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Estrogen plus progestin hormone therapy and ovarian cancer: a complicated relationship explored

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Access Description

Data may be obtained contingent upon approval by appropriate Institutional Review Boards and study Principal Investigators. The data and computing code may be obtained from the corresponding author on request.

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Abstract

Background: Menopausal estrogen–alone therapy is a risk factor for endometrial and ovarian cancers. When a progestin is included with the estrogen daily (continuous estrogen–progestin combined therapy), there is no increased risk of endometrial cancer. However, the effect of continuous estrogen–progestin combined therapy on risk of ovarian cancer is less clear.

Methods: We pooled primary data from five population-based case–control studies in the Ovarian Cancer Association Consortium, including 1,509 postmenopausal ovarian cancer cases and 2,295 postmenopausal controls. Information on previous menopausal hormonal therapy use, as well as ovarian cancer risk factors, was collected using in-person interviews. Logistic regression was used to assess the association between use of continuous estrogen–progestin combined therapy and risk of ovarian cancer by duration and recency of use and disease histotype.

Results: Ever postmenopausal use of continuous estrogen–progestin combined therapy was not associated with increased risk of ovarian cancer overall (OR=0.85, 95% CI 0.72–1.0). A decreased risk was observed for mucinous ovarian cancer (OR=0.40, 95% CI 0.18–0.91). The other main ovarian cancer histotypes did not show an association (endometrioid: OR=0.86, 95% CI 0.57–1.3, clear cell: OR=0.68, 95% CI 0.40–1.2, serous: OR=0.98, 95% CI 0.80–1.2).

Conclusions: Given that estrogen–alone therapy has been shown to be associated with increased risk of ovarian cancer, these findings are consistent with the hypothesis that adding a progestin each day ameliorates the carcinogenic effects of estrogen on the cells of origin for all histotypes of ovarian cancer.

Keywords

Estrogen–progestin hormone therapy; Ovarian cancer; Hormones; Estrogen; Progesterone

Introduction

Menopausal hormonal therapy, either in the form of estrogen–alone therapy or estrogen–progestin combined therapy, supplements the decreased levels of naturally occurring estrogen (and progesterone hereafter referred to as a progestin) after menopause and is highly effective in treating menopausal symptoms. The progestin component of estrogen–progestin combined therapy is given either each day with the estrogen (continuous estrogen–progestin combined therapy), or sequentially, with the estrogen given most days and the progestin given generally between 5 to 15 days, most commonly 10 to 12 days, a month (sequential estrogen–progestin combined therapy).

Observational epidemiologic studies have suggested that estrogen–progestin combined therapy use increases breast cancer risk[1] and this was confirmed by the Women's Health Initiative (WHI) randomized trial of continuous estrogen–progestin combined therapy.[2] Despite these findings, a substantial number of women in the United States (U.S.) have continued using estrogen–progestin combined therapy.[3] Among women with an intact uterus, estrogen–progestin combined therapy is the standard hormonal therapy treatment regimen as estrogen–alone therapy is a confirmed risk factor for endometrial cancer and the addition of the progestin counteracts this effect.[4] When the effect of estrogen–progestin combined therapy on endometrial cancer risk was evaluated according to type of regimen (i.e., sequential versus continuous), sequential estrogen–progestin combined therapy was still associated with an increased risk, although a much lower increased risk than from estrogen–alone therapy, whereas continuous estrogen–progestin combined therapy was associated with no increased risk[5] and more likely a decreased risk.[4]

It has long been hypothesized that progestins are protective with respect to ovarian carcinoma (ovarian cancer) risk.[6] Although there is some evidence to suggest that, like endometrial cancer, adding a progestin ameliorates the effect of estrogen–alone therapy on ovarian cancer risk,[7] the most recent overview analysis by the Collaborative Group on Epidemiological Studies on Ovarian Cancer (Collaborative Group) found the same level of increased risk of ovarian cancer among women who used estrogen–progestin combined therapy as among women who used estrogen–alone therapy.[8]

Studying estrogen–progestin combined therapy can be problematic. Estrogen–alone therapy was first used in the 1960s and it was not until the late 1970s that sequential estrogen–progestin combined therapy began to be commonly used; continuous estrogen–progestin combined therapy was only introduced around 1985. This would not be a problem if recall of hormonal therapy use was error-free, but in our observational studies,[9] we noted women reporting use of a continuous estrogen–progestin combined therapy regimen when this regimen was not typically prescribed (i.e., before 1985) and starting a particular continuous estrogen–progestin combined therapy formulation (e.g., PremPro®) that was not available at that calendar time. In many instances, it appears that women had changed their hormonal therapy formulations over time and were reporting those used at a later date back to an earlier time when they were on other formulations. Thus, when trying to untangle the effects of continuous estrogen–progestin combined therapy from sequential estrogen–progestin combined therapy and estrogen–alone therapy, careful consideration of these issues is required.

We have previously carried out a detailed analysis of estrogen–alone therapy and ovarian cancer risk taking these issues into account using ten epidemiologic studies in the Ovarian Cancer Association Consortium (OCAC), an international collaboration of ovarian cancer studies (http://ocac.ccge.medschl.cam.ac.uk/). That analysis showed that estrogen–alone therapy use was associated with an increased risk of serous and endometrioid ovarian cancers in a duration–response fashion, whereas there was no association with mucinous or clear cell ovarian cancers.[10] We now present the results of a similar pooled analysis of the association between continuous estrogen–progestin combined therapy and ovarian cancer risk using primary data from five of these OCAC studies which included detailed information on the type of estrogen–progestin combined therapy; we did not examine the effects of sequential estrogen–progestin combined therapy in this analysis due to small numbers. We also present the results by histotype, as the effects of many risk factors including the effects of estrogen–alone therapy use differ by histotype.

Materials and Methods

All studies included in this report obtained institutional ethics committee approval. All participants provided written informed consent.

Study Populations

Of the ten epidemiologic studies included in our previous analysis of the effect of estrogen–alone therapy on ovarian cancer risk, seven studies asked detailed questions regarding estrogen–progestin combined therapy use. However, because one study did not record

hysterectomy status and a second study did not record age at menopause, the analysis reported here only included five of these studies, all U.S. population-based case–control studies. Details of each included study have been published previously; their main characteristics and any overlap with the Collaborative Group's meta-analysis are summarized in Table 1. [9,11–14]

Cases were women with a primary first diagnosis of invasive ovarian, fallopian tube, and peritoneal tumors. Serous, endometrioid, clear cell, and mucinous epithelial tumors, as well as invasive epithelial ovarian cancers that were not classified in their original pathology reports as one of these four histotypes, were included in our analyses. Controls were women who reported having at least one intact ovary and who had not been diagnosed with ovarian cancer at or before the date of interview.

Only women recorded as postmenopausal at the reference date (date of diagnosis for cases, date of interview for controls) were included in this analysis. The sample was further restricted to non-Hispanic white, Hispanic white, or black women with no history of a second primary cancer other than non-melanoma skin cancer. A total of 7,030 postmenopausal women (2,818 ovarian cancer cases and 4,212 controls) met these inclusion criteria. Because we were interested in examining the effects of continuous estrogen–progestin combined therapy exposure alone, we had the following additional exclusion criteria: having had a hysterectomy (n=1,482), previous use of estrogen–alone therapy (n=815) or non-continuous forms of estrogen–progestin combined therapy (n=746), and missing or unknown hormonal therapy information (n=79). We also further excluded women who reported using continuous estrogen–progestin combined therapy prior to 1985 (n=140) as this regimen was rarely used before that time. Our final study set included 1,509 ovarian cancer cases and 2,295 controls. A flowchart detailing these exclusions is presented in eFigure 1.

Exposure and Covariate Information

Continuous estrogen–progestin combined therapy users were defined as those who used progestins each day estrogen was used (25 days or more per month); progestin dose and type of progestin were not considered since this information was not available to us. Duration of continuous estrogen–progestin combined therapy use was determined by summing all episodes of use with the total duration categorized as never use, 1 month to <5 years, and 5+ years of use. Continuous estrogen–progestin combined therapy use was also categorized according to its recency of use; we classified current users as those who used it within the previous 2 years and past users as those who last used it 2 or more years prior to their reference date.

All data pertaining to hormonal therapy use as well as potential confounding variables were self-reported at in-person interviews. The questions used to ascertain hormonal therapy use are presented in eTable 1. The questionnaire data considered only hormonal therapy use prior to each woman's reference date. Age, race/ethnicity, education, oral contraceptive (OC) use, parity, endometriosis, tubal ligation, age at menopause, family history of breast or ovarian cancer, and body mass index (BMI (kg/m^2); typically, 1 year before the woman's reference date) were selected a priori as potential confounders. Family history of breast or

ovarian cancer did not affect the relationship between continuous estrogen–progestin combined therapy and ovarian cancer risk and was not included in the final models. There were very limited missing data for the confounders with the exception of age at menopause. Women missing data on potential confounders, with the exception of age at menopause, were excluded (n=42).

All women included in the analysis were recorded at interview as postmenopausal. The age at menopause of 350 women were recorded (i.e., self-reported) as the same age they began continuous estrogen–progestin combined therapy use. There were 329 women (~9%) who were recorded as being postmenopausal but did not have an age at menopause recorded when interviewed. For analysis purposes, among the women missing age at menopause who used continuous estrogen–progestin combined therapy, their age at menopause was coded as either the age at starting continuous estrogen–progestin combined therapy or age 50, whichever was earlier. For women missing age at menopause who did not use continuous estrogen–progestin combined therapy, we coded their age at menopause as the reference age for those under the age of 50 and as age 50 for those 50 years and older. We conducted sensitivity analyses to evaluate the possible effects of these coding decisions, including restricting the analysis to women with a reported age at menopause, assigning an age of 48 and 52 as the age at menopause for those women missing this information, and for women whose age at menopause matched their age at starting continuous estrogen–progestin combined therapy, assigning an age at menopause of 48, 50, and 52 and excluding their continuous estrogen–progestin combined therapy use prior to that age. The results were not materially affected no matter which approach was used to consider age at menopause.

Because age at menopause is an important risk factor for ovarian cancer and is characterized by major changes in endogenous hormone levels, the effects of continuous estrogen–progestin combined therapy when used before menopause could differ from its effects when used after menopause when endogenous hormone levels are much lower.[15] Hence, we ignored use of continuous estrogen–progestin combined therapy before menopause. Women whose only reported use was prior to their age at menopause (n=56) were included in the never user group. We also carried out analyses excluding them and the risk estimates were not materially affected.

Statistical Analysis

We conducted a pooled analysis using logistic regression and calculated odds ratios (ORs), as estimates of relative risk (RRs), and 95% confidence intervals (CIs) to estimate the effect of continuous estrogen–progestin combined therapy use on risk of ovarian cancer. All models were stratified on study, age in 5-year categories (<40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75+), race/ethnicity (non-Hispanic white, Hispanic white, black), and education level (less than high school, high school graduate, some college, college graduate). We also adjusted for duration of OC use (never, 1 month to <5 years, 5 to <10 years, 10+ years), BMI (<18.5, 18.5–24.9, 25–29.9, 30+ kg/m^2), tubal ligation (yes/no), history of endometriosis (yes/no), age at menopause, and parity (0, 1, 2+ births). This was done for ovarian cancer overall as well as for the four main histotypes. We also evaluated the effects of recency and duration of continuous estrogen–progestin combined therapy use.

All tests of statistical significance were two-sided. The analyses were performed using SAS software, release 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Our analyses included 1,509 ovarian cancer cases (920 serous, 180 endometrioid, 105 clear cell, 75 mucinous, and 229 invasive epithelial but not classified as one of the four main histotypes) and 2,295 controls (Table 1). Among these women, 346 cases (~23%) and 680 controls (~30%) reported ever using continuous estrogen–progestin combined therapy postmenopausally.

Overall, postmenopausal use of continuous estrogen–progestin combined therapy was not associated with increased risk of ovarian cancer (OR=0.85, 95% CI 0.72–1.0) (Table 2). When we considered histotype, we did not observe an association between continuous estrogen–progestin combined therapy use and risk of clear cell (OR=0.68, 95% CI 0.40–1.2), endometrioid OR=0.86, 95% CI 0.57–1.3), or serous ovarian cancer (OR=0.98, 95% CI 0.80–1.2; Table 2); we examined high-grade (moderately differentiated, poorly differentiated, undifferentiated) and low-grade (well differentiated) serous ovarian cancers separately and found similar risks for both (OR=1.0, 95% CI 0.82–1.2 for high-grade; OR=0.97, 95% CI 0.42–2.2 for low-grade). However, we observed a decreased risk for the association of continuous estrogen–progestin combined therapy exposure with mucinous tumors (OR=0.40, 95% CI 0.18–0.91). We also evaluated duration and recency of continuous estrogen–progestin combined therapy use, but the results were not materially different from the overall effects (Table 3).

Discussion

With millions of hormonal therapy users in the U.S. presently, a better understanding of the effects of continuous estrogen–progestin combined therapy use on ovarian cancer risk is needed.[8] We found that continuous estrogen–progestin combined therapy use was not associated with an increased overall risk of ovarian cancer or that of individual histotypes, which raises some uncertainty regarding the presence of a positive association between estrogen–progestin combined therapy and ovarian cancer as observed in some previous studies.[8,20,29] It should be noted that while estrogens have been implicated as causative factors for ovarian carcinogenesis as demonstrated by the well-established effects of estrogen–alone therapy,[10] the addition of a progestin has been proposed to diminish estrogens' risk-inducing effects [6] as it does in endometrial cancer,[4,7] and our findings are in line with this evidence.[6,16]

We did not observe any associations for serous, endometrioid, and clear cell cancers although the analyses for the latter two histotypes may be underpowered. The decreased risk of mucinous ovarian cancer we observed with continuous estrogen–progestin combined therapy use is interesting although this result was only based on eight case users (Table 2). In our previous work[10], we observed an OR of 0.93 between estrogen–alone therapy use and risk of mucinous ovarian cancer, but the 95% confidence interval spanned 0.43 to 2.0. Both estrogen–progestin combined therapy and estrogen–alone therapy are associated with a

decreased risk of colon cancer.[17] Mucinous ovarian cancer and colon cancer may share a similar cell of origin[18] and it is also possible that some mucinous ovarian cancer cases in our dataset are truly colon primaries.

Jones and colleagues have illustrated the important impact of analytic strategies in cohort studies when studying hormonal therapy and breast cancer risk;[19] the same issues apply with ovarian cancer and may, in part, explain differences in results between case–control and cohort studies. Some,[8,20] but not all,[21] cohort studies have found estrogen–progestin combined therapy to be associated with an increased risk of ovarian cancer. While cohort studies are generally considered the gold standard of observational studies, this may not be the case for studies of hormonal therapy.[19] It is not uncommon for postmenopausal women to have taken hormonal therapy and later stopped use or to have taken both estrogen–alone therapy and estrogen–progestin combined therapy. For both scenarios, hormonal therapy use defined by the last recorded use, an approach commonly used in cohort studies, may result in misclassification.

In addition, in cohort study analyses of estrogen–progestin combined therapy,[8] previous users of estrogen–alone therapy are generally not excluded from the analysis as changes in hormonal therapy use may not be captured or may be missed at follow-up times. This could lead to an overestimate of the effect of estrogen–progestin combined therapy since estrogen–alone therapy is a well-established risk factor for ovarian cancer and its effect may be muddled with that of estrogen–progestin combined therapy. The Collaborative Group carried out their analysis in this manner and found an increased risk of ovarian cancer among current estrogen–progestin combined therapy users (RR=1.37, 95% CI 1.26–1.48).[8] In addition, the individual reports from two of the larger cohort studies included in the Collaborative Group's analysis used a similar analytic approach in that estrogen–progestin combined therapy users included those who also used estrogen–alone therapy, and they also report an increased risk with estrogen–progestin combined therapy (and continuous estrogen–progestin combined therapy) use.[22,23] Hence, in an effort to untangle estrogen–progestin combined therapy's (and continuous estrogen–progestin combined therapy's) effects from those of estrogen–alone therapy, we restricted our analysis to comparing only never users of any postmenopausal hormones to women whose only use of postmenopausal hormones was continuous estrogen–progestin combined therapy. In contrast to the cohort studies mentioned above, we do not observe a positive association between continuous estrogen–progestin combined therapy and ovarian cancer risk when analyzed in these "clean" exposure groups; this is similar to the findings of other retrospective studies as well.[24,25] When we evaluated the impact of including estrogen–alone therapy users in the exposed group on the association between continuous estrogen–progestin combined therapy use and ovarian cancer risk in our data (i.e., also including women who had previously used estrogen–alone therapy in the continuous estrogen–progestin combined therapy group), we found results that were more in line with the Collaborative Group's. However, it should be noted that the impact of this analytic strategy of including previous users of estrogen–alone therapy on the association between continuous estrogen–progestin combined therapy and ovarian cancer will depend on the frequency of prior estrogen–alone therapy use among participants as well as the duration of that use given that longer use has been shown to be associated with greater increased risk.[10] Hence, individual study results could vary widely.

Around 1980, estrogen–progestin combined therapy use became more common after the increased risk of endometrial cancer associated with estrogen–alone therapy became clear. Sequential estrogen–progestin combined therapy was the commonly used formulation of estrogen–progestin combined therapy until ~1985 when continuous estrogen–progestin combined therapy became more common. Sequential and continuous estrogen–progestin combined therapy have been shown to be differentially associated with endometrial cancer risk[5,26] with the former being associated with inadequate protection against endometrial carcinogenesis. As mentioned previously, our sample size was quite small to analyze sequential estrogen–progestin combined therapy (n=85 case users and n=129 control users) and thus it was not part of our analysis.

Case–control studies are likely to capture hormonal therapy exposure more precisely than cohort studies given that hormonal therapy is an exposure that changes over time. This is particularly true for the studies included in the present analysis, which are all population-based and used in-person interviews with picture aids and life calendars to ascertain exposure information. The argument for case–control studies being biased with respect to information on hormonal therapy use is weak because there is no stigma associated with using hormonal therapy and the proximity from exposure to disease diagnosis is generally short. Even after the WHI when use of hormonal therapy declined sharply, studies observed good agreement between self-reported hormonal therapy use and prescription data, suggesting little stigma attached to reporting use of hormonal therapy despite the WHI's findings.[27,28] In addition, there is no evidence that the population-based ascertainment of controls would have resulted in a group that used hormonal therapy more frequently than the base population that gave rise to the cases. However, we do acknowledge that recall bias and selection bias are generally considered to be limitations of retrospective studies, and they could account for the difference between our findings and the findings of other studies.

It should be noted that the WHI found an increased risk of ovarian cancer of 1.58 (95% CI 0.77–3.24) with continuous estrogen–progestin combined therapy use, contrary to our findings.[29] The progestin dose used in the WHI was 2.5mg of medroxyprogesterone acetate (MPA) whereas older continuous estrogen–progestin combined regimens would have contained 5mg MPA. A dose–response association for MPA with ovarian cancer risk is possible in which the lower MPA dose is insufficient to gain a benefit against ovarian carcinogenesis. This is just speculation, however, because we were not able to address this question in the OCAC data available to us.

Most studies to date have not evaluated the association between continuous estrogen–progestin combined therapy and ovarian cancer in such detail due to limited numbers. However, given our use of primary data from five population-based case–control studies and the detailed nature of each study's questionnaire, we were able to more comprehensively evaluate the effects of continuous estrogen–progestin combined therapy use while considering ovarian cancer's various histotypes. One limitation to our analysis is the self-reported nature of our primary data. However, efforts were taken to aid in the recall of hormonal therapy use, including the use of photobooks and life calendars. In addition, studies have shown high concordance between self-reported hormonal therapy data and prescription records.[27,28,30,31] We also considered that perhaps we had not taken important

confounders into account and to that end we carried out additional analyses on the impact of age at last pregnancy and incomplete pregnancies, which have been suggested as exposures that could be associated with ovarian cancer risk, but neither materially affected our estimates for continuous estrogen–progestin combined therapy use and ovarian cancer. It is possible that a confounder that we did not adjust for is affecting our results (e.g., infertility). However, it is highly unlikely that such a confounder would bias our results to a major extent and thus, at the very least, it is unlikely that continuous estrogen–progestin combined therapy increases risk of ovarian cancer in our analysis.

Given that millions of U.S. women use hormonal therapy for menopausal symptom relief, it is important to understand the effects of hormonal therapy and its various types on female malignancies. While we know that estrogen–alone therapy use is associated with increased risk of endometrial cancer and that adding a progestin is associated with less increased risk or no risk,[4,5] we also know that estrogen–progestin combined therapy regimens are associated with increased risk of breast cancer.[1] When it comes to ovarian cancer, we observed that progestins have a similar effect as they do in endometrial cancer, although this finding is contrary to some previous studies[8,20,29] highlighting the complexity of ovarian carcinogenesis with regard to progestins. Our data support the hypothesis of a beneficial role for progestins, but more work is needed to better understand this finding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Numbers of cases and controls included in analysis by study

Study Name	Geographic Location	Study Period	Controls	Cases	Serous	Mucinous	Endometrioid	Clear cell
Disease of the Ovary and their Evaluation Study [12]	Washington	2002–2009	495	285	171	7	41	25
Hawaii Ovarian Cancer Study [11]	Hawaii	1994–2007	106	90	45	7	10	6
Hormones and Ovarian Cancer Prediction [14][a]	Western Pennsylvania, Northeast Ohio, Western New York	2003–2008	594	253	167	8	26	17
New England Case-Control Study of Ovarian Cancer [13]	New Hampshire, Eastern Massachusetts	1999–2008	362	286	183	16	47	16
University of Southern California, Study of Lifestyle and Women's Health [9][a]	Los Angeles, California	1993–2005	738	595	354	37	56	41
		Total:	2295	1509	920 [b]	75 [b]	180 [b]	105 [b]

[a] Some of the study's primary data were included in the Collaborative Group's analysis [8].

[b] Sum of numbers do not equal total number of cases because some cases were not classified as one of the four histotypes considered.

Table 2.

Association between postmenopausal continuous estrogen–progestin combined therapy use and risk of ovarian cancer by histotype

	Number of controls	Number of cases	OR [a]	95% CI
Serous				
Never use	1615	688	1.00	--
Ever postmenopausal use	680	232	0.98	0.80 – 1.2
Mucinous				
Never use	1615	67	1.00	--
Ever post-menopausal use	680	8	0.40	0.18 – 0.91
Endometrioid				
Never use	1615	139	1.00	--
Ever post-menopausal use	680	41	0.86	0.57 – 1.3
Clear Cell				
Never use	1615	84	1.00	--
Ever post-menopausal use	680	21	0.68	0.40 – 1.2
Overall				
Never use	1615	1163	1.00	--
Ever post-menopausal use	680	346	0.85	0.72 – 1.0

Note: OR=odds ratio, CI=confidence interval.

[a]Adjusted for oral contraceptive use (never, 1 month to <5 years, 5 to <10 years, 10+ years), parity (0, 1, 2+ births), body mass index (<18.5, 18.5–24.9, 25–29.9, 30+ kg/m^2), tubal ligation, age at menopause, and endometriosis; conditioned on age (<40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75+ years), education (less than high school, high school, some college, college graduate), race/ethnicity (non-Hispanic white, Hispanic white, black), and study.

Table 3.

Association between postmenopausal continuous estrogen–progestin combined therapy use and risk of ovarian cancer overall

	Number of controls	Number of cases	Mean duration (years)	OR [a]	95% CI
Never use	1615	1163	--	1.00	--
Ever post-menopausal use	680	346	5.74	0.85	0.72 – 1.0
<5 years	330	174	2.13	0.85	0.69 – 1.1
5+ years	350	172	9.23	0.85	0.68 – 1.1
Current post-menopausal use [b]	360	187	6.27	0.80	0.65 – 0.99
<5 years	166	86	2.32	0.77	0.57 – 1.0
5+ years	194	101	9.65	0.82	0.62 – 1.1
Past post-menopausal use [b]	320	159	5.14	0.92	0.73 – 1.2
<5 years	164	88	1.94	0.95	0.71 – 1.3
5+ years	156	71	8.69	0.90	0.65 – 1.2

Note: OR=odds ratio, CI=confidence interval.

[a] Adjusted for oral contraceptive use (never, 1 month to <5 years, 5 to <10 years, 10+ years), parity (0, 1, 2+ births), body mass index (<18.5, 18.5–24.9, 25–29.9, 30+ kg/m^2), tubal ligation, age at menopause, and endometriosis; conditioned on age (<40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75+ years), education (less than high school, high school, some college, college graduate), race/ethnicity (non-Hispanic white, Hispanic white, black), and study.

[b] Current users include those who used continuous estrogen–progestin combined therapy within the last 2 years prior to their reference age. Past users include those who used continuous estrogen–progestin combined therapy 2 or more years prior to their reference age.