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A Prospective Investigation of Coffee Drinking and Endometrial Cancer Incidence

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Abstract

Coffee drinking may be associated with reduced risk of endometrial cancer; however, prospective data are limited. Further, it is not clear whether any association between coffee and endometrial cancer differs according to coffee caffeine content. The association of coffee drinking with incidence of endometrial cancer was evaluated among 226,732 women, aged 50–71, enrolled in the NIH-AARP Diet and Health Study who completed a baseline epidemiologic questionnaire. Following a mean 9.3 years of follow-up, data were available for 1,486 incident endometrial cancer cases. Cox proportional hazards models were used to estimate associations of coffee with endometrial cancer incidence. Sub-group analyses were performed according to smoking status, hormone therapy use (HT) and body habitus. Coffee drinking was inversely related to incidence of endometrial cancer (Hazard Ratio [HR] comparing drinking of >3 cups/day versus no cups=0.64, 95% CI, 0.51–0.80; $P_{\text{trend}}=0.0004$). The association of coffee with endometrial cancer risk was apparent for consumption of both regular (HR per cup=0.90, 95% CI, 0.86–0.95) and decaffeinated coffee (HR per cup=0.93, 95% CI, 0.87–0.99). The relation of coffee with endometrial cancer incidence varied significantly by HT use ($P_{\text{interaction}}=0.03$) with an association only apparent among HT-never users (HR comparing drinking >3 cups/day versus no cups=0.54, 95% CI, 0.41–0.72; $P_{\text{trend}}=0.0005$). Endometrial cancer incidence appears to be reduced among women that habitually drink coffee, an association that does not differ according to caffeine content.

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy worldwide, with more than 288,000 new cases diagnosed in 2008¹. Emerging observational data suggest that coffee drinking is inversely associated with endometrial cancer incidence. Indeed, a recent meta-analysis that included more than 2,500 endometrial cancer cases from 9 studies reported a statistically significant inverse relationship². However, the overwhelming majority of these investigations were retrospective, case-control study designs where recall

bias is a concern. Nevertheless, a recent, population-based cohort study that included more than 600 cases of incident endometrial cancer reported a 10% reduction in risk of endometrial cancer risk per cup of coffee consumed³. These data corroborated the findings of a prior prospective study which included a much smaller number of cases but which also reported a significant inverse relationship between coffee drinking and endometrial cancer risk⁴.

Despite these findings, several important issues relating to coffee drinking and endometrial cancer etiology remain to be addressed. First, it is unclear whether any potential inverse relationship between coffee and endometrial cancer risk differs according to coffee caffeine content. Prior prospective studies included too few individuals who reported drinking decaffeinated coffee to meaningfully compare the associations of endometrial cancer with regular versus decaffeinated coffee. Additional data on decaffeinated coffee drinking and endometrial cancer risk could provide clues to the mechanism(s) underlying the association of coffee with endometrial cancer (i.e. regarding caffeine as a possible chemopreventive agent). Second, smoking and coffee drinking are strongly correlated and smoking has also been reported to be inversely associated with endometrial cancer incidence. While prior prospective studies of coffee and endometrial cancer controlled for smoking status, statistical adjustment may be insufficient to fully assess whether the inverse associations of endometrial cancer with both smoking and coffee consumption are independent of one another or whether residual confounding by smoking is possible. Therefore, to fully exclude any confounding effects of smoking it may be necessary to assess the association of coffee drinking and endometrial cancer in a population with a large proportion of never-smokers.

We, therefore, investigated the relation of coffee drinking with endometrial cancer incidence in a large, longitudinal cohort of American adults - the NIH-AARP Diet and Health Study in which almost 1,500 incident endometrial cancer cases had developed by December 2006. This investigation included a large number of non-coffee drinkers as well as a sufficient number of participants that reported drinking predominantly decaffeinated coffee to enable an assessment of regular versus decaffeinated coffee consumption in relation to endometrial cancer incidence.

MATERIALS AND METHODS

Study Population

The NIH-AARP Diet and Health Study—The NIH-AARP Diet and Health Study is a large, longitudinal cohort of 566,401 men and women established in 1995–1996 to investigate the role of diet and lifestyle factors in cancer development⁵. In brief, to recruit participants into the cohort, a questionnaire was sent to 3.5 million AARP members aged 50–72 years who were residents of California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania and the metropolitan areas of Atlanta, Georgia; or Detroit, Michigan. The Special Studies Institutional Review Board of the National Cancer Institute approved the study, and all participants provided informed consent.

A total of 567,169 questionnaires were returned. Following exclusion of 179 individuals with duplicate questionnaires, 261 respondents who died before their questionnaire was processed, 321 individuals who moved out of the study area before returning their questionnaire, and 7 additional withdrawals, a prospective cohort of 566,401 individuals was established. Our analysis excluded males (n=339,669), and participants who used a proxy respondent for the baseline questionnaire (n = 1,265), reported a current or prior diagnosis of cancer other than non-melanoma skin cancer on the baseline questionnaire (n = 24,591), reported end-stage renal disease (n = 371), reported a history of hysterectomy (n = 81,696), or menstrual periods that stopped due to surgery (n = 2,234) or radiation or chemotherapy (n

= 110) on the baseline questionnaire. After further excluding participants with extreme calorie intake (defined as participants with calorie intake >2 interquartile ranges above the 75th percentile and below the 25th percentile on the log scale; n = 1,067), those with a body mass index below 12 or above 80 kg/M² (n = 3,957), and subjects with zero person-time (n = 12), 1,486 incident endometrial cancer cases and 109,943 non-cases were available for analysis.

Identification of Incident Endometrial Cancer Cases—Incident endometrial cancer cases were ascertained by record linkage to state cancer registries, based on name, address, sex, date of birth, and, if available, Social Security number. All of the contributing state cancer registries have been certified by the North American Association of Central Cancer Registries as being >90% complete in their case ascertainment^{6, 7}. The incident cases of endometrial cancer were defined by International Classification of Diseases for Oncology codes (ICD-O-3) C54.0–C54.9 and with histology codes consistent with endometrial cancer. Our analysis included all eligible cases of endometrial cancer diagnosed from baseline through December 31st, 2006.

Assessment of Coffee Consumption—Dietary intake, including coffee consumption, was evaluated with a 124-item food frequency questionnaire administered at baseline⁸. Participants were asked to report their usual frequency of coffee consumption as: None; Less than 1 cup per month; 1–3 cups per month; 1–2 cups per week; 3–4 cups per week; 5–6 cups per week; 1 cup per day; 2–3 cups per day; 4–5 cups per day; 6+ cups per day. In addition, participants were asked whether they drank regular (caffeinated) or decaffeinated coffee more than half of the time.

Statistical Analysis

The associations between coffee drinking and risk of endometrial cancer were estimated using hazard ratios (HR) obtained from Cox proportional hazards regression models, with time from study enrollment in days as the underlying time parameter. Individuals were censored at diagnosis of endometrial cancer, death, date of last contact for those who moved out of the study catchment area, or end of follow-up (December 31st, 2006), whichever occurred first. Proportionality of the data was verified by graphical inspection. All multivariable models were adjusted for the following *a priori*-determined established endometrial cancer risk factors: age (<55 [referent], 55–59, 60–64, 65–69, or 70); BMI (<18.5, 18.5–<25 [referent], 25–<30, 30); smoking status (never [referent], former, current); ethnicity (white [referent], black, Asian, other); usual physical activity (never/rarely [referent], 1–3 times/month, 1 time/week); age at menarche (10, 11–12, 13 years), age at first child's birth (<20, 20–29, 30 years), age at menopause (still menstruating, <44, 44–49, 50–54, 55 years), parity (nulliparous, 1–2 children, 3 children), type 2 diabetes (yes/no), hormone therapy use (never, ever), and oral contraceptive use (never, ever). Additional variables, including a family history of endometrial cancer, alcohol consumption, use of non-steroidal anti-inflammatory drugs (NSAIDs), and cigarette pack-years were evaluated as potential covariates but their inclusion in our *a priori*-determined multivariate models did not alter the risk estimates and therefore they were not considered in subsequent models. We performed additional analyses stratified by smoking status (never versus ever), use of HT (never-user or ever-user), and BMI (<25 Kg/M² or ≥ 25 Kg/M²). To test for statistically significant differences in the association between the coffee variables and risk of endometrial cancer between strata of ever use of hormone therapy, BMI and smoking, we compared the fit of multivariable models with and without an interaction term between coffee and the stratified factor using the likelihood ratio tests. All tests of statistical significance were two-sided, and P values less than 0.05 were considered statistically significant. All analyses were performed using SAS version 9.2 (Cary, NC).

RESULTS

Baseline characteristics

During a mean 9.3 years of follow-up, 1,486 women were diagnosed with endometrial cancer. Table 1 presents distributions of endometrial cancer risk factors across categories of frequency of coffee drinking among the non-cancer subjects. Frequency of coffee consumption was strongly, positively associated with current smoking: the prevalence of current smokers among women reporting no habitual drinking of coffee was approximately 8% while 34% of participants who reported consumption of more than 3 cups of coffee per day were current smokers. Coffee drinking was inversely related to obesity such that among non-coffee drinkers, 26% were obese (BMI > 30 Kg/M²) while of the women who reported drinking >3 cups of coffee per day, 18% were obese. A similar, inverse pattern was evident for prevalence of diabetes and for nulliparity. The distributions of the baseline characteristics of the non-cancer subjects did not differ according to consumption of regular coffee only or decaffeinated coffee only (data not shown).

Risk of Endometrial cancer

Table 2 presents age-adjusted and multivariable-adjusted hazard ratios and 95% confidence intervals (CIs) for the association between coffee drinking and endometrial cancer incidence. In a multivariable model that included established endometrial cancer risk factors, the risk of developing endometrial cancer was reduced by 6% for each cup of coffee consumed (HR = 0.94; 95% CI, 0.90–0.97; P-trend = <0.0001). Similarly, when analyzed as a categorical variable, compared to women that reported no coffee drinking, the consumption of more than 3 cups of coffee per day was associated with a >35% reduction in endometrial cancer incidence (HR = 0.64; 95% CI, 0.51–0.80; P-trend = 0.0004). Further, compared to non-drinkers, even the consumption of one cup of coffee was associated with a statistically significant reduced incidence of endometrial cancer (HR = 0.82, 95% CI: 0.68–0.98). The inverse relation between coffee drinking and endometrial cancer risk was maintained following exclusion of women who reported no coffee drinking and restricting the analysis to coffee-drinkers only (HR comparing women drinking >3 cups per day versus those who consumed 1 cup of coffee per day = 0.74, 95% CI, 0.59–0.91).

The association of coffee drinking with endometrial cancer risk was apparent for both caffeinated and decaffeinated coffee drinking (HR per cup of regular coffee = 0.90, 95% CI, 0.86–0.95; HR per cup of decaffeinated coffee = 0.93, 95% CI, 0.87–0.99). When evaluated as a categorical variable, the associations of endometrial cancer with drinking of 2–3 cups of regular and decaffeinated coffee were very similar (HR comparing women who consumed 2–3 cups of regular coffee per day with non-drinkers = 0.74, 95% CI, 0.61–0.90; P_{trend} = <0.0001; HR comparing women who consumed 2–3 cups of decaffeinated coffee per day with non-drinkers = 0.66, 95% CI, 0.51–0.85; P_{trend} = 0.004). However, for consumption of >3 cups of coffee per day, the association with endometrial cancer was only apparent for regular coffee (HR comparing women who consumed >3 cups of regular coffee per day with non-drinkers = 0.46, 95% CI, 0.34–0.63; HR comparing women who consumed >3 cups of decaffeinated coffee per day with non-drinkers = 0.81, 95% CI, 0.54–1.20).

The relation of coffee drinking with endometrial cancer incidence differed according to ever use of hormone therapy (P_{interaction} = 0.03; Table 3). Among women with no history of HT use, coffee drinking was inversely related to endometrial cancer risk (HR comparing consumption of >3 cups of coffee per day compared to non-drinkers = 0.54, 95% CI, 0.41–0.72; P_{trend} = 0.0005), while among ever HT-users, this relationship was much weaker and did not attain statistical significance (HR comparing consumption of >3 cups of coffee per day compared to non-drinkers = 0.88, 95% CI, 0.61–1.26; P_{trend} = 0.138). The inverse

relation of coffee drinking with endometrial cancer risk was also stronger among overweight and obese women (HR comparing consumption of >3 cups of coffee per day compared to non-drinkers = 0.56, 95% CI, 0.43–0.73; P-trend= <0.0001) compared to women with normal body size (HR comparing consumption of >3 cups of coffee per day compared to non-drinkers= 0.84, 95% CI, 0.55–1.29; P_{trend}= 0.17), albeit the test for interaction did not attain statistical significance (P_{interaction}= 0.24). The association of coffee with endometrial cancer incidence did not differ according to smoking status (P_{interaction}= 0.92). Finally, restriction of the analysis to non-diabetics or to those with Type I (endometrioid histology) tumors, did not alter the risk estimates.

DISCUSSION

In this large, prospective investigation of U.S women, we observed a statistically significant inverse association between coffee drinking and endometrial cancer incidence which was strongest among women who had never used hormone therapy and among overweight and obese women. Further, the risk of endometrial cancer appeared to be reduced in both regular coffee drinkers and those drinking decaffeinated coffee most of the time. The results of this investigation contribute to a growing literature on coffee drinking and cancer development and suggest that coffee drinking may offer a potential chemopreventive strategy for endometrial cancer prevention, particularly among those at higher risk of this disease.

Evidence that coffee drinking is inversely related to endometrial cancer development has accumulated from a number of epidemiologic studies. In particular, two recent prospective investigations reported statistically significant inverse associations between coffee consumption and endometrial cancer risk among women in Japan⁴ and Sweden³, and the results of the current investigation are highly consistent with these prior studies.

Several biological mechanisms have been advanced to explain the inverse relationship of coffee drinking with endometrial cancer development. Most notably, it has been hypothesized that coffee reduces the risk of endometrial cancer through an insulin-mediated mechanism. Hyperinsulinemia has been positively associated with endometrial cancer development⁹ and endometrial cancer cell lines express high-affinity insulin receptors, consistent with there being a direct biologic effect of insulin on the growth of endometrial cancer cells¹⁰. Coffee consumption has been demonstrated to improve insulin sensitivity¹¹ and both caffeinated and decaffeinated coffee are associated with reduced insulin levels, particularly among overweight women¹². Hyperinsulinemia may also impact endometrial cancer development through indirect mechanisms, for example, through up-regulation of free, or bioavailable, insulin-like growth factor (IGF)-I, or through suppression of sex hormone binding globulin (SHBG) which elevates estradiol bioactivity. Interestingly, coffee drinking has been associated with higher SHBG levels which would likely reduce endometrial cancer risk through decreased estradiol exposure¹³.

In addition to a potential insulin-mediated mechanism, it is possible that other pathways may mediate the inverse association of coffee consumption and endometrial cancer. It is of note that in addition to coffee, other lifestyle factors have been inversely linked to endometrial cancer risk. For example, several prospective investigations have reported inverse associations between cigarette smoking and endometrial cancer¹⁴, a finding that has been attributed to possible anti-estrogenic effects of tobacco smoke¹⁵. A factor that is common to coffee and tobacco smoke is the presence of bioactive compounds known to induce elements of cytochrome P450 metabolism. Caffeine and other bioactive compounds present in coffee can up-regulate hepatic expression of CYP1A2 and CYP3A4 which lead to clearance of estradiol, or even the synthesis of metabolites that may have anti-proliferative effects on endometrial cells, such as 2-methoxyestradiol¹⁶. Of note, we observed that while the

association between coffee drinking and endometrial cancer risk did not significantly differ according to smoking status, the relation was slightly stronger among those with a history of smoking. This may suggest potential synergy between the bioactive components of coffee and tobacco smoke in endometrial tumorigenesis that may be mediated by a common biologic pathway.

Interestingly, the inverse association of coffee with endometrial cancer was restricted to women without a history of using hormone therapy and was somewhat stronger among overweight and obese participants compared to leaner individuals. These findings corroborate those of Friberg et al. who also reported a more pronounced association of coffee with endometrial cancer among obese women³. Hormone therapy use and obesity have profound effects on the hormonal milieu that may impact upon potential biologic mechanisms hypothesized to underlie the coffee-endometrial cancer relation. Overweight/obese women have, on average, higher levels of insulin, IGF-I and estrogen than leaner women while HT users have low levels of insulin and IGF-I because of the hepatic first pass effect of oral HT which leads to suppression of insulin/IGF axis protein synthesis. Prospective cohort studies of insulin and endometrial cancer have reported similar effect modifications to those reported in the current study whereby the positive association of insulin with endometrial cancer is greatest among obese women and those not using HT at baseline⁹. If the coffee-endometrial cancer relation is indeed driven by hormonal pathways such as insulin, as discussed above, then overweight/obese women and HT non-users may experience the greatest reduction in endometrial cancer risk as a result of coffee drinking since they have higher insulin levels.

A major strength of the current study is a population with a broad range of coffee-drinking habits and a large proportion of women who reported drinking decaffeinated coffee for the majority of the time. Prior investigations of coffee and endometrial cancer included few decaffeinated coffee drinkers and their ability to assess the association of different coffee types with endometrial cancer, with adequate precision, was limited. Our finding that women who reported drinking predominantly decaffeinated coffee were also at reduced risk of endometrial cancer suggests that compounds, other than, or in addition to, caffeine, may underlie the inverse association of coffee with endometrial tumorigenesis. Coffee is known to contain an array of compounds, depending on the roasting and preparation method, that may have anti-oxidative and anti-tumorigenic activity. For example, cafestol and kahweol have been reported to inhibit the effects of several carcinogens including polycyclic aromatic hydrocarbons and chlorogenic acid has potent anti-oxidative and insulin-sensitizing properties¹⁷. Coffee is also a source of phytoestrogens such as isoflavones and lignans¹⁸ which have been associated with reduced risk of endometrial cancer¹⁹. Further research is necessary to delineate the mechanism by which coffee potentially reduces endometrial cancer risk and to isolate the putative chemopreventive agents.

To our knowledge, this is the largest study to have investigated the relation of coffee drinking with endometrial cancer risk in a prospective manner. The well-characterized, longitudinal cohort of more than 200,000 women with almost 1,500 cases verified by tumor registry data and detailed information on coffee drinking habits enabled us to assess risk of endometrial cancer development in relation to consumption of regular coffee and decaffeinated coffee, and to evaluate this relationship among women with different body habitus, smoking history and hormone therapy use - all factors that could have a significant confounding effect on the association of coffee with endometrial cancer. An important limitation is the lack of data on coffee consumption and other pertinent variables both in the past and during the follow-up period. It is possible, for example, that individuals may change coffee drinking habits later in life (e.g. change from regular to decaffeinated coffee drinking) though we note that the youngest study participants were already 50–55 years of

age at enrollment. Multiple repeat-assessment of coffee drinking during follow-up may have enabled more accurate classification of participants with regard to longer-term coffee drinking habits. However, given the prospective nature of this study, it is likely that any misclassification was non-differential and would, in any event, lead to under-estimation of the association of coffee with endometrial cancer risk. In addition, while we were able to obtain information of consumption of caffeinated and decaffeinated coffee, we lacked data on specific types of coffee (e.g. type or roast) and preparation method-both of which have been shown to influence levels of putative bioactive components. Future studies that evaluate specific coffee types and brewing method could be important in yielding further data on biologic mechanism. A further limitation of the study lies in how the data on regular versus decaffeinated coffee intake was collected. Participants were queried on whether they consumed decaffeinated or regular coffee (or both) for more than half of the time, thus it is possible that some individuals who were classified as solely decaffeinated coffee drinkers, did in fact drink regular coffee at least some of the time. However, it is likely that the overwhelming majority of study subjects classified as decaffeinated coffee drinkers did indeed consume decaffeinated coffee most of the time since those who drank both regular and decaffeinated coffee in equal measure would have identified themselves as consumers of both coffee types.

The current study also lacked follow-up data on hysterectomy and failure to control for follow-up hysterectomy status could have potentially led to bias if coffee drinking habits were strongly associated with hysterectomy. While we were unable to assess any relation between coffee drinking patterns and hysterectomy during the follow-up period, we did compare coffee drinking habits among women who had undergone hysterectomy prior to enrollment with those that had an intact uterus at baseline and found coffee drinking patterns to be essentially the same. Therefore, we feel it is unlikely that failure to account for hysterectomy during follow-up led to any substantial bias in the results. Finally, a potential limitation of the current study's findings is lack of generalizability to other populations, given that the NIH-AARP Diet and Health Study achieved a <20% response rate. In light of this, the coffee-endometrial cancer relation should be explored in other population groups; however, the consistency of our results with those from other prospective studies conducted in Japan and Sweden suggests that our findings may well be generalizable to other populations.

In conclusion, we report a statistically significant inverse association between both regular coffee and decaffeinated coffee drinking and endometrial cancer development. Given that many regions of the world are experiencing increasing rates of endometrial cancer, most likely due to rising obesity rates, prevention strategies for endometrial cancer are urgently needed. Further research should be conducted to establish whether there is a true, causal relationship between coffee drinking and endometrial cancer. If so, coffee may offer a potential chemopreventive strategy for endometrial cancer, particularly among women at higher risk of this malignancy.

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Distribution of selected endometrial cancer risk factors by frequency of coffee drinking among non-cancer subjects in the NIH-AARP Diet and Health Study

Table 1

	Frequency of Coffee Drinking			
	0 cups/day	< 1 cup/day	1 cup/day	>3 cups/day
N	43,354	7,897	11,333	10,730
Mean Age ($\pm$ SD)	60.9 $\pm$ 5.6	61.4 $\pm$ 5.6	62.3 $\pm$ 5.4	61.3 $\pm$ 5.4
White Ethnicity (N, %)	12,168 (90.4%)	16,194 (87.1%)	17,222 (88.6%)	14,346 (97.0%)
Obese, BMI $\geq$ 30 (N, %)	3,569 (26.0%)	4,750 (25.1%)	4,528 (23.0%)	2,735 (18.3%)
Diabetes (N, %)	1,103 (8.0%)	1,467 (7.8%)	1,480 (7.5%)	738 (4.9%)
Current Smoker (N, %)	1,078 (8.2%)	1,466 (8.1%)	1,734 (9.1%)	4,917 (34.0%)
Physical Exercise $\geq$ 1 per week (N, %)	8,440 (62.5%)	12,033 (64.4%)	12,373 (63.6%)	9,037 (61.1%)
Ever Use of Hormone Therapy (N, %)	5,054 (36.9%)	7,557 (40.0%)	7,734 (39.3%)	5,648 (37.8%)
Ever Use of Oral contraceptives (N, %)	5,522 (41.3%)	7,769 (41.9%)	7,594 (39.3%)	5,973 (40.6%)
Age at Menarche $<$ 10 Years (N, %)	899 (6.7%)	1,160 (6.2%)	1,145 (5.9%)	1,009 (6.8%)
Age at First Birth $>$ 30 years (N, %)	1,012 (7.6%)	1,533 (8.3%)	1,521 (7.9%)	938 (6.4%)
Nulliparous (N, %)	2,593 (19.3%)	3,563 (19.2%)	3,366 (17.4%)	2,417 (16.4%)
Age at Menopause $\geq$ 55 years (N, %)	1,393 (10.4%)	1,998 (10.8%)	2,153 (11.1%)	1,280 (8.7%)

Table 2
Hazard Ratios and 95% Confidence Intervals for the Association of Coffee Drinking with Endometrial Cancer incidence in the NIH-AARP Diet and Health Study

Total Coffee Consumption	0 cups/day	<1 cup/day	1 cup/day	2-3 cups/day	>3 cups/day	P-trend	Per Cup
Cases (N)	231	276	273	573	133		
Basic Model * HR (95% CI)	1.00 (ref)	0.89 (0.75-1.06)	0.82 (0.69-0.98)	0.85 (0.72-0.99)	0.64 (0.52-0.80)	0.003	0.94 (0.91-0.97)
Full Model [†] HR (95% CI)	1.00 (ref)	0.87 (0.73-1.05)	0.82 (0.68-0.98)	0.83 (0.71-0.97)	0.64 (0.51-0.80)	0.004	0.94 (0.90-0.97)
Regular Coffee [§]	0 cups/day	<1 cup/day	1 cup/day	2-3 cups/day	>3 cups/day	P-trend	Per Cup
Cases (N)	231	80	100	264	56		
Basic Model * HR (95% CI)	1.00 (ref)	0.76 (0.58-0.98)	0.65 (0.51-0.83)	0.67 (0.55-0.81)	0.39 (0.29-0.53)	<0.0001	0.87 (0.83-0.91)
Full Model [†] HR (95% CI)	1.00 (ref)	0.75 (0.57-0.98)	0.68 (0.53-0.87)	0.74 (0.61-0.90)	0.46 (0.34-0.63)	<0.0001	0.90 (0.86-0.95)
Decaffeinated Coffee [‡]	0 cups/day	<1 cup/day	1 cup/day	2-3 cups/day	>3 cups/day	P-trend	Per Cup
Cases (N)	231	112	80	108	30		
Basic Model * HR (95% CI)	1.00 (ref)	0.83 (0.66-1.06)	0.78 (0.60-1.01)	0.64 (0.51-0.82)	0.70 (0.47-1.02)	0.0002	0.91 (0.85-0.97)
Full Model [†] HR (95% CI)	1.00 (ref)	0.88 (0.70-1.12)	0.81 (0.62-1.06)	0.66 (0.51-0.85)	0.81 (0.54-1.20)	0.004	0.93 (0.87-0.99)

* Basic model adjusted for age only;

[†] Multivariable model that additionally adjusted for age, smoking, BMI, age at menarche, age at first child's birth, parity, age at menopause, HT use, oral contraceptive use, diabetes and physical activity

[§] Excludes participants who also reported drinking decaffeinated coffee;

[‡] Excludes participants who also reported drinking regular coffee;

Multivariable Hazard Ratios and 95% Confidence Intervals for the Association of Total Coffee Consumption with Endometrial Cancer Incidence with Stratification by Hormone Therapy use, Body Mass Index and Smoking Status.

Table 3

	Cases (N)	Frequency of Coffee Drinking				P (trend)	HR per cup
		<1 cup/day	1 cup/day	2 – 3 cups/day	>3 cups/day		
Hormone Therapy¹							
Never used HT	633	0.84 (0.68–1.05)	0.74 (0.59–0.92)	0.78 (0.64–0.95)	0.54 (0.41–0.72)	0.0005	0.92 (0.88–0.96)
Ever used HT	441	0.98 (0.72–1.35)	1.03 (0.75–1.40)	0.96 (0.72–1.27)	0.88 (0.61–1.26)	0.1380	0.97 (0.92–1.03)
P-interaction	0.03						
Body Mass Index²							
BMI < 25 Kg/M2	340	0.82 (0.56–1.21)	1.19 (0.83–1.69)	0.91 (0.66–1.27)	0.84 (0.55–1.29)	0.1704	0.95 (0.89–1.02)
BMI ≥ 25 Kg/M2	734	0.90 (0.73–1.10)	0.69 (0.56–0.85)	0.78 (0.65–0.93)	0.56 (0.43–0.73)	<0.0001	0.92 (0.88–0.96)
P-interaction	0.24						
Smoking status³							
Never smoked	568	0.98 (0.78–1.24)	0.86 (0.68–1.08)	0.86 (0.70–1.06)	0.70 (0.50–0.98)	0.0256	0.93 (0.89–0.98)
Ever Smoked	506	0.72 (0.54–0.97)	0.74 (0.56–0.99)	0.74 (0.58–0.95)	0.54 (0.39–0.73)	0.0008	0.93 (0.89–0.97)
P-interaction	0.92						

¹ Adjusted for age, ethnicity, BMI, smoking, oral contraceptive use, age at menarche, age at first child's birth, parity, age at menopause, physical activity and diabetes.

² Adjusted for age, ethnicity, smoking, HT use, oral contraceptive use, age at menarche, age at first child's birth, parity, age at menopause, physical activity and diabetes.

³ Adjusted for age, ethnicity, BMI, HT use, oral contraceptive use, age at menarche, age at first child's birth, parity, age at menopause, physical activity and diabetes.