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Intrauterine devices and endometrial cancer risk: a pooled analysis of the Epidemiology of Endometrial Cancer Consortium

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Abstract

Intrauterine devices (IUDs), long-acting and reversible contraceptives, induce a number of immunological and biochemical changes in the uterine environment that could affect endometrial cancer (EC) risk. We addressed this relationship through a pooled analysis of data collected in the Epidemiology of Endometrial Cancer Consortium. We combined individual-level data from 4 cohort and 14 case-control studies, in total 8,801 EC cases and 15,357 controls. Using multivariable logistic regression, we estimated pooled odds ratios (pooled-ORs) and 95% confidence intervals (CIs) for EC risk associated with ever use, type of device, ages at first and last use, duration of use, and time since last use, stratified by study and adjusted for confounders. Ever use of IUDs was inversely related to EC risk (pooled-OR=0.81, 95% CI=0.74–0.90). Compared with never use, reduced risk of EC was observed for inert IUDs (pooled-OR=0.69, 95% CI=0.58–0.82), older age at first use (≥35 years pooled-OR=0.53, 95% CI=0.43–0.67), older age at last use (≥45 years pooled-OR=0.60, 95% CI=0.50–0.72), longer duration of use (≥10 years pooled-OR=0.61, 95% CI=0.52–0.71), and recent use (within 1 year of study entry pooled-OR=0.39, 95% CI=0.30–0.49). Future studies are needed to assess the respective roles of detection biases and biologic effects related to foreign body responses in the endometrium, heavier bleeding (and increased clearance of carcinogenic cells), and localized hormonal changes.

Keywords

contraception; pooled analysis; endometrial neoplasm; etiology

INTRODUCTION

The intrauterine device (IUD) is a form of long-term reversible birth control initially marketed in the United States (US) in 1964 [1]. Several types of IUDs have been designed and sold over the years. Early IUDs were either inert devices made from plastic or stainless steel or progesterone-releasing devices [2]. By the late 1980's inert IUDs had been withdrawn from US markets because of safety concerns associated with a particular inert IUD, the Dalkon Shield [3]. In the 1990's, two IUDs were available in the US – a copper-bearing device (ParaGard) and a progesterone-releasing device (Progestasert); however, because of lingering concerns regarding the Dalkon Shield, the overall prevalence of IUD use dropped to its lowest frequency (0.5% of reproductive aged women) during this time period [3]. Since

2001, ParaGard and Mirena (levonorgestrel-releasing IUD), both of which have pregnancy rates of less than 0.1 per 100 woman-years [4], have been available to US women. Compared with the US, IUDs are used extensively in European and Asian countries, particularly China [5]. Of 150 million current IUD users worldwide, 100 million reside in China. In northern Europe, approximately 30% of contracepting women use the IUD [5].

Although the exact mechanism by which IUDs prevent pregnancy is unknown, and may vary by type of device, in the uterus, all IUDs elicit a local foreign body reaction characterized by increases in macrophages, neutrophils, and lymphocytes [6–8]. This inflammatory environment has been suggested to affect pre-fertilization factors (inhibition of sperm migration, loss of sperm viability, altered cervical mucus, damage to ovum before fertilization) and post-fertilization factors (damage of the early embryo before it reaches the uterus, prevention of implantation) [9]. Additionally, hormone-releasing devices suppress growth of the endometrial lining resulting in a thin endometrium [10].

IUDs may have long-term consequences on endometrial tissues given their direct placement in the uterine cavity and ability to evoke foreign body responses [11, 12]. In 2007 and 2008, two meta-analyses examined the relationship between IUD use and endometrial cancer (EC) risk [1, 13]. These analyses summarized ten epidemiologic studies [14–23] which together included 4,243 EC cases and 269,428 controls. These two meta-analyses reported odds ratios (ORs) of 0.54 [1] [95% confidence interval (CI)=0.47–0.63] and 0.60 [13] (95% CI=0.40–0.70) associated with ever use of IUDs. Furthermore, Beining et al. [1] showed that longer duration of use and longer time since first or last use were associated with lower EC risk. While informative, these meta-analyses lacked in-depth explorations of specific types of IUDs, as only three published reports provided this information [17–19]. Furthermore, analysis of quantitative metrics of IUD use (ages at first and last use, duration, time since last use) was limited by the small number of studies that reported these associations. Other issues that remain to be addressed include associations with EC tumor characteristics and potential effect modification by EC risk factors. Since the publication of these meta-analyses no additional studies have been published on the relationship between IUD use and EC risk.

Recent data from the National Survey of Family Growth indicate that the prevalence of IUD use is increasing in the US [24]; therefore, further epidemiological investigations of long-term consequences are warranted. We sought to pool observational studies to examine relationships between IUD use and EC risk in the Epidemiology of Endometrial Cancer Consortium (E2C2).

METHODS

Study population

The E2C2, sponsored in part by the National Cancer Institute, combines data from cohort and case-control studies to study EC etiology [25]. Studies that collected information on ever use of IUDs were eligible for the current analysis. For the cohort studies, a nested case-control design was employed, with inclusion of up to four controls who were women with intact uteri and no EC diagnoses at the time of matching date, randomly selected and matched to the corresponding EC case on year of birth, date of cohort entry (within 6

months), and any additional matching criteria as appropriate in the individual study. Information on IUD use was differently collected in the cohort studies: ever use was assessed on the baseline questionnaire in three studies [Cancer Prevention Study II Nutrition Cohort (CPS-II) [26], Nurses' Health Study (NHS) [27], and Swedish Women's Lifestyle and Health Study (WLHS) [28]], current use was collected on the baseline, 1997, and 1999 questionnaires in one study [Black Women's Health Study (BWHS) [29]], and information on ever use was collected at the time of a nested study interview obtained from a case-control study in two cohorts [California Teachers' Study (CTS) [30] and New York University Women's Health Study (NYU) [31]]. As such, the latter two studies are classified as case-control studies. Cases in the cohort studies were identified through annual linkage to state or national cancer registries (WLHS and CTS), or by self-report on follow-up questionnaires and confirmed through medical record review, linkage to cancer registries, or the National Death Index (BWHS, CPS-II, NHS, and NYU).

In the case-control studies, hospital-based controls [Patient Epidemiologic Data System Study (PEDS) [32], Milano Endometrial Cancer Case Control Study 1 (MILANO 1) [33], Milano Endometrial Cancer Case Control Study 2 (MILANO 2) [34], and Switzerland Endometrial Cancer Study (SWEC) [35]] or population-based controls were selected within each source population using random digit dialing [Connecticut Endometrial Cancer Study (CECS) [36], Estrogen, Diet, Genetics, and Endometrial Cancer Study (EDGE) [37], Fred Hutchinson Cancer Research Center Study 1 (FHCRC 1) - which also included Health Care Financing Administration (HCFA) controls and comparable controls from the Contraceptive and Reproductive Experiences Study (CARE) [38], Fred Hutchinson Cancer Research Center Study 2 (FHCRC 2) [39], Alberta Endometrial Cancer and Physical Activity Study (ALBERTA) [40], and US Case-Control Study (US) [41]] or random selection from data registries of all citizens [Australian National Endometrial Cancer Study (ANECS) [42] and Shanghai Endometrial Cancer Study (SECS) [43]]. Frequency matching was used in all case-control studies except in the US study where individual 1:1 matching was employed. Frequency matching in FHCRC 2 was to the frequency of ovarian cancer cases in the same geographical area which has a similar age distribution as that for EC cases. For all case-control studies, eligible controls were women with intact uteri and no histories of EC. Matching factors differed by study, but typically included age, race, and geographic region.

Women who were missing information for ever use of IUD (293 cases and 663 controls) were excluded from the analyses, leaving 8,801 EC cases and 15,357 control subjects. Three studies (US, SECS, MILANO 1) included in the previous meta-analyses [1, 13] contributed data to the E2C2 and therefore were included in our study. The remaining seven studies included in the previous meta-analyses did not contribute data to the E2C2 and were not included in our analysis. All studies were approved by the institutional review boards (IRBs) of their parent institutions, and informed consent was obtained from all participants.

Data collection

De-identified data from the participating studies were collected and harmonized at Memorial Sloan Kettering Cancer Center. Age at first IUD use was reported in 12 studies (ALBERTA, CTS, CECS, CPS-II, MILANO 1, MILANO 2, NYU, PEDS, SECS, SWEC, US, WLHS)

and age at last IUD use was reported in 8 studies (CECS, CPS-II, MILANO 1, MILANO 2, SECS, SWEC, US, WLHS). Duration of IUD use was either calculated as the time between dates of first and last IUD use or reported from questionnaire items asking about total length of use and was available in 13 studies (ALBERTA, ANECS, CTS, CECS, CPS-II, MILANO 1, MILANO 2, NYU, PEDS, SECS, SWEC, US, WLHS). If multiple episodes of IUD use were reported, the duration is an accumulation across the time periods. Time since last IUD use was available in 8 studies (ALBERTA, CECS, CPS-II, MILANO 1, MILANO 2, SECS, SWEC, US). Seven studies provided information on the type of IUD used which included copper, inert, hormone-releasing, or use of combinations of devices (ANECS, CTS, FHCRC 1, FHCRC 2, SECS, US, WLHS).

Available information on potential confounders differed by study. All studies provided information on age at diagnosis (cases), age at interview/reference date (controls), race, weight and height, ever use of menopausal hormone therapy (MHT), oral contraceptive (OC) use, and smoking. Some studies did not provide specific information on parity (NYU), age at last birth (ALBERTA, ANECS, CPS-II, CTS, EDGE, MILANO 1, MILANO 2, NYU, PEDS, SWEC, US), menopausal status (FHCRC 1, FHCRC 2), history of diabetes (WLHS, PEDS), or duration of OC use (ALBERTA, CECS, MILANO 1, MILANO 2, NYU, SWEC, WLHS). We considered number of pregnancies lasting at least 7 months as a surrogate for parity (NYU) and age at last pregnancy as a surrogate for age at last birth (ANECS, CTS, EDGE, PEDS, US). Missing values were coded as a separate category for each variable.

Case definitions

Women with incident, histologically confirmed diagnoses of EC were included as case patients in the current analysis. International Classification of Diseases for Oncology (ICD)-O-3 morphology codes were provided by 12 studies (ALBERTA, ANECS, CTS, CECS, CPS-II, EDGE, FHCRC 1, FHCRC 2, NYU, PEDS, US, WLHS) while four studies (BWHS, NHS, SECS, SWEC) supplied summary histology variables for each case. Specific histology information was unavailable in the MILANO 1 and MILANO 2 studies; however, all cases were histologically confirmed. EC cases with the following ICD-O-3 histology codes or summary descriptions were included in the analysis: endometrioid (codes 8380–8383), adenocarcinoma tubular (codes 8210 and 8211), papillary adenocarcinoma (codes 8260, 8262, and 8263), adenocarcinoma with squamous metaplasia (code 8570), mucinous adenocarcinoma (codes 8480 and 8481), adenocarcinoma not otherwise specified [(NOS) code 8140], clear cell (code 8310), serous (code 8441), papillary serous (codes 8460 and 8461), squamous cell (codes 8050, 8070–8072), adenosquamous (code 8560), small-cell carcinoma (code 8041), and mixed-cell adenocarcinoma (code 8323). We classified these histologic subtypes into the broad Type I and Type II categories based on a previous study as described below [44].

Statistical methods

We employed two methods to analyze the association between IUD use and EC risk. First, we used a two-stage approach in which unconditional logistic regression was used to estimate study-specific ORs and 95% CIs for the association between ever use of IUDs and

EC risk adjusted for age at diagnosis or interview (continuous), race (White, Black, Asian, Other), body mass index [BMI (<25kg/m^2, 25–30 kg/m^2, ≥30 kg/m^2), age at menarche (<11, 11–12, 13–14, ≥15), duration of OC use (never use, <5, 5–9, ≥10 years, unknown duration), a combination of parity and age at last birth (nulliparous, 1–2 births and <25, 1–2 births and 25–29, 1–2 births and 30–34, 1–2 births and ≥35, ≥3 births and <25, ≥3 births and 25–29, ≥3 births and 30–34, ≥3 births and ≥35), menopausal status (premenopausal, postmenopausal), MHT use (never, ever), diabetes (never, ever), and smoking (never, former, current), when possible. These variables were identified as potential confounders given their known association with EC risk in this study population [44] and their association with IUD use among control subjects in the current analysis. The natural logarithms of the study-specific ORs were combined using the DerSimonian and Laird [45] random effects model that accounts for within- and between-study heterogeneity. The I^2 test statistic was used as a measure of between-study heterogeneity [46]. We conducted univariate random-effects meta-regression to investigate features of the studies as sources of heterogeneity, including design (cohort vs. case-control), geography (North America vs. Europe, China, Australia), year of exposure ascertainment (<1990, 1990–2000, ≥2001), and prevalence of IUD use (<10%, 10–19%, 20–49%, ≥50%) [47]. We also conducted a sensitivity analysis excluding each study and re-estimating the meta-OR and I^2 to determine whether any studies disproportionately contributed to our estimates.

Next, we combined the individual-level data from each study into one dataset and performed logistic regression analyses stratified by study to determine pooled-ORs and 95% CIs. Associations of EC risk with IUD use (never, ever), IUD type (copper, inert, hormone-releasing, combination, unknown), age at first use (<25, 25–29, 30–34, or ≥ 35 years), age at last use (<30, 30–39, 40–44, or ≥ 45 years), duration of use (<1, 1–4, 5–9, or ≥10 years), and time since last use (within 1 year of study entry, 1–4, 5–9, or ≥10 years) were examined. In the analyses of ages at first and last use, duration, and time since last use, we first included all studies that provided information on the pertinent variable. Subsequently, we re-ran the analyses restricted to case-control studies as these variables were assessed near the time of case diagnosis or control selection which differs from the assessment in the cohort studies, where the exposure was ascertained at baseline. Tests for linear trend were performed among IUD users (i.e., excluding never users) by entering the ordinal values representing the categories for each quantitative IUD-related variable. We also explored relationships between the quantitative IUD measures (ages at first and last use, duration, time since last use) according to type of device used.

We examined whether the association of EC risk with IUD use varied over strata of other EC risk factors, including age at diagnosis/interview, parity, BMI, menopausal status, OC use, MHT use, smoking status, and diabetes. Tests for effect modification were done using the likelihood-ratio procedure, comparing models with and without the interaction term between IUD use and the covariate of interest. Women with missing values for potential effect modifier variables were excluded. We also examined the association between IUD use and tumor characteristics (histological subtype and stage) using polytomous logistic regression models. Other than endometrioid tumors, we had a limited number of histological subtypes in our study population, which precluded analyses of specific histologies. Instead,

we broadly classified tumors by histology as Type I (endometrioid, adenocarcinoma NOS, adenocarcinoma with squamous metaplasia, and adenosquamous) or Type II (serous, papillary serous, and mixed-cell adenocarcinoma) [44]. The Surveillance, Epidemiology, and End Results (SEER) classification of stage (local, regional, distant) was available in 6 studies (BWHS, CTS, CPS-II, EDGE, FHCRC, PEDS) while the International Federation of Gynecology and Obstetrics (FIGO) stage (1988 criteria) was available in 6 studies (ALBERTA, ANECS, NYU, SECS, US, WLHS). We consolidated FIGO stage into three categories to recapitulate the SEER summary stage groupings (Localized=FIGO stages 1 and 2; Regional=FIGO stage 3; Distant=FIGO stage IV). Differences in ORs between case groups were quantified using case-only models. Analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC) and STATA 11.2 (StataCorp LP, College Station, TX).

RESULTS

Table 1 describes the characteristics of the four cohort and 14 case-control studies that contributed to the analysis. The prevalence of IUD use among controls ranged between 1.7% (BWHS) and 56.1% (WLHS). The time periods in which IUD use was ascertained also varied considerably, spanning from 1980 (NHS) to 2009 (CECS). Characteristics of the controls according to IUD use are shown in Supplemental Table 1. A total of 2,288 controls (14.9%) reported ever use of IUDs and these women were more likely to be younger at study entry, Asian, normal-weight, and older at menarche compared with non-IUD users. While IUD users were more likely to be parous than non-users (93.9% vs. 85.8%), IUD users tended to have a lower number of live births compared to non-IUD users. IUD users were more likely to be younger at last birth, premenopausal at study entry, use OCs for short durations, and never smoke relative to non-users.

The study-specific ORs and 95% CIs for EC risk associated with ever use of IUDs are displayed in Figure 1. Estimates of the association were significantly heterogeneous between studies (meta-OR=0.83, 95% CI=0.72–0.96, I^2=68.6%, p<0.0001). The association was not heterogeneous among the cohort studies (OR=0.86, 95% CI=0.67–1.10, I^2=0%, p=0.87) but was heterogeneous among the case-control studies (OR=0.82, 95% CI=0.69–0.98, I^2=75.8%, p<0.0001); however, study design was not a significant source of between-study heterogeneity in the univariate meta-regression (p=0.79). We also performed univariate meta-regression analyses among the case-control studies and found no significant heterogeneity by geography (p=0.84), year of exposure ascertainment (p=0.59), or prevalence of IUD use (p=0.50, data not tabled). In sensitivity analyses where we excluded each study in turn and re-analyzed the estimates, one study contributed to the heterogeneous effect estimates (SECS: OR=0.57, 95% CI=0.46–0.69). After excluding the SECS, the meta-OR was 0.83 (95% CI=0.74–0.94) and the between-study heterogeneity improved (I^2=42.6%, p=0.04). In subsequent analyses that combined data across the 18 studies, we stratified by study to account for between-study heterogeneity and additionally ran sensitivity analyses excluding SECS.

Table 2 presents associations between IUD characteristics and EC risk in the pooled dataset. The pooled-OR of 0.81 (95% CI=0.74–0.90) for ever versus never use of IUDs was similar to the meta-OR. The inverse association between IUD use and EC risk was strongest among

users of inert IUDs (pooled-OR=0.69, 95% CI=0.58–0.82), with weaker associations being observed among users of copper IUDs (pooled-OR=0.89, 95% CI=0.66–1.21), hormone-releasing IUDs (pooled-OR=0.97, 95% CI=0.44–2.14), or use of a combination of IUDs (pooled-OR=0.88, 95% CI=0.65–1.19). Compared with never use, older age at first use (≥35 years pooled-OR=0.53, 95% CI=0.43–0.67, p-trend =0.17), older age at last use (≥ 45 years pooled-OR=0.60, 95% CI=0.50–0.72, p-trend =0.01), longer duration (≥10 years pooled-OR=0.61, 95% CI=0.52–0.71, p-trend=0.16), and recent use (within 1 year of study entry pooled-OR=0.39, 95% CI=0.30–0.49) were inversely related to EC risk.

We re-analyzed the associations between the quantitative IUD variables (ages at first and last use, duration, time since last use) and EC risk in models restricted to case-control studies (Supplemental Table 2). We did not observe major differences in these analyses compared with the full model; however, the estimates in the case-control only analyses typically showed a greater reduction in EC risk compared with estimates from the models including all studies. Further, all analyses shown in Table 2 were re-analyzed excluding the major outlier, SECS (Supplemental Table 3). Overall, the IUD variables showed similar magnitudes of association with EC risk compared with the full models, but some associations were attenuated.

Table 3 presents associations between EC risk and quantitative IUD metrics by device type. Among the inert IUD users, older ages at first and last use, longer duration, and recent use were inversely related to EC risk – the magnitudes of associations were similar to the associations observed in the full cohort. Among copper IUD users, none of the associations reached statistical significance. We did not assess associations among hormone-releasing IUD users because of small numbers of exposed women.

Potential effect modification of the relationship between IUD use and EC risk by established EC risk factors using a common referent group is shown in Table 4. Parity (p-interaction=0.001), menopausal status (p-interaction=0.006), and MHT use (p-interaction=0.008) were significant effect modifiers. Compared to nulliparous women who never used IUDS, nulliparous women who ever used IUDs had a reduced risk of EC (pooled-OR=0.48, 95%CI=0.34–0.68) that was more pronounced than EC risks among parous never IUD users (pooled-OR=0.74, 95% CI=0.65–0.85) or parous ever IUD users (pooled-OR=0.63, 95% CI=0.54–0.74). Postmenopausal women who ever used IUDs had a reduced EC risk (pooled-OR=0.72, 95% CI=0.62–0.83) compared to premenopausal never IUD users. For MHT use, we changed the referent category to MHT users who never used an IUD to clearly demonstrate patterns of association. Of note is the finding that among MHT users, IUD use reduced the risk of EC from 1.00 to 0.60 (95% CI=0.50–0.72). The association between IUD use and EC risk was not significantly modified by age at diagnosis, BMI, OC use, smoking status, or diabetes.

Ever use of IUDs was inversely associated with Type I (pooled-OR=0.87, 95% CI=0.79–0.95) but not Type II EC subtypes (pooled-OR=1.05, 95% CI=0.81–1.36) (data not tabled). The p-value for tumor heterogeneity indicated no difference in the associations (p-heterogeneity=0.98). The inverse association with ever use of IUDs was more strongly associated with distant stage tumors (pooled-OR=0.45, 95% CI=0.24–0.86) than local stage

tumors (pooled-OR=0.90, 95% CI=0.81–1.00) but the observed differences were not statistically significant (p-heterogeneity=0.12) (data not tabled).

DISCUSSION

The present pooled analysis of individual level data from 18 epidemiologic studies is the largest and most comprehensive investigation of IUDs and EC risk to date. Ever use of IUDs was inversely associated with EC risk, independent of known risk factors. Analysis of specific characteristics of IUD use showed that inert IUDs, older ages at first and last use, and recent use were significantly related to lower EC risk.

Our findings agree with the majority of previous studies. However, our pooled-OR of 0.81 is a more modest estimate of the association compared with previous studies, which reported ORs between 0.37 and 0.61 [15, 19–23]. Three previous studies examined specific types of IUDs [17–19], none of which demonstrated significant associations with any particular device, probably due to small numbers of cases and controls exposed to specific IUD types. We observed a significant association with inert IUDs, which was the most prevalent IUD type used in our study population. This observation likely reflects the fact that inert IUDs were most commonly used in the 1980s which provided a suitable latency period for ECs to occur. Although not statistically significant, the OR for copper IUDs suggested an inverse relationship. With only 21 cases and 12 controls exposed to hormone-releasing IUDs, we could not generate meaningful estimates for this device. Because the hormone-releasing type of IUD is now the most commonly used IUD in the US, future epidemiologic studies are needed to investigate a possible association with this type of IUD. Data from a recent Finnish study showed that the levonorgestrel-releasing intrauterine system is inversely associated with EC risk [48].

No previous individual study has demonstrated a dose-response association with quantitative characteristics of IUD use [15, 17–19, 22]. A meta-analysis [1] summarizing these individual studies observed a lower EC risk with increasing duration of use, longer time since first use, and longer time since last use. We observed lower EC risks with longer duration of use, both in the overall study population and among inert IUD users. Our findings that older age at first use and recent use are inversely related to EC risk are not in line with the meta-analysis findings, possibly suggesting that the underlying mechanism of IUD protection is complex. Disentangling which quantitative IUD characteristics specifically drive the relationship is needed, but difficult given the high correlation between these variables. Even in our study including a large number of cases and controls, we could only explore the contribution of two quantitative IUD metrics at one time in a given model, and these models were restricted to IUD users. Future studies conducted on this topic that are subsequently combined with existing data may be able to shed light on these complex relationships.

Sporadic endometrial carcinogenesis is believed related to risk factors that increase estrogen exposure relative to progesterone [49]. Imbalances in these hormones lead to increases in mitotic activity of endometrial cells with increased opportunities for DNA replication errors and subsequent neoplastic transformation [50]. As such, the possibility that IUDs protect the endometrium by changing the balance of hormone receptors in the uterus is an attractive

hypothesis, but clinical studies with similar sample sizes have provided inconsistent evidence. For example, following insertion of copper IUDs, some have shown decreases in progesterone receptor (PR) but not estrogen receptor (ER) [51, 52], no changes in ER or PR [53], or decreases in ER but not PR [54]. Only the last study is consistent with a mechanism that would decrease EC risk through lower estrogen sensitivity relative to progesterone. Hormone-releasing devices, which deliver levonorgestrel directly to the endometrial lining, have been shown to down-regulate ER and PR in some studies [55–58], while others report down-regulation of PR only [59, 60]. Again, these studies are inconsistent with a mechanism that would decrease EC risk through lower ER activity compared to PR. Moreover, the literature provides conflicting evidence regarding variations in serum ovarian steroid-hormone levels between IUD users and non-users [60–64]. At this time it is unclear whether IUDs, particularly inert IUDs, lower EC risk through hormonal mechanisms.

Another mechanism that may account for lower EC risk among IUD users is through increased decidual loss, which transiently increases following insertion of all types of IUDs [65–70]. This process may allow for more complete shedding of the endometrial lining, with subsequent removal of premalignant or hyperplastic endometrial cells. Along the same lines, the foreign body response elicited by IUDs may lead to the elimination of pre-malignant endometrial cells. Although inflammation is thought to promote carcinogenesis [71], and has even been offered as a hypothesis to explain etiologic factors and EC risk [72], we suspect that the timing of the IUD-elicited foreign body response relative to the stage of carcinogenesis is central to this relationship. We hypothesize that the inflammatory milieu stimulated by IUDs offers protection to women who may be more likely to have premalignant or hyperplastic changes (i.e. ages 40–50) compared with younger women with no evidence of these changes. Our finding of an inverse trend with increasing age at last IUD use is consistent with this hypothesis. The role of these potential mechanisms should be considered in future studies.

In our analysis, parity, menopausal status, and MHT use modified the relationship between IUD use and EC risk. The odds of EC range between 1.5 and 3.5 for nulliparous compared with parous women [73–75], a finding we noted in the current study. We observed that nulliparous women who ever used an IUD had a 52% lower risk of EC compared with nulliparous women who never used an IUD. A potential shared mechanism by which parity and IUD use may lower EC risk is through shedding of precancerous cells in the endometrial lining of the uterus. IUDs may afford greater protection to nulliparous women who lack such a mechanism compared to parous women. Among postmenopausal women, we observed a 28% reduced EC risk with IUD use whereas no association was observed for premenopausal women. Younger EC cases are more likely to have a genetic predisposition to the disease [76] which may not be reduced by IUD use, whereas postmenopausal EC is more likely to represent a sporadic disease influenced by modifiable risk factors. Finally, we observed that IUD use lowered EC risk among MHT users, which may indicate that IUDs exert an anti-hormonal influence; however, these findings should be interpreted cautiously as the type and duration of MHT use were unavailable in this study.

The major strength of this study is the large sample size, which offered more statistical power than in any of the individual published studies which included between 85–1,204 EC

cases. Further strengths include uniform adjustment for confounders and use of consistent categories for the IUD variables across studies, which was a limitation of the previous meta-analysis [1]. However, our study had limitations as well. Although we included a large number of studies in our analysis, very few studies collected detailed IUD information, limiting our assessment of IUD type, ages at first and last use, duration, and time since last use. Furthermore, although we adjusted for factors that differed between IUD users and non-users, residual confounding by other factors for which we did not have information could have occurred, including postmenopausal hormone use and contra-indications for IUD use. Not all studies included in our analyses have detailed information on the usage of postmenopausal hormones among cases and controls to allow an overall evaluation on whether hormone use might confound the observed results. To address the question of potential confounding by hormone use, we analyzed the data from the FHCRC case-control studies, which have detailed information on the type, dosage, duration and recency of hormone use among the study participants. The results showed that the use of estrogen-alone or estrogen plus progestin for less than 10 days per month did not confound the association between IUD use and EC risk, nor did inclusion of duration and recency. So, at least based on the FHCRC studies, postmenopausal hormone use does not seem to be a confounder. Regarding contra-indications for IUD use as a potential confounder, women with conditions that result in irregular bleeding (*i.e.* fibroids, polycystic ovary syndrome) may be discouraged from using IUDs, but these women may be at higher risk of developing EC. This would cause a downward bias of the OR for IUD use.

Another potential limitation of our study is that we observed significant heterogeneity in the meta-OR among the case-control studies, driven in large part by the SECS. While the estimate obtained in the SECS is stronger than any of the other studies, the association was in the same direction. In this large case-control study, a lower prevalence of other EC risk factors, namely, obesity, coupled with a high prevalence of IUD use may have driven the lower risk associated with IUDs. Finally, our finding that recent IUD use lowers EC risk suggests potential surveillance bias, which could arise if IUD users have more interactions with healthcare providers compared with non-users and were more often treated for premalignant conditions. We could not directly test this in our study population; however, studies that prospectively evaluate the risk of developing endometrial hyperplasia would be well-suited to analyze this relationship.

In summary, our pooled analysis provides evidence that IUD use is associated with a lower risk of developing EC. Future studies incorporating endometrial tissue samples collected before and after IUD insertion would be useful in describing the biological mechanisms underlying the observed inverse association. Additionally, future studies will need to include a larger number of hormone-releasing device users to adequately address the long-term effects of the devices in primary use today. A better understanding of the relationship between IUD use and EC risk may guide healthcare recommendations for the use of IUDs beyond family planning indications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Impact Statement

Worldwide, intrauterine devices (IUDs) are an increasingly common contraceptive. In the uterus, IUDs elicit immunological and biochemical changes that could have implications for cancer risk. We examined the association between IUDs and endometrial cancer (EC) risk. Inert devices, older ages at first and last use, longer duration, and recent use were inversely associated with EC risk. Our results may be useful to health care providers that counsel patients regarding benefits and risks of IUDs.

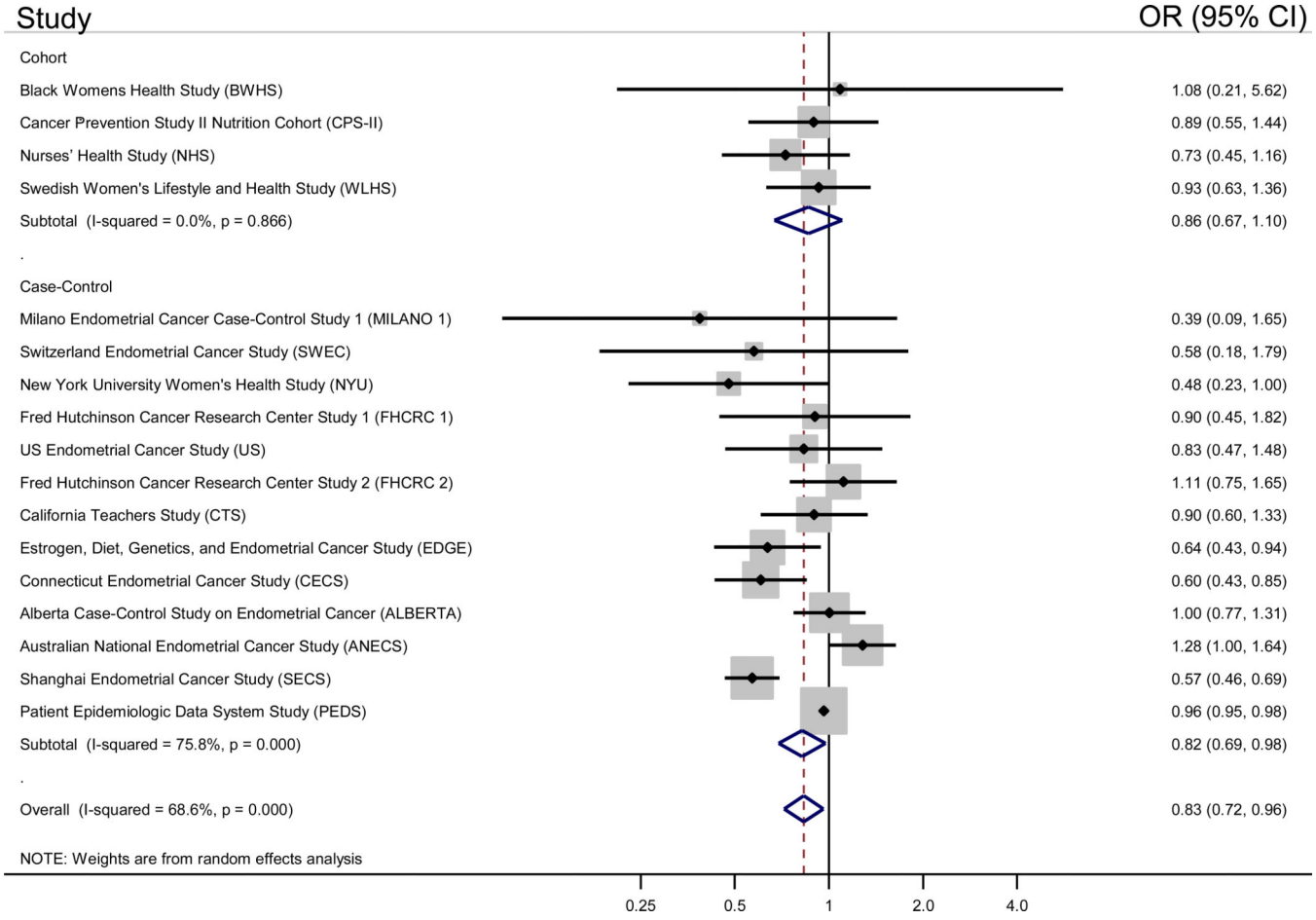

Figure 1.

Forest plot of intrauterine device use and endometrial cancer risk

Footnote: One study (MILANO 2) was not included in the forest plot as ORs and 95% CIs were not estimable due to zero exposed cases.

Table 1

Characteristics[1] of the 18 observational studies included in the pooled analysis of intrauterine device use and endometrial cancer risk

Study	Location	Cases (n)	Controls (n)	IUD Ascertainment	Ever used an IUD		Availability of IUD variables
					Cases	Controls	
Cohort							
Black Women's Health Study (BWHS)	US	132	528	1995, 1997, 1999	1.5%	1.7%	current use
Cancer Prevention Study II Nutrition Cohort (CPS-II)	US	666	2,664	1992–1993	3.6%	3.8%	age at first use, age at last use, duration of use, time since last use
Nurses' Health Study (NHS)	11 US states	611	1,639	1980	4.3%	5.9%	ever use
Swedish Women's Lifestyle and Health Study (WLHS)	Sweden	163	649	1991	51.5%	56.1%	type, age at first use, age at last use, duration of use
Case-control							
Alberta Case-Control Study on Endometrial Cancer (ALBERTA)	Canada	542	1,032	2002–2006	22.0%	25.0%	age at first use, duration of use, time since last use
Australian National Endometrial Cancer Study (ANECS)	Australia	1,356	696	2005–2007	22.6%	21.8%	type, duration of use
Connecticut Endometrial Cancer Study (CECS)	Connecticut	668	663	2004–2009	12.0%	17.9%	age at first use, age at last use, duration of use, time since last use
California Teachers Study (CTS)[2]	California	399	681	1995–1996	13.8%	14.4%	type, age at first use, duration of use
Estrogen, Diet, Genetics, and Endometrial Cancer Study (EDGE)	New Jersey	469	467	2001–2005	14.3%	19.1%	ever use
Fred Hutchinson Cancer Research Center Study 1 (FHCRC 1)	Washington	136	211	1994–1995	13.2%	16.6%	type
Fred Hutchinson Cancer Research Center Study 2 (FHCRC 2)	Washington	409	356	2003–2005	24.9%	24.7%	type
Milano Endometrial Cancer Case-Control Study 1 (MILANO 1)	Italy	527	2,394	1982–1991	0.4%	2.8%	age at first use, age at last use, duration of use, time since last use
Milano Endometrial Cancer	Italy	226	224	1992–2006	0.0%	3.1%	age at first use, age at last

Study	Location	Cases (n)	Controls (n)	IUD Ascertainment	Ever used an IUD		Availability of IUD variables
Case-Control Study 2 (MILANO 2)							use, duration of use, time since last use
New York University Women's Health Study (NYU)[2]	New York	121	333	1985–1991	11.6%	15.0%	age at first use, duration of use
Patient Epidemiologic Data System Study (PEDS)	New York	536	531	1982–1998	5.0%	6.2%	age at first use, duration of use
Shanghai Endometrial Cancer Study (SECS)	China	1,168	1,195	1997–2003	41.1%	53.2%	type, age at first use, age at last use, duration of use, time since last use
Switzerland Endometrial Cancer Study (SWEC)	Switzerland	240	568	1988–1992	1.7%	4.7%	age at first use, age at last use, duration of use, time since last use
US Endometrial Cancer Study (US)	5 US clinics	432	526	1987–1990	5.1%	11.0%	type, age at first use, age at last use, duration of use, time since last use
Pooled studies		**8,801**	**15,357**		13.8%	16.8%	

[1] Based on women included in the pooled analysis (after excluding women with missing IUD data)

[2] Cohort study with IUD data collected in case-control interviews

Table 2

Odds ratios (ORs) and 95% confidence intervals (CIs) of IUD characteristics and endometrial cancer risk

	Cases	Controls	OR (95% CI)[1]
	n (%)		
IUD use			
Never user	7368 (83.7)	13069 (85.1)	Ref
Ever user	1433 (16.3)	2288 (14.9)	0.81 (0.74, 0.90)
IUD type[2]			
Never user	2995 (73.7)	2883 (66.8)	Ref
Copper	108 (2.7)	405 (9.4)	0.89 (0.66, 1.21)
Inert	385 (9.5)	521 (12.1)	0.69 (0.58, 0.82)
Hormone-releasing	21 (0.5)	12 (0.3)	0.97 (0.44, 2.14)
Combination	86 (2.1)	140 (3.2)	0.88 (0.65, 1.19)
p_{Wald}			0.005
Age at first IUD use[3]			
Never user	4777 (84.0)	9642 (84.1)	Ref
<25	125 (2.2)	279 (2.4)	0.84 (0.66, 1.06)
25–29	321 (5.6)	588 (5.1)	0.74 (0.63, 0.87)
30–34	325 (5.7)	563 (4.9)	0.72 (0.61, 0.86)
≥35	131 (2.3)	361 (3.1)	0.53 (0.43, 0.67)
p_{trend}[4]			0.17
Age at last IUD use[5]			
Never user	3394 (83.0)	7504 (74.5)	Ref
<30	85 (2.1)	203 (2.3)	0.73 (0.55, 0.97)
30–39	206 (5.3)	383 (4.3)	0.92 (0.75, 1.13)
40–44	101 (2.5)	255 (2.9)	0.58 (0.44, 0.75)
≥45	276 (6.7)	485 (5.5)	0.60 (0.50, 0.72)
p_{trend}[4]			0.01
Duration of use (years)[6]			
Never user	5403 (81.6)	9412 (82.7)	Ref
< 1	260 (3.9)	399 (3.5)	0.86 (0.68, 1.09)
1–4	342 (5.2)	565 (5.0)	0.80 (0.68, 0.94)
5–9	176 (2.7)	262 (2.3)	0.99 (0.80, 1.24)
≥10	400 (6.0)	694 (6.1)	0.61 (0.52, 0.71)
p_{trend}[4]			0.16
Time since last IUD use (years)[7]			
Never user	3738 (83.6)	7993 (86.3)	Ref
Within 1 year of study entry	157 (3.5)	337 (3.6)	0.39 (0.30, 0.49)

	Cases	Controls	OR (95% CI)[1]
	n (%)		
1–4	108 (2.4)	136 (1.5)	0.83 (0.62, 1.11)
5–9	87 (1.9)	117 (1.3)	0.85 (0.62, 1.17)
≥10	365 (8.2)	645 (7.0)	0.78 (0.67, 0.91)
P_{trend}[4]			<0.0001

[1] Adjusted for age (continuous), race (White, Black, Asian, Other), BMI (< 25kg/m^2, 25–30 kg/m^2, ≥30 kg/m^2), age at menarche (<11, 11–12, 13–14, ≥15), duration of oral contraceptive use (never, <5, 5–9, ≥10 years), parity/age at last birth (nulliparous, 1–2 births and <25, 1–2 births and 25–29, 1–2 births and 30–34, 1–2 births and ≥35, ≥3 births and <25, ≥3 births and 25–29, ≥3 births and 30–34, ≥3 births and ≥35), menopausal status (premenopausal, postmenopausal), any menopausal hormone use (never, ever), smoking status (never, former, current), and stratified by study

[2] Available in ANECS, CTS, FHCRC 1, FHCRC 2, SECS, US, WLHS

[3] Available in ALBERTA, CTS, CECS, CPS-II, MILANO 1, MILANO 2, NYU, PEDS, SECS, SWEC, US, WLHS

[4] p-value for trend was calculated using the Wald test for the ordinal variable based on the categories shown excluding never IUD users

[5] Available in CECS, CPS-II, MILANO 1, MILANO 2, SECS, SWEC, US, WLHS

[6] Available in ALBERTA, ANCES, CTS, CECS, CPS-II, MILANO 1, MILANO 2, NYU, PEDS, SECS, SWEC, US, WLHS

[7] Available in ALBERTA, CECS, CPS-II, MILANO 1, MILANO 2, SECS, SWEC, US

Table 3

Odds ratios (ORs) and 95% confidence intervals (CIs) of quantitative IUD variables and endometrial cancer risk according to IUD type

	Inert IUD users			Copper IUD users		
	Cases	Controls		Cases	Controls	
	n (%)		OR (95% CI)[1]	n (%)		OR (95% CI)[1]
Age at first IUD use[2]						
Never user	1521 (82.3)	1895 (80.5)	Ref	1521 (94.3)	1895 (83.4)	Ref
<25	9 (0.5)	28 (1.2)	0.23 (0.10, 0.52)	22 (1.4)	83 (3.6)	1.11 (0.65, 1.91)
25–29	128 (6.9)	146 (6.2)	0.68 (0.51, 0.91)	38 (2.4)	119 (5.2)	1.32 (0.84, 2.07)
30–34	144 (7.8)	198 (8.4)	0.61 (0.47, 0.80)	19 (1.2)	91 (4.0)	0.78 (0.44, 1.39)
≥35	45 (2.4)	87 (3.7)	0.49 (0.33, 0.72)	10 (0.6)	69 (3.0)	0.52 (0.25, 1.10)
p_{trend}[3]			0.43			0.08
Age at last IUD use[4]						
Never user	1177 (78.3)	1312 (74.1)	Ref	1177 (92.7)	1312 (77.7)	Ref
<30	22 (1.5)	31 (1.7)	0.73 (0.40, 1.32)	16 (1.3)	66 (3.9)	0.98 (0.52, 1.82)
30–39	87 (5.8)	95 (5.4)	0.85 (0.60, 1.19)	39 (3.1)	130 (7.7)	1.30 (0.83, 2.03)
40–44	49 (3.3)	88 (5.0)	0.44 (0.29, 0.66)	16 (1.3)	81 (4.8)	0.83 (0.45, 1.54)
≥45	162 (10.8)	241 (13.6)	0.56 (0.44, 0.72)	18 (1.4)	80 (4.7)	0.82 (0.45, 1.50)
p_{trend}[3]			0.03			0.91
Duration of use (years)[5]						
Never user	2570 (88.7)	2439 (84.2)	Ref	2570 (96.5)	2439 (86.8)	Ref
< 1	20 (0.7)	33 (1.1)	0.69 (0.39, 1.24)	0 (0.0)	10 (0.4)	0.94 (0.22, 4.04)
1–4	50 (1.7)	65 (2.2)	0.82 (0.55, 1.22)	36 (1.3)	122 (4.3)	1.15 (0.72, 1.83)
5–9	50 (1.7)	53 (1.8)	0.82 (0.53, 1.25)	18 (0.7)	79 (2.8)	0.98 (0.55, 1.76)
≥10	200 (6.9)	307 (10.6)	0.53 (0.42, 0.67)	38 (1.4)	152 (5.4)	1.03 (0.65, 1.61)
p_{trend}[3]			0.06			0.55
Time since last IUD use (years)[6]						
Never user	1098 (77.1)	1027 (69.1)	Ref	1098 (99.3)	1027 (98.8)	Ref

	Inert IUD users			Copper IUD users		
	Cases	Controls		Cases	Controls	
	n (%)		OR (95% CI)[1]	n (%)		OR (95% CI)[1]
Within 1 year of study entry	99 (6.9)	187 (12.6)	0.38 (0.28, 0.52)	0 (0.0)	1 (0.1)	NE
1–4	68 (4.8)	76 (5.1)	0.71 (0.48, 1.03)	1 (0.9)	2 (0.2)	2.52 (0.20, 31.15)
5–9	50 (3.5)	58 (3.9)	0.71 (0.46, 1.08)	5 (0.4)	2 (0.2)	6.33 (1.03, 38.96)
≥10	103 (7.2)	134 (9.0)	0.77 (0.57, 1.04)	2 (0.2)	6 (0.6)	0.75 (0.14, 3.96)
p_{trend}[3]			<0.0001			NE

[1] Adjusted for age (continuous), race (White, Black, Asian, Other), BMI (< 25kg/m^2, 25–30 kg/m2, ≥30 kg/m^2), age at menarche (<11, 11–12, 13–14, ≥15), duration of oral contraceptive use (never, <5, 5–9, ≥10 years), parity/age at last birth (nulliparous, 1–2 births and <25, 1–2 births and 25–29, 1–2 births and 30–34, 1–2 births and ≥35, ≥3 births and <25, ≥3 births and 25–29, ≥3 births and 30–34, ≥3 births and ≥35), menopausal status (premenopausal, postmenopausal), any menopausal hormone use (never, ever), smoking status (never, former, current), and stratified by study

[2] Available in CTS, SECS, US, WLHS

[3] p-value for trend was calculated using the Wald test for the ordinal variable based on the categories shown among IUD users

[4] Available in SECS, US, WLHS

[5] Available in ANECS, CTS, SECS, US, WLHS

[6] Available in SECS and US

NE: Not estimable

Table 4

Odds ratios (ORs) and 95% confidence intervals (CIs) of IUD use and endometrial cancer risk according to endometrial cancer risk factors

	Cases	Controls	OR (95% CI)[1]	Cases	Controls	OR (95% CI)[1]	$P_{interaction}$
	Age at diagnosis						
	< 65 years (n=15,386)			**≥ 65 years (n=8,745)**			
IUD use							0.93
Never	4,464	7,751	Ref	2,904	5,291	0.97 (0.90, 1.05)	
Ever	1,216	1,955	0.81 (0.73, 0.89)	217	333	0.77 (0.63, 0.94)	
	Parity						
	Nulliparous (n=3,458)			**Parous (n=20,531)**			
IUD use							0.001
Never	1,477	1,781	Ref	5,826	11,198	0.74 (0.65, 0.85)	
Ever	66	134	0.48 (0.34, 0.68)	1,364	2,143	0.63 (0.54, 0.74)	
	BMI						
	<30 kg/m^2 (n=18,277)			**≥30 g/m^2 (n=5,631)**			
IUD use							0.19
Never	4,494	10,840	Ref	2,767	2,114	2.83 (2.62, 3.05)	
Ever	974	1,969	0.80 (0.72, 0.88)	445	305	2.34 (1.98, 2.76)	
	Menopausal status						
	Premenopausal (n=5,446)			**Postmenopausal (n=17,497)**			
IUD use							0.006
Never	1,182	2,652	Ref	5,732	9,920	0.99 (0.88, 1.11)	
Ever	561	1,051	0.93 (0.80, 1.08)	739	1,106	0.72 (0.62, 0.83)	
	OC use						
	Never (n=13,818)			**Ever (n=9,975)**			
IUD use							0.26
Never	4,527	7,846	Ref	2,779	5,063	0.69 (0.64, 0.75)	
Ever	613	832	0.78 (0.68, 0.89)	785	1,348	0.59 (0.53, 0.67)	
	MHT use[2]						

	Cases	Controls	OR (95% CI)[1]	Cases	Controls	OR (95% CI)[1]	$p_{interaction}$
	Never (n=11,095)			**Ever (n=6,248)**			0.008
IUD use							
Never	3,703	6,254	0.69 (0.64, 0.75)	2,000	3,553	Ref	
Ever	481	657	0.57 (0.49, 0.66)	254	441	0.60 (0.50, 0.72)	
	Smoking status						
	Never (n=14,648)			**Former/Current (n=9,338)**			
IUD use							0.18
Never	4,765	7,499	Ref	2,559	5,457	0.76 (0.71, 0.82)	
Ever	986	1,398	0.77 (0.69, 0.86)	444	878	0.68 (0.59, 0.79)	
	Diabetes						
	No (n=18,275)			**Yes (n=2,040)**			
IUD use							0.62
Never	5,110	10,554	Ref	972	730	1.73 (1.53, 1.95)	
Ever	1,025	1,586	0.81 (0.73, 0.90)	209	129	1.50 (1.17, 1.94)	

[1] Adjusted for age (continuous), race (White, Black, Asian, Other), BMI (< 25kg/m^2, 25–30 kg/m^2, ≥30 kg/m^2), age at menarche (<11, 11–12, 13–14, ≥15), duration of oral contraceptive use (never, <5, 5–9, ≥10 years), parity/age at last birth (nulliparous, 1–2 births and <25, 1–2 births and 25–29, 1–2 births and 30–34, 1–2 births and ≥35, ≥3 births and <25, ≥3 births and 25–29, ≥3 births and 30–34, ≥3 births and ≥35), menopausal status (premenopausal, postmenopausal), any menopausal hormone use (never, ever), smoking status (never, former, current), and stratified by study. For each effect modifier, women with missing values were excluded from the model

[2] Among postmenopausal women