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Coffee consumption and risk of endometrial cancer

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Coffee consumption and risk of endometrial cancer: a pooled analysis of individual participant data in the Epidemiology of Endometrial Cancer Consortium (E2C2)

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ABSTRACT

Background: Epidemiologic studies suggest that coffee consumption may be inversely associated with risk of endometrial cancer (EC), the most common gynecological malignancy in developed countries. Furthermore, coffee consumption may lower circulating concentrations of estrogen and insulin, hormones implicated in endometrial carcinogenesis. Antioxidants and other chemopreventive compounds in coffee may have anticarcinogenic effects. Based on available meta-analyses, the World Cancer Research Fund (WCRF) concluded that consumption of coffee probably protects against EC.

Objectives: Our main aim was to examine the association between coffee consumption and EC risk by combining individual-level data in a pooled analysis. We also sought to evaluate potential effect modification by other risk factors for EC.

Methods: We combined individual-level data from 19 epidemiologic studies (6 cohort, 13 case–control) of 12,159 EC cases and 27,479 controls from the Epidemiology of Endometrial Cancer Consortium (E2C2). Logistic regression was used to calculate ORs and their corresponding 95% CIs. All models were adjusted for potential confounders including age, race, BMI, smoking status, diabetes status, study design, and study site.

Results: Coffee drinkers had a lower risk of EC than non–coffee drinkers (multiadjusted OR: 0.87; 95% CI: 0.79, 0.95). There was a dose–response relation between higher coffee consumption and lower risk of EC: compared with non–coffee drinkers, the adjusted pooled ORs for those who drank 1, 2–3, and >4 cups/d were 0.90 (95% CI: 0.82, 1.00), 0.86 (95% CI: 0.78, 0.95), and 0.76 (95% CI: 0.66, 0.87), respectively (P-trend < 0.001). The inverse association between coffee consumption and EC risk was stronger in participants with BMI > 25 kg/m^2.

Conclusions: The results of the largest analysis to date pooling individual-level data further support the potentially beneficial health effects of coffee consumption in relation to EC, especially among females with higher BMI. *Am J Clin Nutr* 2022;00:1–10.

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Keywords: coffee consumption, risk factors, endometrial cancer, pooled analysis, epidemiology

Introduction

Endometrial cancer (EC) is the most common gynecological malignancy and the fourth most common cancer among females in developed countries, affecting mainly postmenopausal females. In 2020, >400,000 females worldwide were diagnosed with EC and >90,000 died from the disease (1, 2). EC is a hormone-related cancer (3); well-known risk factors include obesity, and factors that elevate circulating concentrations of estrogen (e.g., estrogen-only postmenopausal hormone therapy, greater number of menstrual cycles, and nulliparity, among others) and insulin (i.e., diabetes). In contrast, smoking and physical activity are inversely associated with EC risk (4, 5).

Coffee is among the most widely consumed beverages worldwide (6, 7). Thus, an inverse association between coffee consumption and EC risk could have substantial implications for public health. Coffee contains a complex mixture of chemicals that have been shown to elicit antimutagenic, anticarcinogenic, and antioxidant properties in experimental studies (8). In contrast, coffee (and other dietary components) also contains acrylamide, which is considered to be a carcinogen; however, results on the association between acrylamide and EC risk are inconsistent (9). Previous studies have reported an inverse association between coffee consumption and circulating concentrations of estrogen and C-peptide, a marker of insulin secretion, both of which are involved in endometrial carcinogenesis (10–12). Furthermore, observational studies have shown that increased coffee consumption might be associated with a reduced risk of EC (as well as other chronic diseases) (8, 13, 14).

Several meta-analyses have been conducted to summarize existing evidence on the association between coffee consumption and the risk of EC (15–19). Most have reported an inverse association between coffee consumption and EC risk. Those associations seem to be stronger in postmenopausal females with higher BMI. Based on available data through 2018, the World Cancer Research Fund (WCRF) concluded that consumption of coffee probably protects against EC (5). However, some unanswered questions remain, including the possibility of effect modification by other EC risk factors. In addition, no pooled analyses combining individual-level data (especially from prospective studies) have been performed to date.

The aim of the present study was to assess the association between coffee consumption and EC risk by combining individual-level data of 12,159 EC cases and 27,479 controls from 19 epidemiologic studies (6 cohort, 13 case–control) from the Epidemiology of Endometrial Cancer Consortium (E2C2). In addition, we sought to assess whether this association is modified by other risk factors for the disease. This will be the largest analysis to date pooling individual-level data to address the coffee–EC relation and with the ability to stratify by key EC risk factors.

Methods

Participating studies

A total of 19 epidemiologic studies (6 cohort, 13 case-control) from the E2C2 that collected information on coffee consumption were included in the pooled analysis with a total of almost 40,000 individuals (12,159 EC cases and 27,479 controls) [see **Supplemental Table 1** for the full list of participating studies and their characteristics; note that 5 of the included

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Where authors are identified as personnel of the International Agency for Research on Cancer / WHO, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer / WHO.

Supplemental Tables 1–3 and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: BMI, body mass index; EC, endometrial cancer; E2C2, Epidemiology of Endometrial Cancer Consortium; OC, oral contraceptive; PMH, postmenopausal hormone.

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studies have previously published on coffee consumption (20–24)].

The E2C2 is an international consortium established in 2006 to provide a collaborative environment to study EC by pooling resources and data from many EC studies, in an effort to increase statistical power to identify genetic and environmental risk factors for EC (25). Cohort studies were included as nested case–control studies, with ≤4 controls selected per case from females with an intact uterus at the time of study participation and without EC before the diagnosis of the index case. In each study, controls were frequency-matched to cases based on year of birth and race/ethnicity.

Out of 39,638 individuals from all participating studies, a total of 37,091 individuals had complete information on coffee consumption, thus they were included in the present analysis: 11,109 EC cases and 25,982 controls (see **Supplemental Figure 1** for a flowchart of the participants included in the present study). Controls were frequency-matched with EC cases by age. For most studies, the majority of participants were self-reported non-Hispanic whites. The number of EC cases in each study ranged from 132 to 1850. Informed consent was obtained from all study participants as part of the original studies and in accordance with each study's Institutional Review Board.

Data collection

De-identified individual-level data from participating studies were sent to the E2C2 coordinating center at Memorial Sloan Kettering Cancer Center for initial data harmonization and cleaning. Data sets were checked for inconsistencies and completeness and queries were sent to the investigators to resolve any data issues. Questions regarding data or missing variables were referred to the site study coordinator and/or principal investigator. Each study also provided information regarding age at diagnosis (cases), age at interview or reference date (controls), interview year, tumor characteristics (cases), demographic variables, anthropometric measures, and known/potential risk factors for EC and covariates. These variables were defined and uniformly recoded in accordance with the E2C2 data dictionary (available upon request).

Incident cases of EC were included in the present analysis [International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) primary site codes: C54 and C55.9]. EC diagnosis was confirmed by medical records, or by linkage with state tumor registries.

All included studies provided information on the main exposure variables (related to coffee consumption). Information on coffee consumption was obtained from FFQs. Variables related to the frequency (times per month, week, or day), amount (cups/d; mg/d), type (caffeinated or decaffeinated), and duration (y) of coffee consumption were requested for each individual study. After reviewing the questionnaires from each individual study, exposure variables provided were recoded into the following uniform variables: coffee drinking (yes/no); cups of coffee per day; and type of coffee (caffeinated or decaffeinated) when available. Regarding the latter, only the studies that provided information on coffee type were included in the corresponding analysis. In addition, individuals who reported drinking both caffeinated and decaffeinated coffee were excluded from this particular analysis.

Statistical methods

We analyzed the complete individual data using a pooled analysis. Logistic regression models were used to calculate ORs and the corresponding 95% CIs. Unmatched logistic regression models were performed, thus matching factors (i.e., age) were included in the model as potential confounders. Stratified analyses by study design, BMI, smoking status, and diabetes status were also performed. Tests of interaction were calculated using log-likelihood test statistics comparing models with and without an interaction term. Tests for linear trend were calculated from linear models including the exposures as continuous variables.

Given the potential that females with EC in case–control studies may have changed their diet in response to early unrecognized symptoms, or potential recall bias in these studies, analyses including cases and controls from prospective cohort studies only were also performed. Heterogeneity across studies and by study design was also examined by means of the I^2 statistic (26).

The following covariates were considered potential confounders: age (matching factor; y), study design (case–control compared with cohort studies), study site (each individual study), ethnicity/race (white/black/Asian/Hispanic/mixed/other), BMI (in kg/m^2), smoking (pack-years of smoking), alcohol (g/d), energy intake (kcal/d), parity (number of children), postmenopausal hormone (PMH) therapy use (yes/no), oral contraceptive (OC) use (yes/no), diabetes status (yes/no), and hypertension (yes/no). Models were adjusted for each potential confounder and variables were included in the final model if they were associated with the outcomes and exposures in the bivariate data analysis (P value < 0.05), or caused a change in the model estimate for coffee (β) ≥10%. Variables included in the final models were age, race, BMI, smoking, energy intake, study design, and study site. Most of those variables have already been described as potential confounders according to the previous literature. Additional analyses including other potential confounders (e.g., reproductive-related variables) were also performed. Not all studies had complete information available for all covariables included in the present analysis (e.g., energy intake, OC use, PMH use), especially some case–control studies. Complete-case analyses, which exclude participants with only partially available data on the variables of interest, were performed for the main pooled analysis (the sample size for each particular model, and the covariables included in each analysis, are specified in the corresponding tables). Sensitivity analyses using the missing-indicator method (i.e., using a dummy variable in the statistical model to indicate whether the value for that variable is missing, with all missing values set to the same value) were also performed. Additional analyses excluding confounders with missing information (such as energy intake) were also performed.

All reported P values are 2-sided, and an α level of 0.05 was used to define statistical significance. All analyses were conducted using SAS version 9.2 (SAS Institute) and R software version 3.6.3 (R Foundation).

Results

All studies included in the present analysis are part of the E2C2 and are presented in Supplemental Table 1 [more details in Olson

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TABLE 1 Characteristics of EC cases and controls from the Epidemiology of Endometrial Cancer Consortium[1]

Characteristic	Controls ($n = 27,479$)	EC cases ($n = 12,159$)
BMI, kg/m^2	26.1 ± 5.4	29.1 ± 7.4
Smoking		
Never	17,281 (63)	7527 (65)
Former	6405 (23)	2826 (24)
Current	3713 (14)	1165 (11)
Pack-years[2]	10.7 ± 16.4	9.7 ± 17.1
Race		
Caucasian	21,757 (83)	9467 (87)
African American	1694 (6)	500 (5)
Asian	1429 (5)	519 (5)
Hawaiian	503 (2)	162 (2)
Mixed	53 (0)	38 (0)
Other	848 (3)	240 (2)
Alcohol,[3] g/wk	100.8 ± 250.5	81.5 ± 229.6
Energy, kcal/d	1663 ± 742	1772 ± 719
Parity, % nulliparity	3832 (14)	2090 (17)
Menopausal hormone therapy use		
No	15,027 (64)	5844 (61)
Yes	8615 (36)	3672 (39)
Oral contraceptive use		
No	11,520 (62)	5393 (64)
Yes	6974 (38)	3023 (36)
Diabetes		
No	15,163 (86)	6462 (80)
Yes	2500 (14)	1585 (20)
Hypertension		
No	13,698 (66)	4558 (56)
Yes	7165 (34)	3579 (44)
Coffee consumption		
Never	3895 (15)	1939 (18)
Ever	22,087 (85)	9170 (83)
Coffee cups,[4] *n*/d	1.9 ± 1.8	1.7 ± 1.7

[1] Values are mean ± SD or *n* (%). EC, endometrial cancer.
[2] Among ever smokers.
[3] Among alcohol drinkers.
[4] Among coffee drinkers.

et al. (25)]. **Table 1** shows characteristics of the cases and controls included in the present analysis. EC cases tended to have higher BMI, smoke less, drink less alcohol, have higher energy intake, exercise less, use more PMH therapy and less OC, and drink less coffee than controls. The proportion of white participants was also higher among cases, as well as the proportion of nulliparous females, females with diabetes, and females with hypertension. Mean ± SD age at diagnosis for EC was 63.5 ± 8.9 y. **Table 2** shows characteristics of control participants by coffee consumption categories. Participants who drank more coffee had lower BMI, smoked more, drank less alcohol, had higher energy intake, and exercised more than participants who did not drink coffee. A higher proportion of participants who drank more coffee were Caucasian, whereas a higher proportion of those who did not drink coffee were nulliparous.

Table 3 shows the results from the pooled analysis regarding the association between coffee consumption and EC risk. In multivariable analysis, coffee consumption was inversely associated with EC. The pooled age- and race-adjusted OR for coffee drinkers compared with nondrinkers was 0.92 (95% CI: 0.85, 0.98); the pooled multivariable OR was 0.87 (95% CI: 0.79, 0.95). Coffee consumption was linearly associated with a lower risk of EC: the higher the coffee consumption, the stronger the inverse association (P-trend < 0.001).

The inverse association between coffee consumption and EC risk was limited to caffeinated coffee consumption (**Table 4**). The proportion of participants who only drank decaffeinated coffee (28% of coffee drinkers) was lower than that for caffeinated coffee (72% of coffee drinkers).

When all studies (cohort and case–control) were included to assess the association between coffee consumption and EC risk, heterogeneity across studies was observed ($P = 0.026$). **Table 5** presents the results from the pooled analysis on the association between coffee and EC risk, stratified by study design. The inverse association between coffee consumption and EC was slightly stronger when limited to prospective studies (total number of participants: 20,290; 15,693 controls, 4597 cases). Compared with non–coffee drinkers, ever coffee drinkers had 13% lower odds of EC in cohort studies (pooled multivariable OR: 0.87; 95% CI: 0.78, 0.96), with no significant heterogeneity observed across studies ($P = 0.10$). Compared with non–coffee drinkers, the pooled ORs for those who drank >1 cup of coffee per day, 2–3 cups/d, and >4 cups/d were 0.90 (95% CI: 0.81, 1.00), 0.87 (95% CI: 0.77, 0.97), and 0.74 (95% CI: 0.63, 0.87), respectively (P-trend $= 3.26 \times 10^{-4}$) in cohort studies. Although

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TABLE 2 Characteristics of Epidemiology of Endometrial Cancer Consortium participants by coffee consumption (controls only)[1]

Characteristic	Coffee consumption No coffee	1 cup/d	2–3 cups/d	>4 cups/d
n	3985	8711	8703	3779
Diagnostic age, cases only, y	61.8 ± 10.3	63.8 ± 9.3	62.9 ± 9.5	61.4 ± 9.6
BMI, kg/m^2	27.0 ± 6.9	27.2 ± 6.4	26.7 ± 6.0	26.3 ± 5.6
Pack-years[2]	8.7 ± 15.0	8.2 ± 14.6	11.3 ± 17.8	14.8 ± 19.7
Race				
Caucasian	84	81	90	90
African American	6	6	2	2
Asian	5	7	4	5
Hawaiian	3	2	1	1
Other	2	4	3	2
Alcohol,[3] g/wk	119.6 ± 290.4	126.0 ± 286.1	73.7 ± 196.3	59.7 ± 171.7
Energy, kcal/d	1668 ± 742	1661 ± 725	1685 ± 709	1775 ± 748
Parity, % nulliparity	18.8	15.6	15.8	15.5
Menopausal hormone therapy use				
No	65	60	63	65
Yes	35	40	37	35
Oral contraceptive use				
No	65	64	65	64
Yes	35	36	35	36
Diabetes				
No	87	87	85	72
Yes	13	13	15	28
Hypertension				
No	62	62	67	64
Yes	38	38	33	36

[1]Values are mean ± SD or percentages unless otherwise indicated.
[2]Among ever smokers.
[3]Among alcohol drinkers.

an inverse association between coffee consumption and EC was also suggested in case–control studies, the effect sizes were smaller and the CIs wider.

The inverse association between coffee consumption and EC risk was stronger in participants with higher BMI (**Table 6**). Among females with BMI ≥25, coffee drinkers had 21% lower odds of EC (OR: 0.79; 95% CI: 0.71, 0.89) compared with 8% smaller odds in females with BMI <25 (OR: 0.92; 95% CI: 0.79, 1.07). There was an interaction between coffee consumption and BMI on EC risk (*P*-interaction < 0.001). Among females with a BMI <25, only the highest level of coffee consumption (>4 cups/d) was negatively associated with EC (OR: 0.72; 95% CI: 0.57, 0.92). Additional analyses stratified by smoking and diabetes status were conducted. Even though lower odds of EC associated with coffee drinking were observed mainly in never smokers, no interactions were found between those EC risk factors and coffee consumption. Specifically, among participants who never smoked, coffee drinkers had 14% lower odds of EC (95% CI: 0.77, 0.95) compared with 10% lower odds in ever smokers (95% CI: 0.79, 1.16). However, there was no differential effect of coffee consumption on EC risk by smoking status (*P*-interaction = 0.58). No differences regarding diabetes status subgroups were observed (**Supplemental Tables 2** and **3**, respectively).

TABLE 3 Association between coffee consumption and endometrial cancer risk[1]

Coffee exposure	Controls, *n*	Cases, *n*	OR[2] (95% CI)	*P* value	OR[3] (95% CI)	*P* value
Coffee consumption	25,982	11,109				
No	3895	1939	1.00 (Ref.)	0.016	1.00 (Ref.)	0.0028
Yes	22,087	9170	0.92 (0.85, 0.98)		0.87 (0.79, 0.95)	
Coffee cups per day	25,088	10,734				
No coffee	3895	1939	1.00 (Ref.)	1.76×10^{-5}	1.00 (Ref.)	9.21×10^{-5}
1 cup/d	8711	3821	0.96 (0.88, 1.03)		0.90 (0.82, 1.00)	
2–3 cups/d	8703	3678	0.93 (0.85, 1.00)		0.86 (0.78, 0.95)	
>4 cups/d	3779	1296	0.78 (0.70, 0.86)		0.76 (0.66, 0.87)	

[1]Reported sample sizes correspond to model 1 (adjusting for age and race only). For the multiadjusted model 2, the sample size for the complete-case analysis was 21,389 controls and 8873 cases.
[2]ORs adjusted for age and race.
[3]ORs adjusted for age, race, BMI, pack-years of smoking, energy intake, study design, and study site.

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TABLE 4 Association between type of coffee consumed and endometrial cancer risk[1]

Type of coffee	Controls ($n = 16{,}440$)	Cases ($n = 6915$)	OR (95% CI)	P value
No coffee	2607	1298	1.00 (Ref.)	
Caffeinated only	9794	4137	0.83 (0.75, 0.92)	5.11×10^{-4}
Decaffeinated only	4039	1480	0.93 (0.82, 1.05)	0.23

[1]ORs adjusted by age, race, BMI, pack-years of smoking, energy intake, study design, and study site. Studies that did not ask about coffee type and individuals who reported drinking both caffeinated and decaffeinated coffee were excluded from the present analysis.

Discussion

In the present study, we performed a pooled analysis of individual-level data from almost 40,000 females to evaluate the association between coffee consumption and EC risk. Our results suggest that, after adjusting for potential confounders, coffee drinkers have a ≥10% lower risk of EC than non–coffee drinkers, an association that was even stronger when restricting the analysis to prospective studies. Moreover, we observed an inverse dose–response relation between coffee consumption and EC risk. Results of the pooled analysis also showed that the inverse association between coffee consumption and EC risk was especially stronger in females with higher BMI.

Several meta-analyses have summarized existing evidence on the association between coffee consumption and the risk of EC. In 2015, Yang et al. (27) meta-analyzed 7 prospective and 4 retrospective studies (10,545 cases) and reported a weak inverse association between coffee consumption and EC (OR: 0.96; 95% CI: 0.95, 0.98 for prospective studies; OR: 0.91; 95% CI: 0.87, 0.95 for retrospective studies). Wang et al. (18) included 12 prospective studies (6033 cases) and reported an inverse association for EC (highest compared with lowest coffee consumption category RR: 0.73; 95% CI: 0.67, 0.81) and confirmed that the strongest protective effect was found in females with BMI >25. However, there was no evidence of a linear association between coffee consumption and EC risk. In another dose-response meta-analysis of 12 studies (10,548 cases) published in 2017 by Lafranconi et al. (17), the authors showed an association between coffee consumption and a decreased risk of postmenopausal EC, with an RR of 0.79 (95% CI: 0.73, 0.87) of EC for the highest compared with the lowest category of coffee consumption. In a subanalysis including only 4 of the 12 studies, these authors analyzed the associations by coffee type (caffeinated compared with decaffeinated coffee) and reported inverse associations with both types of coffee but heterogeneity among studies was present. In the most recent publication by Lukic et al. (16), including 12 cohort studies and 8 case–control studies (2746 EC cases and 11,663 controls), the authors found an inverse association. After combining the results from cohort and case–control studies, which showed a moderate level of heterogeneity, they reported a protective effect of highest compared with lowest coffee consumption on EC risk. Among the studies that provided sufficient information, these authors performed a dose-response analysis and reported that 1-cup increment per day was associated with a 3% risk reduction in cohort studies and 12% in case–control studies. After a meta-analysis of the results from cohort studies, the association remained significant only among participants with obesity (BMI >30), not among overweight participants (BMI: 25–30) or participants with BMI <25. Most recently, another cohort study in 3185 Canadian females also showed that total coffee and caffeinated coffee consumption and caffeine intake were inversely associated with EC risk, whereas no

TABLE 5 Association between coffee consumption and endometrial cancer risk, stratified by study design[1]

	Controls, n	Cases, n	OR (95% CI)	P value
Cohort studies ($n = 6$)				
Coffee consumption	15,693	4597		
No	2271	908	1.00 (Ref.)	4.01×10^{-3}
Yes	13,422	3689	0.87 (0.78, 0.96)	
Coffee cups, n/d	14,845	4405		
No coffee	2271	908	1.00 (Ref.)	3.26×10^{-4}
1	5452	1581	0.90 (0.81, 1.00)	
2–3	5044	1374	0.87 (0.77, 0.97)	
>4	2078	542	0.74 (0.63, 0.87)	
Case–control studies ($n = 13$)				
Coffee consumption	10,289	6512		
No	1624	1031	1.00 (Ref.)	0.31
Yes	8665	5481	0.89 (0.71, 1.11)	
Coffee cups, n/d	10,224	6489		
No coffee	1625	1031	1.00 (Ref.)	0.10
1	3259	2240	0.94 (0.74, 1.20)	
2–3	3659	2304	0.85 (0.63, 1.09)	
>4	1701	914	0.82 (0.60, 1.12)	

[1]ORs adjusted by age, race, BMI, pack-years of smoking, energy intake, and study site.

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TABLE 6 Association between coffee consumption and endometrial cancer risk, stratified by BMI[1]

	Controls, *n*	Cases, *n*	OR (95% CI)	*P* value
BMI ≤25				
Coffee consumption	12,681	3746		
No	1878	590	1.00 (Ref.)	0.30
Yes	10,803	3156	0.92 (0.79, 1.07)	
Coffee cups, *n*/d	12,362	3695		
No coffee	1878	590	1.00 (Ref.)	0.031
1 cup/d	4105	1266	0.95 (0.81, 1.22)	
2–3 cups/d	4396	1309	0.94 (0.79, 1.12)	
>4 cups/d	1983	530	0.72 (0.57, 0.92)	
BMI >25				
Coffee consumption	12,782	7158		
No	1932	1301	1.00 (Ref.)	3.91×10^{-5}
Yes	10,850	5857	0.79 (0.71, 0.89)	
Coffee cups, *n*/d	12,216	6996		
No coffee	1932	1301	1.00 (Ref.)	8.83×10^{-7}
1 cup/d	4419	2473	0.84 (0.75, 0.95)	
2–3 cups/d	4140	2314	0.76 (0.67, 0.86)	
>4 cups/d	1725	908	0.69 (0.58, 0.82)	

[1]BMI in kg/m^2. ORs adjusted by age, race, pack-years of smoking, energy intake, study design, and study site. *P*-interaction < 0.001.

associations were observed in relation to breast or ovarian cancer (28).

The meta-analyses published to date are not completely independent because there is some overlap in relation to the included studies. By combining individual participant data from 19 epidemiologic studies (some of them also included in the previously mentioned studies), our pooled analysis of nearly 40,000 participants is the largest available to date. Our results support the inverse association between coffee intake and EC risk found in previous meta-analyses, with a clear dose–response effect, which confirms a protective association between coffee consumption and EC risk. This inverse association is especially strong in females with higher BMI, and within the lowest and intermediate categories of coffee consumption. No effect modification by other EC risk factors has been observed in previous meta-analyses. Even though several meta-analyses were available with consistent results regarding the association between coffee intake and EC risk, some questions remain regarding effect modification by other EC risk factors and coffee type. As the first pooled analysis, our study was able to overcome some of the limitations of meta-analyses including differences in study design, methods, and analysis that could influence the combined results. More reliable results can be expected if individual data are available for a pooled analysis, because more consistent control for confounding is possible, although some heterogeneity still remains (29).

Several studies have reported that coffee constituents may have anticarcinogenic properties; thus, coffee could reduce EC risk through several biological mechanisms such as oxidative damage, DNA methylation, induction of angiogenesis, loss of apoptosis, oncogene activation, or tumor suppressor gene inactivation, among others (13). Active coffee compounds include not only caffeine, but also other bioactive agents with antioxidant properties such as polyphenols, lipids in the form of diterpenes, melanoidins, and trigonelle (30, 31). In particular, it has been reported that among all beverages, coffee has the highest concentration of polyphenols (26), which have been associated with decreased mortality and cancer risk, and may be mediators of the potential effects of coffee on cancer prevention (32). Polyphenols in coffee might counteract carcinogenesis by improving insulin sensitivity and suppressing the production of free radicals, therefore minimizing oxidative stress, DNA damage, and other potentially carcinogenic processes (15, 33–36).

Caffeine and other compounds in coffee have been shown to increase clearance of estradiol and inhibit estradiol-mediated carcinogenesis in endometrial cells (37). In addition, coffee might have a role in reducing circulating estrogens, which is a well-established risk factor for EC, through different mechanisms: coffee and caffeine consumption/intake have been positively associated to sex hormone-binding globulin in postmenopausal females, which is the major carrier of estrogens and testosterone, thus lowering the circulating concentrations of free hormones; enzymes converting androgens into estrogens have also been shown to be inhibited after coffee consumption (38–40). Additional effects of coffee consumption on hormonal functions may be related to improved insulin sensitivity; thus, coffee could have a protective effect against diabetes, which is another known risk factor for EC (41, 42). Even though an interaction with diabetes was biologically plausible, our analysis might be underpowered to detect such an association.

The stronger association observed in participants within the higher BMI categories could be explained through the impaired metabolism of females with obesity and the higher concentrations of circulating estrogens in females with obesity, especially postmenopausal. Higher BMI and obesity have been associated with cancer risk through several mechanisms such as chronic inflammation, oxidative stress, obesity-induced hypoxia, and cross-talk between tumor cells and surrounding adipocytes, among others. In addition, metabolic risk factors such as obesity, impaired glucose tolerance, or dyslipidemia have been associated with elevated systemic inflammation and oxidative stress. Thus, impaired metabolism may induce oxidative stress and inflammation which, in turn, may lead to carcinogenesis (43–45).

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Our study had limitations that need to be considered. Potential residual confounding is possible because we had missing data for some confounding factors, specifically those related to dietary factors, that were not available for the present study (e.g., energy intake, which was available for 15 out of the 19 studies). We performed a "complete-case" analysis, which included only those participants without missing observations on the variables of interest, and found similar results. Even though this method is the most widely used technique in epidemiology to handle missing data, this approach may result in biased estimates of the associations between covariates and outcomes, in addition to reducing statistical power (46). However, the percentage of missing data (18.4%) was mainly regarding the case–control, not cohort studies; and the complete-case analysis included a large number of participants. Additional analyses excluding such confounders (i.e., energy intake) were performed with no change in results. Furthermore, sensitivity analyses using the missing-indicator method were also performed and results did not change. Furthermore, it is worth mentioning that missing data was an issue for the case–control analyses, but not for prospective cohort studies (e.g., individuals excluded because of missing information on energy intake were from case–control studies). Higher missing rates in case–control studies might partially explain the weaker associations found in those studies. In relation to the results on type of coffee, it is worth mentioning that the proportion of participants who drank only decaffeinated coffee was lower than those who drank only caffeinated coffee. In addition, not all the studies provided information on coffee type, so the sample size for that analysis was smaller, and the results on decaffeinated coffee might be underpowered compared with caffeinated coffee (numbers of EC cases are 1480 and 4137, respectively). Finally, it is worth mentioning that, as in all observational studies, residual confounding cannot be ruled out. Several potential confounders could not be included in the present analysis because they were not available for most of the included studies (e.g., income, overall dietary patterns). However, the most relevant predictors of EC risk and coffee consumption have been considered, including menopausal status, BMI, smoking habits, and energy intake, among others.

Potential measurement error in coffee intake might also be possible (47). We are aware that coffee consumption (mostly reported as cups/d) is a heterogeneous measure owing to numerous preparation methods and cup sizes, which might lead to misclassification. Heterogeneity in exposure assessment, that is, in how each study asked about certain exposures, is a general limitation of pooled analyses. However, we expect this type of error to bias our results toward the null (especially when including prospective studies). Furthermore, the risks reported in our pooled study are consistent with findings from other studies. In addition, because differential misclassification is most likely related to case–control designs, we performed a sensitivity analysis only including prospective cohort studies, and the observed inverse associations were even stronger.

To the best of our knowledge, this study is the largest and most comprehensive analysis on coffee consumption and EC risk to date, combining nearly 40,000 participants from 19 epidemiologic studies (6 cohort, 13 case–control studies). Because of the potential that participants with EC in case–control studies changed their diet in response to early unrecognized symptoms, or potential recall bias in these studies, analyses including only prospective cohort studies were performed as well (total number of participants: 20,290; 15,693 controls, 4597 cases), and the inverse association between coffee intake and EC risk was even stronger.

In conclusion, we found that increased coffee consumption is associated with a lower risk of EC. The inverse association between coffee consumption and EC risk was especially strong among females who were overweight or obese. No effect modification by other EC risk factors was observed. Our results further support the potential beneficial health effects of coffee consumption in relation to EC. Further research to assess the potential causality of such an association as well as gain a better understanding of the underlying biological mechanisms is warranted.

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Data availability

Data described in the article will be made available upon request pending E2C2 Executive Committee approval.

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