Research Article

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A Prospective Cohort Study of Coffee Consumption and Risk of Endometrial Cancer over a 26-Year Follow-Up

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Abstract

Background: Coffee has been reported to lower levels of estrogen and insulin, two hormones implicated in endometrial carcinogenesis, but prospective data on the relation between coffee consumption and risk of endometrial cancer are limited.

Methods: We prospectively assessed coffee consumption in relation to endometrial cancer risk in the Nurses' Health Study (NHS) with 67,470 female participants aged 34 to 59 in 1980. Cumulative average coffee intake was calculated with all available questionnaires to assess long-term effects. Cox regression models were used to calculate incidence rate ratios (RR), controlling for other risk factors.

Results: Fewer than 4 cups of coffee per day were not associated with endometrial cancer risk. However, women who consumed 4 or more cups of coffee had 25% lower risk of endometrial cancer than those who consumed less than 1 cup per day (multivariable RR = 0.75; 95% CI = 0.57–0.97; $P_{trend} = 0.02$). We found the similar association with caffeinated coffee consumption (RR for ≥4 vs. <1 cup/d = 0.70; 95% CI = 0.51–0.95). For decaffeinated coffee consumption, a suggestive inverse association was found among women who consumed 2 or more cups per day versus <1 cup/mo. Tea consumption was not associated with endometrial cancer risk.

Conclusions: These prospective data suggest that four or more cups of coffee per day are associated with a lower risk of endometrial cancer.

Impact: Drinking of coffee, given its widespread consumption, might be an additional strategy to reduce endometrial cancer risk. However, addition of substantial sugar and cream to coffee could offset any potential benefits. *Cancer Epidemiol Biomarkers Prev; 20(12); 2487–95. ©2011 AACR.*

Introduction

Endometrial cancer is the most common gynecologic cancer in the United States. Prolonged exposure to excessive unopposed estrogens results in continued stimulation of the endometrium, which is a key mechanism in endometrial carcinogenesis (1). In addition, chronic hyperinsulinemia may play a role in endometrial cancer risk (2). Recent nested case–control studies showed that at baseline, high circulating levels of estrogens (3, 4), C-peptide, a marker of insulin secretion (5, 6), and fasting insulin (7) were associated with an increased risk of endometrial cancer.

Coffee consumption may be related to endometrial cancer development due to the potential role of caffeine or its components on hormonal modulation. Some studies have shown that coffee or caffeine intake influenced circulating levels of sex hormone binding globulin (SHBG), free estradiol, C-peptide, and adiponectin (8–13). Several epidemiologic studies have reported an inverse association between coffee intake and endometrial cancer risk, but data from prospective studies are limited (14–16). Few studies attempted to control for caffeine intake to see whether the association was due to caffeine itself or combinations with other coffee components. None of the studies examined the association with long-term intake of decaffeinated coffee, even though the prevalence has increased over time. Another caffeinated beverage, tea, might be beneficial against endometrial cancer if caffeine is largely responsible for the risk reduction in endometrial cancer, but reports on the association between tea consumption and the risk of endometrial cancer are inconclusive (15, 17–22).

Increasing exercise and maintaining normal body weight are probably the most important ways to prevent endometrial cancer (2). However, additional strategies are needed and dietary habits such as coffee drinking could provide one option, given its widespread consumption. Thus, we prospectively examined the association between coffee consumption and endometrial cancer risk in the Nurses' Health Study (NHS). The main advantages of this

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study were the long follow-up, large cohort, and repeated measurement of decaffeinated coffee, as well as regular coffee and tea consumption. To further clarify the role of coffee among different subgroups, we conducted stratified analyses by several important endometrial cancer risk factors.

Materials and Methods

Study population

The NHS began in 1976 when 121,700 female registered nurses from 11 states in the United States aged 30 to 55 years completed a mailed questionnaire about medical history and lifestyle information. We excluded participants who died ($n = 747$) or reported any type of cancer (except for nonmelanoma skin cancer) before 1980 ($n = 3,672$), had a history of hysterectomy ($n = 20,612$), and did not complete the 1980 food frequency questionnaire (i.e., more than 10 blank items or implausibly high or low energy intake <500 or >3,500 kcal per day; $n = 28,487$). We additionally excluded women who did not provide information about coffee consumption at baseline ($n = 598$). Women with missing body mass index (BMI, kg/m^2) in 1978 or 1980 were also excluded at baseline ($n = 166$) because obesity is an important risk factor for endometrial cancer (but such women were allowed to reenter the analysis once information on BMI was available), leaving 67,470 women who were followed from 1980 to 2006.

During each follow-up cycle, we excluded women who died, were diagnosed with any cancer (except nonmelanoma skin cancer) including endometrial cancer, or had their uterus removed in the previous period. For the expanded FFQ assessment post 1980, women with more than 70 blank food items and total caloric intakes <600 or >3,500 kcal/d were also excluded.

Ascertainment of endometrial cancer cases

Beginning in 1978 and on each biennial questionnaire, women were asked whether they had been diagnosed with endometrial cancer during the previous 2 years. When a woman reported a diagnosis of cancer, we sought permission to obtain the relevant medical records and pathology reports, and study physicians blinded to all questionnaire data reviewed the documents to verify diagnosis and establish an exact date of diagnosis. Cases included in this study were invasive endometrial adenocarcinoma. Deaths in the cohort were identified by reports from family members and the U.S. Postal Service as well as a search of the National Death Index; at least 98% of deaths were ascertained (23).

Assessment of coffee and dietary intake

Dietary intake including coffee and tea was assessed using a previously validated semiquantitative food frequency questionnaire completed in 1980, 1984, 1986, 1990, 1994, 1998, and 2002 (24). Participants were asked to report their average use over the preceding year for a specified serving size of each food and beverage using 9 mutually exclusive responses ranging from never/less than once per month to 6 or more times per day. The frequency of consumption was converted to cups per day (237 mL = an 8 oz cup). Decaffeinated coffee consumption was first assessed in 1984. To estimate caffeine content, we used information obtained from U.S. Department of Agriculture food composition sources, assuming 137 mg caffeine per 8 oz cup of coffee, 47 mg caffeine per 8 oz cup of tea, 46 mg caffeine per 12 oz can or bottle of cola or other caffeinated carbonated beverage, and 7 mg caffeine per 1 oz serving of chocolate. Total caffeine intake was assessed by summing the caffeine content for a serving of each item multiplied by a weight proportional to the frequency of its use.

In the validation study among a subsample of our cohort ($n = 173$), we found high correlations for the average consumption for coffee and tea as assessed by 2 FFQs administrated approximately 12 months apart and multiple 7-day diet records obtained during the 1-year interval, correcting for within-person weekly variation in diet (coffee, Pearson $r = 0.78$; tea, Pearson $r = 0.93$; ref. 25). Alcohol intake as a potential confounder was calculated as the sum of the daily number of drinks (beer, wine, and liquor) multiplied by the average alcohol content per type of each alcoholic beverage (12.8 g of alcohol for a 12-oz bottle or can of beer, 11.0 g for a 5-oz glass of wine, and 14.0 g for a drink of liquor). Alcohol assessed by FFQ was also highly correlated with intake as calculated from diet record assessment completed by a sample of study participants (Spearman $r = 0.90$; ref. 26).

Assessment of anthropometric data and other lifestyle factors

On the 1976 baseline questionnaires, we requested information about age, weight and height, menopausal status, postmenopausal hormone (PMH) use, oral contraceptive use, parity, age at last birth, age at menarche, age at menopause, and smoking. Information on duration of oral contraceptive use and parity was asked on each questionnaire through 1984, whereas most other covariate data (except height) have been updated on all subsequent biennial questionnaires. From the time women returned questionnaires reporting natural menopause, they were classified as postmenopausal. Self-report of menopausal status has been shown to be valid in this cohort (27). Information on type of postmenopausal hormone used, that is, estrogen alone or estrogen with progesterone, was asked from 1978. Pack-years of smoking were calculated by multiplying the duration and dose of smoking; 1 pack-year is equivalent to having smoked 1 pack per day for 1 year. If data were not available for any updated covariate, except for BMI, in a given 2-year period, those women were assigned to a missing category for that period. Weight from the previous questionnaire cycle was carried forward if missing. If weight was not reported for 2 consecutive time periods, women were excluded from follow-up until an updated weight was reported.

Statistical analysis

For each woman, we calculated person-years of follow-up from the date of return of the 1980 baseline questionnaire to the date of diagnosis of endometrial cancer, the date of death, the date of report of other cancer except nonmelanoma skin cancer, hysterectomy, or the end of follow-up, June 1, 2006, whichever occurred first. Cox proportional hazard regression models were used to estimate incidence rate ratios (RR) and 95% CIs of developing endometrial cancer in each category of coffee, tea, or caffeine intake compared with participants in the lowest category of the consumption as the reference (28). To control as finely as possible for confounding by age, calendar time, and any possible 2-way interactions between these 2 time scales, we stratified the analysis jointly by age in month at start of follow-up and calendar year of the current questionnaire cycle.

To represent the long-term consumption patterns for individual subjects as accurately as possible and to reduce random within-person variation, we assessed endometrial cancer risk in relation to cumulative average intake calculated from all of the preceding dietary questionnaires. For example, we used dietary data from the 1980 questionnaire for the 1980–1984 follow-up period; the average of 1980 and 1984 intakes was used for the1984–1986 follow-up period; the average of 1980, 1984, and 1986 intakes was used for 1986–1990 follow-up period, and so forth.

In multivariable models, we adjusted for the following covariates: BMI, age at menopause, age at menarche, parity and age at last birth, duration of oral contraceptive use, PMH use, pack-years of smoking, and alcohol intake. Total energy intake was also included in the multivariable model to minimize extraneous variation due to general under- or overreporting of food intake on the FFQ (29). All covariates, except age at menarche, were updated in each questionnaire cycle when new data were available. We additionally adjusted for total sugar intake, red meat intake, dairy intake, soda intake, fruit and vegetable intake, family history of endometrial cancer, history of hypertension, and physical activity in the multivariable model one at a time. Because the adjustment did not substantially change the association, we did not include these variables in the final model.

To test for linear trend across categories, we modeled coffee, tea, or caffeine intake as a continuous variable by assigning the median values to each exposure category to minimize the influence of outliers. We also examined the possibly nonlinear relation between coffee, tea, or caffeine intake and the RR of endometrial cancer, nonparametrically with restricted cubic splines (30). Tests for nonlinearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms. In addition, we used repeated measures to analyze latency (time from exposure to cancer diagnosis) by relating coffee intake to endometrial cancer incidence during specific time periods (4–8 years, 8–12 years, and 12–16 years after exposure).

We conducted analyses stratified by BMI, smoking status, menopausal status, and PMH use (among postmenopausal women). We added cross-product interaction terms of coffee intake as a continuous variable (a median value of each category) with the interaction variable of interest to the Cox model, and compared the nested models with and without the interaction terms by using the likelihood ratio test. SAS PROC PHREG with SAS version 9.1 was used for all analyses above (SAS Institute Inc.).

Results

During 26 years of follow-up, we documented a total of 672 cases of endometrial cancer. Characteristics of the study population at the midpoint (1992) are summarized in Table 1. Women who consumed the most coffee were more likely to be ever-smokers and have a lower BMI. Daily coffee drinkers consumed more alcohol and less tea.

The age-adjusted RR by coffee consumption categories [i.e., <1, 1, 2–3, and ≥4 cups/d] were 1.00, 0.95, 0.81, and 0.61 (95% CI = 0.47–0.79; $P_{trend} < 0.001$); the associations were slightly attenuated after multivariable adjustment (Table 2). Fewer than 4 cups of coffee per day were not associated with endometrial cancer risk. However, the RR for ≥4 cups/d versus <1 cup/d remained significant even after multivariable adjustment (RR = 0.75; 95% CI = 0.57–0.97; $P_{trend} = 0.02$). Smoking, BMI, and alcohol consumption were the primary confounders in the multivariable model. To examine the possibility that preclinical disease influenced dietary assessment, thereby biasing our results, we conducted an analysis excluding all cases that occurred during the first 2-year follow-up period ($n = 33$). The relationship became slightly stronger (RR ≥ 4 vs. <1 cup/d = 0.68; 95% CI = 0.52–0.90; $P_{trend} = 0.01$). When we removed women who reported on the baseline FFQ having changed their coffee intake greatly during the past 10 years ($n = 142$ cases), the relationship was slightly stronger as well (RR ≥ 4 vs. <1 cup/d = 0.68; 95% CI = 0.50–0.92; $P_{trend} = 0.01$, data not shown).

By type of coffee, women consuming 4 or more cups of caffeinated coffee per day had a 30% lower risk of endometrial cancer compared with those who drank less than 1 cup per day (RR = 0.70; 95% CI = 0.51–0.95; $P_{trend} = 0.02$). For decaffeinated coffee consumption, a suggestive inverse association was found among women who consumed 2 or more cups per day versus <1 cup/mo (RR = 0.78; 95% CI = 0.57–1.08). Both caffeinated and decaffeinated coffee consumption showed stronger inverse associations for the highest versus lowest category of coffee intake when excluding cases that occurred during the first 2-year of follow-up. As a secondary analysis, we excluded women who consumed both caffeinated and decaffeinated coffee, leaving 175 cases and 90 cases for caffeinated and decaffeinated coffee analyses, respectively. The RR for ≥4 cups/d versus <1 cup/d of caffeinated coffee was 0.69 (95% CI = 0.41–1.18), and the RR for ≥2 cups/d versus <1 cup/mo of decaffeinated coffee was 0.78 (95% CI = 0.35–1.73), which were similar to results of main analyses.

Table 1. Age-standardized characteristics by categories of cumulative average coffee consumption among women in the NHS cohort, 1992[a]

	Coffee intake			
Characteristic	**<1 cup/d**	**1 cup/d**	**2–3 cups/d**	**≥4 cups/d**
Age, y	56.0	57.9	57.7	57.2
BMI, kg/m^2	26.5	26.2	25.9	25.9
BMI ≥ 30, %	22	19	17	17
Ever smoked, %	41	51	61	72
Diabetes, %	6	6	4	3
Hypertension, %	32	33	28	25
Age at menarche, y	12.5	12.5	12.5	12.4
Oral contraceptive use, %	48	50	50	49
Nulliparous, %	7	7	6	6
Parity among parous women	3.1	3.1	3.2	3.2
Age at last birth, y	31.5	31.5	31.5	31.3
Postmenopausal, %	64	66	67	66
Age at menopause, y[b]	50.2	50.2	50.0	49.8
Current postmenopausal hormone use, %[b]	24	25	27	26
Alcohol, g/d	4.1	5.8	7.3	6.8
Tea, cup/d	1.2	0.8	0.6	0.5

[a]Values that are not percentages are means unless otherwise indicated. Data, except age, were directly standardized to the age distribution of the cohort.
[b]Age at menopause and postmenopausal hormone use were calculated among postmenopausal women only.

Another caffeinated beverage, tea consumption was not associated with risk of endometrial cancer and did not show a nonlinear relation either (P for nonlinear relation = 0.77). There was a significant inverse association between total caffeine intake and the risk of endometrial cancer ($RR_{Q5\ vs.\ Q1} = 0.72$; 95% CI = 0.55–0.95; $P_{trend} = 0.02$; Table 3).

To further investigate the association of coffee consumption among different subgroups, we conducted stratified analyses (Table 4). The inverse associations with 4 or more cups of coffee seemed stronger among obese women (BMI ≥ 30 kg/m^2; RR = 0.62; 95% CI = 0.38–1.01; $P_{trend} = 0.02$), past or current smokers (RR = 0.65; 95% CI = 0.44–0.95; $P_{trend} = 0.02$), postmenopausal women (RR = 0.74; 95% CI = 0.55–1.00; $P_{trend} = 0.04$) and those without current PMH use (RR = 0.69; 95% CI = 0.48–1.00; $P_{trend} = 0.03$), but no significant interactions between these variables and coffee intake were observed. In the latency analysis, coffee intake tended to show a slightly stronger inverse association with risk of endometrial cancer for the shorter latency periods, but the analyses with longer latency intervals did not substantially change the results (data not shown).

Discussion

In this large prospective cohort of women, long-term coffee consumption with 4 or more cups per day was associated with 25% lower risk of endometrial cancer compared with less than 1 cup of coffee, although fewer than 4 cups of coffee per day were not associated with endometrial cancer risk. Tea consumption was not associated with endometrial cancer risk.

There is some biological evidence that coffee might reduce the development of endometrial cancer. Coffee is a primary dietary source of caffeine and also contains many other biologically active components. Chlorogenic acid has relatively strong antioxidant properties that can prevent oxidative DNA damage and improves insulin resistance by increasing insulin sensitivity or inhibiting glucose absorption in the intestine (31). Caffeine has been shown to upregulate hepatic expression of CYP1A2, which can catalyze oxidation of estradiol to 2-hydroxyestradiol, which subsequently yields 2-methoxyestradiol, a metabolite with possible antitumorigenic properties (32). We previously found lower C-peptide concentrations with high caffeinated (≥4 cups/d) and decaffeinated (≥1 cup/d) coffee intake, but not tea, especially among overweight obese women (11), and higher SHBG levels with high caffeinated coffee (≥4 cups/d) or caffeine (>371 mg/d) intake among postmenopausal women, which was somewhat stronger among overweight obese women (13). Therefore, coffee may have contributed to a decreased risk of endometrial carcinogenesis due to the potential ability to lower concentrations of insulin and free estradiol in addition to the antioxidant ability of phenolic compounds in coffee.

The inverse association between coffee consumption and endometrial cancer risk in this study agrees with 2 recent prospective cohort studies in Japan and Sweden (15, 16), and 4 case–control studies (17, 33, 35, 36). A small

Table 2. Cumulative average coffee and tea consumption and risk of endometrial cancer in the NHS cohort

	Coffee intake, RR (95% CI)				
	<1 cup/d	1 cup/d	2–3 cups/d	≥4 cups/d	P_{trend}
Person-years	301,317	211,400	514,014	256,514	
No. of cases	168	140	275	89	
Age-adjusted	1.00	0.95 (0.76–1.19)	0.81 (0.67–0.98)	0.61 (0.47–0.79)	<0.001
Multivariable-adjusted[a]	1.00	1.04 (0.83–1.31)	0.93 (0.76–1.14)	0.75 (0.57–0.97)	0.02
Multivariable-adjusted[b]	1.00	0.94 (0.73–1.19)	0.94 (0.77–1.16)	0.68 (0.52–0.90)	0.01
	Caffeinated coffee intake, RR (95% CI)				
	<1 cup/d	1 cup/d	2–3 cups/d	≥4 cups/d	P_{trend}
Person-years	423,877	240,812	434,482	184,075	
No. of cases	255	151	212	54	
Age-adjusted	1.00	0.94 (0.77–1.15)	0.79 (0.66–0.95)	0.57 (0.43–0.77)	<0.001
Multivariable-adjusted[a]	1.00	1.01 (0.82–1.24)	0.89 (0.74–1.08)	0.70 (0.51–0.95)	0.02
Multivariable-adjusted[b]	1.00	0.97 (0.79–1.21)	0.92 (0.76–1.12)	0.66 (0.48–0.91)	0.02
	Decaffeinated coffee intake, RR (95% CI)[c]				
	<1 cup/mo	1 cup/mo to <1 cup/d	1 cup/d	≥2 cups/d	P_{trend}
Person-years	311,761	368,383	139,250	107,655	
No. of cases	170	245	98	54	
Age-adjusted	1.00	1.02 (0.84–1.24)	1.10 (0.85–1.41)	0.87 (0.64–1.19)	0.57
Multivariable-adjusted[a]	1.00	0.92 (0.75–1.14)	0.96 (0.74–1.25)	0.78 (0.57–1.08)	0.23
Multivariable-adjusted[b]	1.00	0.90 (0.72–1.11)	1.01 (0.78–1.32)	0.72 (0.52–1.01)	0.20
	Tea intake, RR (95% CI)				
	<1 cup/mo	1 cup/mo to <1 cup/d	1 cup/d	≥2 cups/d	P_{trend}
Person-years	235,463	677,960	194,971	162,849	
No. of cases	92	385	117	71	
Age-adjusted	1.00	1.18 (0.94–1.49)	1.39 (1.06–1.84)	1.20 (0.88–1.63)	0.25
Multivariable-adjusted[a]	1.00	1.10 (0.87–1.40)	1.24 (0.94–1.65)	1.06 (0.77–1.46)	0.70
Multivariable-adjusted[b]	1.00	0.97 (0.77–1.22)	1.21 (0.92–1.59)	0.94 (0.69–1.30)	0.77

[a]Adjusted for age (mo, continuous), BMI (kg/m^2, continuous), age at menopause [pre-/unknown menopause, <45 y, 45–46 y, 47–48 (ref), 49–50 y, 51–52 y, and ≥53 y], age at menarche [<12 y, 12 y (ref), and >12 y], parity and age at last birth [nulliparous (ref), parity 1–2 and age at last birth <30 y, parity 1–2 and age at last birth parity ≥30 y, parity 3–4 and age at last birth <30 y, parity 3–4 and age at last birth ≥30 y, parity ≥5 and age at last birth <30 y, and parity ≥5 and age at last birth ≥30 y], duration of oral contraceptive use [never (ref), <3 y, past 3–5 y, and past >5 y], postmenopausal hormone use [premenopausal, postmenopausal never (ref), past PMH, current PMH estrogen only, current PMH estrogen with progesterone], pack-years of smoking [never (ref), >0–10 pack-years, >10–20 pack-years, >20–30 pack-years, >30–40 pack-years, >40 pack-years], alcohol intake [0 (ref), 0.1–4.9g/d, 5.0–14.9g/d, >15.0g/d], and total energy intake [kcal/d, continuous]. Caffeinated coffee and decaffeinated coffee intakes were mutually adjusted in the model. Total coffee intake was adjusted for tea analysis.

[b]Excluded cases that occurred during the first 2-year follow-up period ($n = 33$ cases) to minimize the possibility that preclinical disease influenced dietary assessment. For decaffeinated coffee analysis, 28 cases were excluded.

[c]Follow-up from 1984.

prospective study including 117 cases of endometrial cancer in Japan found a RR of 0.38 for 3 or more cups of coffee per day versus 2 cups or less per week (15). A large Swedish cohort study found a RR of 0.75 for 4 or more cups of coffee per day versus 1 cup or less per day, using baseline intake (16). Four case–control studies (18, 36–38) and 2 cohort studies in Norway (39) and Sweden (40) reported a nonsignificant inverse association, whereas 2 case–control studies in Europe (41, 42) reported a nonsignificant positive association.

Only 2 case–control studies assessed the relationship between decaffeinated coffee and risk of endometrial

Table 3. Cumulative average caffeine intake and risk of endometrial cancer in the NHS cohort

	Caffeine intake, RR (95% CI)					
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P_{trend}
Median intake (mg/d)	64.0	177.6	304.6	410.0	666.5	
Person-years	226,482	249,283	269,561	265,467	272,451	
No. of cases	134	144	151	140	103	
Age-adjusted	1.00	0.93 (0.74–1.18)	0.88 (0.70–1.12)	0.85 (0.67–1.08)	0.62 (0.48–0.80)	0.002
Multivariable-adjusted[a]	1.00	0.98 (0.77–1.24)	0.98 (0.77–1.24)	0.96 (0.75–1.22)	0.72 (0.55–0.95)	0.02
Multivariable-adjusted[b]	1.00	0.99 (0.78–1.27)	0.96 (0.75–1.23)	0.97 (0.76–1.24)	0.69 (0.52–0.91)	0.01

[a]Adjusted for age (mo, continuous), BMI (kg/m^2, continuous), age at menopause [pre-/unknown menopause, <45 y, 45–46 y, 47–48 (ref), 49–50 y, 51–52 y, and ≥53 y], age at menarche [<12 y, 12 y (ref), and >12 y], parity and age at last birth [nulliparous (ref), parity 1–2 and age at last birth <30 y, parity 1–2 and age at last birth parity ≥30 y, parity 3–4 and age at last birth <30 y, parity 3–4 and age at last birth ≥30 y, parity ≥5 and age at last birth <30 y, and parity ≥5 and age at last birth ≥30 y], duration of oral contraceptive use [never (ref), <3 y, past 3–5 y, and past >5 y], postmenopausal hormone use [premenopausal, postmenopausal never (ref), past PMH, current PMH estrogen only, current PMH estrogen with progesterone], pack-years of smoking [never (ref), >0–10 pack-years, >10–20 pack-years, >20–30 pack-years, >30–40 pack-years, >40 pack-years], alcohol intake [0 (ref), 0.1–4.9 g/d, 5.0–14.9 g/d, >15.0g/d], and total energy intake (kcal/d, continuous).

[b]Excluded cases that occurred during the first 2-year follow-up period ($n = 33$) to minimize the possibility that preclinical disease influenced dietary assessment.

cancer and found no association (18, 41). We found a nonsignificant inverse association with decaffeinated coffee intake of ≥2 cups/d. Due to a narrower range of intake and shorter term use of decaffeinated coffee compared with caffeinated coffee in our cohort, we may have been underpowered to detect a significant association with decaffeinated coffee intake. Only less than 2% of the population in our cohort consumed decaffeinated coffee of ≥4 cups/d. The recent case–control study from Japan, where coffee is not the major source of caffeine, showed a

Table 4. Multivariable-adjusted RR and 95% CI of endometrial cancer according to category of cumulative average coffee intake stratified by covariates in the NHS cohort[a]

		Coffee intake, RR (95% CI)					
Covariates	No. of cases	<1 cup/d	1 cup/d	2–3 cups/d	≥ 4 cups/d	P_{trend}	$P_{interaction}$
BMI, kg/m^2							
<25	219	1.00	1.03 (0.65–1.62)	1.17 (0.80–1.69)	0.93 (0.58–1.49)	0.92	
25–29.9	207	1.00	1.05 (0.68–1.62)	0.98 (0.67–1.42)	0.78 (0.48–1.26)	0.30	0.22
30	246	1.00	1.16 (0.81–1.66)	0.77 (0.55–1.08)	0.62 (0.38–1.01)	0.02	
Smoking status							
Never	350	1.00	1.06 (0.79–1.44)	0.95 (0.73–1.25)	0.87 (0.59–1.29)	0.44	0.33
Ever	322	1.00	1.00 (0.69–1.44)	0.89 (0.65–1.22)	0.65 (0.44–0.95)	0.02	
Menopausal status							
Premenopausal	94	1.00	1.35 (0.70–2.61)	1.16 (0.66–2.03)	1.02 (0.52–2.01)	0.99	0.81
Postmenopausal	546	1.00	1.02 (0.79–1.32)	0.92 (0.73–1.15)	0.74 (0.55–1.00)	0.04	
Postmenopausal -BMI ≥25	373	1.00	1.05 (0.78–1.41)	0.84 (0.64–1.10)	0.67 (0.46–0.98)	0.02	
Postmenopausal hormone use[b]							
Never/Past use	374	1.00	0.96 (0.71–1.30)	0.84 (0.64–1.10)	0.69 (0.48–1.00)	0.03	0.24
Current use	172	1.00	1.13 (0.68–1.87)	1.11 (0.72–1.71)	0.87 (0.50–1.54)	0.68	

[a]Adjusted for the same covariates for coffee analyses in Table 2 (BMI as a continuous variable was kept in the models for <25, 25 to 29.9, and ≥30 kg/m^2. Pack-years of smoking as a categorical variable was kept in the model for past or current smokers. Past hormone use variable was kept in the model for never/past hormone users. Type of postmenopausal hormone was kept in the model for current hormone users).

[b]Among postmenopausal women only.

significant inverse association with ≥3 cups/d of coffee, but not with total caffeine intake, for endometrial cancer, suggesting potential benefits of other coffee components (17). This inference was consistent with the null association with tea intake in this study, which is another source of caffeine, although we cannot rule out the possibilities that some of tea components negate the potential benefits of caffeine in tea or that the amount of caffeine in tea is too small to observe an effect.

In subgroup analyses, we found a stronger inverse association with high coffee intake among obese women, which was consistent with findings in the Swedish cohort study (16). Because obese women tend to have insulin resistance, oxidative stress, and relatively low levels of SHBG (2), the potential abilities of coffee to improve those conditions may have contributed to a decreased risk of endometrial cancer among obese women (11, 13). We also found a stronger inverse association with high coffee intake among ever-smokers. Cigarette smoke has been shown to stimulate the synthesis of CYP1A2 as caffeine in coffee does (43). It is possible that caffeine intake in the presence of cigarette smoking substantially enhances CYP1A2 activity, thereby increasing clearance of estradiol (44, 45). No previous studies examined the possibility of caffeine as an interacting factor by smoking status, so the results should be interpreted with caution. The inverse association with higher coffee intake among postmenopausal women, but not premenopausal women, was similar for ovarian and breast cancer (46, 47). The hormonal modulation of coffee on endometrium seems to be notable for women who have naturally low estrogen levels (i.e., postmenopausal women) or those who are not using postmenopausal hormone currently.

To our knowledge, this is the largest prospective cohort study that has evaluated coffee and tea consumption using repeated dietary questionnaires, and the first cohort study to examine the long-term intake of decaffeinated coffee on risk of endometrial cancer. Using the cumulative average intake can more precisely estimate the long-term intake and reduce within-person variation. Although the use of repeated measures of coffee and tea consumption can minimize exposure misclassification, some measurement error in the dietary assessment may still have occurred due to self-reported intake and between-person variation in cup size and strength of the coffee brew. However, coffee and tea consumption assessed by questionnaires has been shown to be valid and reproducible, and any remaining misclassification would have likely biased the results toward the null (25). We carefully controlled for potential confounders in the analysis, but we cannot rule out the possibility of residual confounding. Unmeasured factors associated with coffee drinking habit may also have influenced our results. However, the factors are likely to be related to unhealthy lifestyles rather than healthy lifestyles, which make the observed association more inverse after adjusting for the factors. For example, we did not have information on substances added to coffee. Adding substantial amounts of sugar and cream to the coffee, which could contribute to insulin resistance or weight gain, may negate the potential beneficial role of coffee in relation to endometrial cancer risk. Due to the relatively small number of cases among premenopausal women in our cohort, we may have been underpowered to examine the effect modifying potential of menopausal status for the risk of endometrial cancer. A narrow range of decaffeinated coffee compared with caffeinated coffee in our cohort limited the possibility to observe an association with higher decaffeinated coffee intake. All of the findings were limited by the fact that most coffee consumption was of the caffeinated variety and most caffeine came from coffee in our cohort. However, the findings of a nonsignificant modest inverse association with 2 or more cups of decaffeinated coffee intake and lack of association with caffeine-containing tea consumption may suggest the importance of coffee components against endometrial cancer.

In conclusion, our findings provide prospective evidence with the potential beneficial role of 4 or more cups of coffee per day against endometrial cancer risk. However, recommendations about high coffee consumption should be made with caution. Because our population is relatively health conscious and thus may tend not to add substantial sugar and cream, the results of risk reduction with 4 cups of coffee per day may not be generalizable to coffee drinkers who typically add sugar or cream to coffee.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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