64 | 161 (21) | 215 (20) | 22 (24) | 60 (26) |
| 65–69 | 147 (19) | 179 (16) | 11 (12) | 36 (16) |
| 70–74 | 44 (6) | 81 (7) | 4 (4) | 7 (3) |
| **Education** | | | | |
| < High school | 70 (9) | 110 (10) | 5 (6) | 14 (6) |
| High school graduate | 246 (31) | 315 (28) | 16 (18) | 55 (24) |
| Some college | 245 (32) | 355 (32) | 25 (28) | 63 (28) |
| College graduate | 213 (28) | 366 (30) | 44 (49) | 95 (42) |
| **Body mass index (kg/m$^2$)** | | | | |
| < 25.0 | 193 (25) | 600 (54) | 41 (46) | 136 (60) |
| 25.0 – 29.9 | 195 (25) | 290 (26) | 28 (31) | 58 (26) |
| ≥ 30.0 | 381 (50) | 221 (20) | 21 (23) | 33 (15) |
| Unknown | 5 | 5 | 0 | 0 |
| **Age at menarche (years)** | | | | |
| ≤ 11 | 204 (26) | 244 (22) | 18 (20) | 50 (22) |
| 12 | 212 (27) | 278 (25) | 20 (22) | 52 (23) |
| ≥ 13 | 358 (46) | 593 (53) | 52 (58) | 125 (55) |
| Unknown | 0 | 1 | 0 | 0 |
| **Oral contraceptive use** | | | | |
| Never use | 450 (59) | 629 (57) | 34 (38) | 67 (30) |
| Ever use: | | | | |
| 6 months – 5 years | 203 (26) | 250 (23) | 35 (39) | 78 (35) |
| > 5 years | 114 (15) | 231 (21) | 20 (22) | 81 (36) |
| Unknown | 7 | 6 | 1 | 1 |
| **Parity** | | | | |
| Nulliparous | 145 (19) | 146 (13) | 19 (21) | 26 (11) |
| 1 | 92 (12) | 128 (11) | 14 (16) | 20 (9) |
| 2 | 217 (28) | 325 (29) | 30 (33) | 79 (35) |
| ≥ 3 | 319 (41) | 517 (46) | 27 (30) | 102 (45) |
| Unknown | 1 | 0 | 1 | 0 |
| **Age at first birth (years)** | | | | |
| Nulliparous | 145 (19) | 146 (13) | 19 (21) | 26 (11) |

| | Never users of any hormone therapy | | Users of continuous-combined EPT[a] | |
|---|---|---|---|---|
| | Cases (N=774) N (%) | Controls (N=1116) N (%) | Cases (N=90) N (%) | Controls (N=227) N (%) |
| < 20 | 148 (19) | 156 (14) | 13 (14) | 36 (16) |
| 20 – 24 | 306 (40) | 445 (40) | 32 (36) | 89 (39) |
| ≥ 25 | 174 (23) | 369 (33) | 26 (29) | 76 (33) |
| Unknown | 1 | 0 | 0 | 0 |
| **Cigarette smoking status** | | | | |
| Never smoker | 448 (58) | 534 (48) | 57 (63) | 116 (51) |
| Former smoker | 234 (30) | 359 (32) | 23 (26) | 73 (32) |
| Current/recent smoker | 92 (12) | 223 (20) | 10 (11) | 38 (17) |

[a] EPT = estrogen-progestin therapy

**Table 2**

Exclusive Continuous-Combined EPT Use and Endometrial Cancer Risk, by Duration and Recency of Use, for the 2003–2005 Study and for Combined Studies from 1985–2005[a]

| | 2003–2005 Only | | | Overall (1985–2005) | | |
|---|---|---|---|---|---|---|
| | Case N (%)[b] | Control N (%)[b] | OR (95% CI)[c] | Case N (%)[b] | Control N (%)[b] | OR (95% CI)[c] |
| Never used any hormone therapy | 238 | 146 | 1.0 (ref) | 774 | 1116 | 1.0 (ref) |
| Used continuous-combined EPT | 38 | 90 | 0.32 (0.20–0.50) | 90 | 227 | 0.50 (0.37–0.67) |
| *Duration of use (years)* | | | | | | |
| 0.5 – < 5 | 21 (55) | 37 (41) | 0.43 (0.24–0.80) | 41 (46) | 108 (48) | 0.46 (0.31–0.69) |
| 5 – < 10 | 11 (29) | 24 (27) | 0.37 (0.17–0.80) | 31 (34) | 61 (27) | 0.69 (0.43–1.12) |
| ≥ 10 | 6 (16) | 29 (32) | 0.14 (0.05–0.35) | 18 (20) | 58 (26) | 0.37 (0.21–0.66) |
| *Recency of use (years)* | | | | | | |
| < 2 | 16 (42) | 50 (56) | 0.27 (0.14–0.51) | 66 (73) | 177 (78) | 0.53 (0.38–0.74) |
| ≥ 2 | 22 (58) | 40 (44) | 0.37 (0.20–0.68) | 24 (27) | 50 (22) | 0.41 (0.24–0.71) |

[a] EPT = estrogen-progestin therapy

[b] % corresponds to proportion of continuous-combined EPT users

[c] Adjusted for age at reference date, county of residence, reference year, and body mass index

**Table 3**

Exclusive continuous-combined EPT use and endometrial cancer risk, by BMI, Seattle, Washington, 1985–2005[a]

| | BMI < 25.0 kg/m$^2$ | | | BMI 25.0–29.9 kg/m$^2$ | | | BMI ≥ 30.0 kg/m$^2$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | Case N (%)[b] | Control N (%)[b] | OR (95% CI)[c] | Case N (%)[b] | Control N (%)[b] | OR (95% CI)[c] | Case N (%)[b] | Control N (%)[b] | OR (95% CI)[c] |
| Never used hormone therapy | 193 | 600 | 1.0 (ref) | 195 | 290 | 1.0 (ref) | 381 | 221 | 1.0 (ref) |
| Used continuous-combined EPT | 41 | 136 | 0.67 (0.44, 1.0) | 28 | 58 | 0.56 (0.33, 0.96) | 21 | 33 | 0.26 (0.14, 0.47) |
| *Duration of use (years)* | | | | | | | | | |
| 0.5 – < 5 | 17 (41) | 63 (46) | 0.63 (0.35, 1.1) | 11 (39) | 28 (48) | 0.43 (0.20, 0.93) | 13 (62) | 17 (52) | 0.33 (0.19, 0.57) |
| 5 – < 10 | 16 (39) | 37 (27) | 0.94 (0.49, 1.8) | 11 (39) | 15 (26) | 0.91 (0.39, 2.1) | 4 (19) | 9 (27) | 0.19 (0.06, 0.64) |
| ≥ 10 | 8 (20) | 36 (26) | 0.47 (0.20, 1.1) | 6 (21) | 15 (26) | 0.48 (0.17, 1.3) | 4 (19) | 7 (21) | 0.19 (0.05, 0.68) |
| *Recency of use (years)* | | | | | | | | | |
| < 2 | 34 (83) | 105 (77) | 0.77 (0.49, 1.2) | 21 (75) | 48 (83) | 0.54 (0.30, 0.98) | 11 (52) | 24 (73) | 0.22 (0.10, 0.47) |
| ≥ 2 | 7 (17) | 31 (23) | 0.39 (0.16, 0.95) | 7 (25) | 10 (17) | 0.63 (0.22, 1.8) | 10 (48) | 9 (27) | 0.34 (0.13, 0.89) |

[a] EPT = estrogen-progestin therapy; BMI = body mass index

[b] % corresponds to proportion of continuous-combined EPT users

[c] Adjusted for age at reference date, county of residence, and reference year