

Does caffeine intake and coffee consumption associate with endometrial cancer among postmenopausal women in America using NHANES 2003–2012?

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Background: In 2015, it has been estimated that 54,870 new cases of endometrial cancer will be diagnosed and about 10,170 women will die from it in United States. Previous studies suggested that high levels of coffee consumption may be associated with reduced risk of endometrial cancer among women ages 50–71. Although caffeine is a major ingredient of coffee, one study stated this inverse association does not differ according to caffeine content (regular coffee/decaffeinated coffee). However, the specific measurement of caffeine intake was not clear in that previous study. This study tries to investigate endometrial cancer risk in relation to caffeine intake and coffee consumption.

Methods: The National Health and Nutrition Examination Survey (NHANES) 2003–2012 surveys were used in this study. A total of 5,847 postmenopausal women with valid cancer status were included in this study. Chi-square tests and *t*-tests were used to examine differences in proportions. Multiple logistic regression models were used to determine whether there was an association between the caffeine intake and endometrial cancer, after adjustment of various potential confounding variables. Weighting is supplied by NHANES data.

Results: Among the women in the study, 1.37% of them were diagnosed with endometrial cancer. After multivariate adjustment, compared to women who did not have any caffeine intake, a significant increase in endometrial cancer was found in all levels of caffeine intake [OR =25.646 (\leq 93 mg/day *vs.* non-taken), 95% confidence interval (CI): 3.248–202.481; OR =17.299 (>93 mg/day *vs.* non-taken), 95% CI: 2.210–135.434] and coffee consumption [OR =42.865 (\leq 358 g/day *vs.* non-taken), 95% CI: 5.260–349.347; OR =16.354 (>358 g/day *vs.* non-taken), 95% CI: 1.880–142.301]. The results also showed that black women and women using birth control pills were less likely to get endometrial cancer, but women who are excessively obese have a significantly higher risk of getting endometrial cancer.

Conclusions: Our findings suggested that caffeine intake was associated with endometrial cancer. Compared to no caffeine intake, all level of coffee consumption and caffeine intake were risk factors of endometrial cancer. Black women had lower risk of endometrial cancer. A history of birth control pill use was a protected factor, while excess obesity was risk factor of endometrial cancer.

Keywords: Caffeine; coffee; endometrial cancer; cancer

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Introduction

Endometrial cancer is the most common gynecologic cancer in the United States (US). In 2016, it has been estimated that about 60,050 new cases of endometrial cancer will be diagnosed and about 10,470 women will die from it in the US. It is more common in women who are after menopause. Some endometrial cancer may be hardly found by signs and symptoms before reaching an advanced stage, and the 5-year survival rate for women with stage IV endometrial cancer is just around 16% (1). There are several known risk factors for endometrial cancer, such as obesity, insulin resistance, estrogen use after menopause, and decreased plasma sex hormone binding globulin (SHBG) (2-6). Interestingly, cigarette smoking has been reported as a beneficial factor to endometrial cancer by some studies (7,8).

Coffee has been one of the most widely consumed beverages for centuries. In the United States, 59% of Americans saying they drink coffee every day, while 71% saying they drink coffee at least once per week (9). It contains some beneficial phytochemicals such as antioxidants and anti-mutagenic properties (10,11). Some studies found that coffee consumption may reduce the total cancer incidence (12,13) and even lower the risk of allcause mortality (14,15). Additionally, coffee consumption may have an inverse association with some type of cancers. In Arnlöv's study, coffee consumption may reduce the risk of kidney cancer by improving insulin sensitivity (16). Cavin and his colleagues found that cafestol and kahweol in coffee may fight against colorectal cancer and may induce excretion of bile acids and neutral sterols into the colon (17). The results from Setiawan's study suggested that coffee consumption has an inverse association with risk of liver cancer (18). Nagata's study found that high intake of caffeine may increase sex hormone-binding globulin, and this hormone change may have an inverse association with breast or endometrial cancer risk (19).

In recent years, the connection between coffee consumption and associated risk of endometrial cancer has held great interest. Several epidemiological studies have shown evidence that coffee consumption has an inverse association with endometrial cancer (20-25). Coffee naturally contains numerous compounds, such as caffeine, antioxidants, diterpenes, acrylamide and furan, whose concentrations vary widely by coffee processing and preparation. Among those compounds, caffeine is the major pharmacological active component in coffee. To our knowledge, no study has attempted to measure and control for caffeine intake directly to see whether caffeine is the key cause associated with endometrial cancer.

Therefore, the main objective of this study was to investigate the association of caffeine intake and endometrial cancer risk using the National Health and Nutrition Examination Survey (NHANES).

Methods

Study population

The NHANES, initiated by the Centers for Disease Control and Prevention (CDC) and National Center for Health Statistics (NCHS), is a population-based survey that assesses the health and nutritional status of adults and children in the United States. It is unique for combining interviews and physical examinations. Every cycle year about 5,000 participants are sampled to be representative of the noninstitutionalized US residents, and it oversamples persons 60 and older, African Americans, Asians, and Hispanics to ensure adequate sample size for evaluation of the subgroups (26). For the purpose of this study, 2003–2012 NHANES were used, which combined five data sets of 2-year cycles (2003–2004, 2005–2006, 2007–2008, 2009–2010 and 2011–2012).

This study limited the analysis to postmenopausal female participants aged 20 years and above who answered the reproductive questionnaire and attended medical examination and dietary recall interview. Self-reported menopause was identified when the participants answered "menopause/change of life" to the question, "What is the reason that you have not had a period in the past 12 months?" Endometrial cancer status was identified by questions "Have you ever been told by a doctor or other health professional that you had cancer or a malignance of any kind?" and "What kind of cancer was it?" In this study, a total of 5,847 post-menopausal women aged \geq 20 with complete information were included in the analysis, and 84 of them have been diagnosed as endometrial cancer. This analysis was IRB approved by NHANES.

Measurements

Dietary data

The US Department of Agriculture (USDA) developed and validated a multiple-pass dietary recall method for NHANES to collect dietary data. Two dietary recall interviews are conducted in person by trained dietary interviewers. The first one was a face-to-face interview in the Mobile Examination Center (MEC), and the second one

would be done in 3–10 days later by telephone. Participants reported an uninterrupted listing of all foods and beverages consumed in a 24-hour period the day before (27,28). The volume and dimensions of the food items consumed were estimated by a standard set of measuring tools. The USDA's food and Nutrient Database for Dietary Studies was used to code dietary intake data and calculate nutrient intakes. USDA calculated nutrient content accurately for every food and beverage. For example, according to their database, 6 ounces restaurant-prepared brewed espresso contains 377 mg caffeine, 6 ounces restaurant-prepared brewed decaffeinated espresso contains 2 mg caffeine, and 6 ounces milk based hot chocolate contains 4 mg caffeine (29).

Data on caffeine intake (mg/day), coffee consumption (g/day), sugar intake (g/day) and energy intake (kcal/day) were obtained from the total nutrient file, which contains total nutrients from food and beverages during a 24-hour period. According to USDA National Nutrient Database for Standard Reference Release 28 (29), one 6 fluid ounce serving of instant regular coffee, which is prepared only with water, should be 179 g. And it contains about 47 mg caffeine. A report showed the average coffee consumption in US is 2.1 cups per day (9). Therefore, in this study, the variable of coffee consumption was categorized in two groups, which were equal or less than two serving (358 g) per day and greater than two serving (358 g) per day. Equivalently, caffeine intake was classed in two groups: equal or less than two serving (93 mg) per day and greater than two serving (93 mg) per day. Sugar intake and energy intake were kept continuous, and continuous caffeine intake and continuous coffee consumption would still be in analysis.

Demographic data

Age, race, education level, poverty level and marital status during the past 30 days were self-reported during the NHANES interview. NHANES categorized race as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, non-Hispanic Asian, and non-Hispanic multiracial. In this study, Mexican American, other Hispanic, non-Hispanic Asian and non-Hispanic multiracial were grouped in one as "other". Education level was classed in four groups: less than high school, high school diploma/ GED, some college or AA degree, and college graduate or above. Marital status was categorized in three groups: never married, married/living with partner, and divorced/widowed/ separated. The income level was measured by using incometo-poverty ratio: the ratio of family or unrelated individual income to their appropriate poverty threshold, which is family size adjusted. Ratio below 1.00 indicates that the income for the respective family or unrelated individual is below the official definition of poverty.

Reproductive data

Twelve years and older female MEC participants were eligible to answer the reproductive health questionnaire during the NHANES interview. Self-report birth control use history status was identified by question "Ever taken birth control pills?" Information on hormone use history status was obtained from the answer of "Have you ever used female hormones such as estrogen and progesterone?"

Other covariates

Body mass index (BMI) is a measure of body fat based on height and weight. Some studies reported it as related to endometrial cancer. It is calculated as weight in kilograms divided by height in meters squared. In this study, participants were categorized into four BMI groups: underweight/normal (BMI <25), overweight ($25 \le BMI < 30$), obese ($30 \le BMI < 35$), and excessively obese (BMI ≥ 35).

This study used "pack/year" to measure the smoking status. Average amount of cigarettes the individual participants smoked in 1 year were calculated based on these questions: "Have you smoked at least 100 cigarettes in your entire life?"; "Do you now smoke cigarettes?"; "How old when you first started to smoke cigarettes fairly regularly?"; "How old were you when you last smoked cigarettes?"; "At that time, about how many cigarettes did you usually smoke per day?"; "On how many of the past 30 days did you smoke a cigarette?" and "During the past 30 days, on the days that you smoked, about how many cigarettes did you smoke per day?" After obtaining the total number of cigarettes the participant smoked in 1 year, the "pack/year" was calculated by the total number divided by 20. The participant who smoked less than 100 cigarettes in his/her life was considered as non-smoker.

Statistical analyses

Descriptive statistics of all the characteristics, including demographic characteristic, dietary intake, and reproductive health status, were presented by cancer status (yes/no). The Rao-Scott chi-square test with an adjusted F statistic and *t*-test were used to evaluate the difference of the means of continuous variables and the difference of the frequency of categorical variables.

A logistic regression model with appropriate weight

was used to evaluate whether caffeine intake or coffee consumption was a predictor of endometrial cancer. The outcome variable was endometrial cancer status. Both univariate and multivariable analyses were applied. In order to determine a final model, the stepwise variable selections (with a P value of 0.05 as entry and removal criteria) were performed. The covariates included demographic characteristics (age, race, education, income-to-poverty ratio, and marital status), dietary intake (sugar intake, calorie intake), reproductive characteristics (birth control use status, hormones use status), BMI, and smoking status. These covariates were forced in the multivariate models.

All statistical analyses were computed using survey commands (e.g., PROC SURVEYMEANS, PROC SURVEYREG, PROC SURVEYLOGISTIC) of SAS 9.2 to incorporate sample weights (30) and adjust for clusters and strata of the complex sample design. The 2-year MEC survey weight divided by 5 applied to each participant in this 10-year survey (31). The difference estimates, adjusted odds ratios (ORs), and the corresponding 95% confidence intervals (CIs) of those variables were calculated. All P values were 2-sided and considered as significant when <0.05.

Results

The distribution of all characteristics in women with or without an endometrial cancer history after applying sample weights is shown in *Table 1*. Among post-menopausal women who self-reported a history of endometrial cancer, they were most often white (white 84.76% *vs.* black 6.13% *vs.* 9.12% Hispanic/other), of higher education level (less than high school 22.16% *vs.* high school diploma/GED 29.94%, some

Table 1 Demographic and risk factors of endometrial cancer status

Characteristics	Women with endometrial cancer	Women without endometrial cancer	P value
Age			0.4009
Ν	84	5,763	
Mean ± SE	63.77±1.4384	62.55±0.2261	
Race, N (%)			0.1653
White	53 (84.76)	2,998 (77.45)	
Black	12 (6.13)	1,252 (10.70)	
Hispanic/other	19 (9.12)	1,513 (11.85)	
Education level, N (%)			0.6476
Less than high school	29 (22.16)	1,804 (20.32)	
High school diploma/GED	22 (29.94)	1,481 (27.68)	
Some college or AA degree	19 (21.34)	1,529 (29.38)	
College graduate or above	14 (26.55)	940 (22.63)	
Family poverty income ratio, N (%)			0.8499
≤1.00	15 (12.44)	976 (11.00)	
1.01–2.00	20 (21.00)	1,561 (23.21)	
2.01–4.00	20 (26.88)	1,456 (30.54)	
>4	20 (39.68)	1,302 (35.25)	
Marital status, N (%)			0.6067
Never married	2 (2.80)	361 (5.19)	
Married/living with partner	47 (62.28)	2,809 (57.84)	
Divorced/widowed/separated	34 (34.91)	2,592 (36.97)	

Table 1 (continued)

Table 1 (continued)

Characteristics	Women with endometrial cancer	Women without endometrial cancer	P value
Daily total caffeine intake (mg)			0.0182
Ν	84	5,762	
Mean ± SE	126.48±15.4977	166.43±3.7125	
Daily total caffeine intake level (mg), N (%)			0.2609
0	3 (0.99)	349 (4.37)	
≤93	39 (43.82)	2,498 (36.78)	
> 93	42 (55.17)	2,916 (58.85)	
Daily coffee consumption (gm)			0.1864
Ν	84	5,762	
Mean ± SE	261.15±38.1714	315.62±8.5497	
Daily coffee consumption level (gm), N (%)			0.0250
0	33 (31.80)	2,523 (41.53)	
≤358	30 (39.96)	1,580 (23.04)	
>358	21 (28.24)	1,660 (35.44)	
Daily total sugars intake (gm)			0.4048
Ν	84	5,763	
Mean ± SE	97.55±3.6184	94.35±1.0198	
Daily total energy intake (kcal)			0.2993
Ν	84	5,763	
Mean ± SE	1,731.02±69.6564	1,659.10±11.5802	
BMI categories, N (%)			0.0528
Underweight/normal	22 (26.49)	1,477 (29.13)	
Overweight	21 (19.66)	1,799 (32.15)	
Obesity	13 (22.13)	1,287 (20.56)	
Excess obesity	27 (31.72)	1,103 (18.15)	
Ever use birth control pills, N (%)			0.0132
Yes	38 (46.88)	3,305 (64.91)	
No	45 (53.12)	2,442 (35.10)	
Ever use female hormones, N (%)			0.9012
Yes	32 (46.94)	2,253 (46.07)	
No	52 (53.06)	3,469 (53.93)	
Smoking pack-year			0.9257
Ν	81	5,556	
Mean ± SE	9.9273±3.0782	10.2082±0.4128	

All results are weighted. Tested using Rao-Scott chi-square test or *t*-test.

college or AA degree 21.34% vs. college graduate or above 26.55%) and married or living with partner (never married 2.80% vs. married/living with partner 62.28% vs. divorced/ widowed/separated 34.91%). Post-menopausal women who had an endometrial cancer history took in less caffeine daily than those who did not have an endometrial cancer history (126.48±15.4977 vs. 166.43±3.7125, respectively. P value =0.0182). Post-menopausal women who drank ≤358 grams (2 cups of 6 oz) coffee daily had a significantly different rate of having an endometrial cancer history (did not drink coffee 31.80% vs. drank \leq 358 g coffee daily 39.96% vs. drank >358 g coffee daily 28.24%, P value=0.0250). Postmenopausal excessively obese women (BMI \geq 35) had an almost significantly different rate of endometrial cancer history than other groups (underweight/normal 26.49% vs. overweight 19.66% vs. obese 22.13% vs. excess obese 31.72%, P value =0.0528). Post-menopausal women who had a history of birth control use and who did not had one had a significant different rate of holding an endometrial cancer history than the group did not use any birth control (46.88% vs. 53.12%, respectively. P value =0.0132).

The univariate and multivariate logistic regression analysis results are shown in Table 2; the appropriate weights and clusters and strata adjustments of the complex sample design are applied. Compared to post-menopausal women who had no caffeine intake, both of two other groups, those who intake ≤93 mg and >93 mg caffeine daily, were 4.134 (95% CI: 1.187– 14.397; P value =0.0094) and 5.257 (95% CI: 1.502-18.400; P value =0.0258) times more likely to have endometrial cancer, respectively. Compared to post-menopausal women who did not drink coffee, women who drank ≤358 g of coffee daily had a significant higher rate of developing endometrial cancer (OR =7.650; 95% CI: 2.146-27.264; P value =0.0017). Meanwhile, post-menopausal women who drank >358 g of coffee daily were 3.514 (95% CI: 0.975-12.667; P value =0.0547) times more likely to have endometrial cancer. Black post-menopausal women were significantly less likely to develop endometrial cancer than white post-menopausal women (OR =0.523; 95% CI: 0.274-0.999; P value =0.0496). Compared to postmenopausal women who never use birth control pills, those who had a history of birth control pill use were 0.477 (95% CI: 0.261-0.872; P value =0.0162) times less likely to have endometrial cancer.

After controlling for age, race, education level, incometo-poverty ratio, marital status, sugar intake, calorie intake, BMI, birth control use history, female hormones use history, and smoke status, the first multivariate logistic regress model showed that, compared to post-menopausal women who did not intake any caffeine, women who took in \leq 93 mg of caffeine in a day were 25.646 (95% CI: 3.248–202.481; P value =0.0021) times more likely to develop endometrial cancer, and women who intake >93 mg of caffeine daily were 17.299 (95% CI: 2.210–135.434; P value =0.0066) times more likely to develop endometrial cancer. In this model, being black and having a history of birth control pill use had significant inverse association with developing endometrial cancer—the ORs were 0.401 (95% CI: 0.180–0.893); P value =0.0253) and 0.396 (95% CI: 0.171–0.915; P value =0.0303, respectively). Being excessively obese increased the rate of endometrial cancer significantly (OR =2.535; 95% CI: 1.135–5.663; P value =0.0233).

In the second multivariate model, post-menopausal women who drank ≤358 g of coffee daily were 42.865 (95%) CI: 5.260-349.347; P value =0.0004) times more likely to develop endometrial cancer, compared to those who did not drank coffee. Meanwhile, those who drank >358 g of coffee in a day had 16.354 (95% CI: 1.880-142.301; P value =0.0114) times higher rate of endometrial cancer. The rate of endometrial cancer was significantly lower in those who had a history of birth control pill use than in those who did not (OR =0.242; 95% CI: 0.091-0.646, P value =0.0046). Compared to post-menopausal women who were underweight or normal weight, women who were excessively obese increased rate of developing endometrial cancer significantly (OR =3.166; 95% CI: 1.212-8.271; P value =0.0187). However, there is no significant association between race and endometrial cancer in this model.

Discussion

In this large national population-based study of US postmenopausal women, a statistically significant association between caffeine intake and endometrial cancer was observed. Compared to women who didn't take in any caffeine, daily intake of ≤ 93 mg caffeine, which is equivalent to 2 cups of 6 oz instant regular coffee, increased endometrial cancer prevalence by almost 26 times. Although the risk was a little lower in those who take in >93 mg caffeine a day, it still was 17 times higher than the risk among women who did not take in any caffeine. In addition, the results in this study showed coffee consumption was a significant risk factor of endometrial cancer as well. Drinking ≤ 2 cups of 6 oz instant regular coffee daily was nearly 43 times higher possibilities to get endometrial cancer than post-menopausal women who didn't drink coffee at all. The risk went down remarkably when women drank >2 cups

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	Univariable		Multivariable (coffee consi	umption)	Multivariable (caffeine inta	ke)
CHARACTERISTICS	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Daily coffee consumption (gm)	0.992 (0.979–1.006)	0.2540	1	I	1	I
Daily coffee consumption level (gm)						
0	1	I	1	I	I	I
≤358	7.650 (2.146–27.264)	0.0017	42.865 (5.260–349.347)	0.0004	I	I
>358	3.514 (0.975–12.667)	0.0547	16.354 (1.880–142.301)	0.0114	I	I
Daily total caffeine intake (mg)	0.983 (0.964–1.001)	0.0653	I	I	1	I
Daily total caffeine intake level (mg)						
0	1	I	I	I	-	I
≤93	4.134 (1.187–14.397)	0.0094	I	I	25.646 (3.248–202.481)	0.0021
>93	5.257 (1.502–18.400)	0.0258	I	I	17.299 (2.210–135.434)	0.0066
Age	0.992 (0.979–1.006)	0.2540	0.769 (0.508–1.165)	0.2160	0.981 (0.682–1.410)	0.9155
Race						
White	-	I	1	I	-	I
Black	0.523 (0.274–0.999)	0.0496	0.497 (0.162–1.530)	0.2232	0.401 (0.180–0.893)	0.0253
Hispanic/other	0.703 (0.328–1.506)	0.3647	0.649 (0.217–1.941)	0.4389	0.629 (0.273–1.450)	0.2765
Education level						
Less than high school	-	I	-	I	-	I
High school diploma/GED	0.992 (0.521–1.886)	0.9798	1.719 (0.601–4.919)	0.3122	0.912 (0.438–1.901)	0.8067
Some college or AA degree	0.666 (0.323–1.374)	0.2713	0.708 (0.183–2.735)	0.6167	0.637 (0.260–1.559)	0.3233
College graduate or above	1.076 (0.443–2.614)	0.8719	1.456 (0.414–5.119)	0.5583	1.202 (0.461–3.131)	0.7063
Marital status						
Never married	-	ı	1	I	-	I
Married/living with partner	1.993 (0.427–9.305)	0.3806	1.697 (0.197–14.604)	0.6301	2.357 (0.414–13.407)	0.3338
Divorced/widowed/separated	1.747 (0.367–8.322)	0.4834	2.436 (0.237–25.074)	0.4542	2.051 (0.351–11.973)	0.4250
Family poverty income ratio						
	1	I	1	I	-	I
Table 2 (continued)						

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Table 2 (continued)						
	Univariable		Multivariable (coffee cons	umption)	Multivariable (caffeine int	ake)
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
1.01-2.00	0.800 (0.378–1.693)	0.5593	0.456 (0.127–1.637)	0.2284	0.752 (0.315–1.794)	0.5120
2.01-4.00	0.778 (0.380–1.594)	0.4929	0.792 (0.259–2.424)	0.6829	0.723 (0.314–1.665)	0.4456
>4	0.995 (0.445–2.228)	0.9906	1.446 (0.470–4.453)	0.5203	1.033 (0.425–2.510)	0.9434
Daily total sugars intake (gm)	1.012 (0.985–1.041)	0.3851	0.956 (0.902–1.013)	0.1299	1.002 (0.948–1.059)	0.9379
Daily total energy intake (kcal)	1.022 (0.983–1.063)	0.2673	1.067 (0.995–1.144)	0.0673	1.018 (0.963–1.076)	0.5276
BMI categories						
Underweight/normal	1	I	-	I	-	I
Overweight	0.672 (0.321–1.410)	0.2933	0.720 (0.263–1.973)	0.5233	0.860 (0.394–1.875)	0.7047
Obesity	1.184 (0.557–2.514)	0.6608	1.717 (0.436–6.767)	0.4400	1.486 (0.610–3.618)	0.3830
Excess obesity	1.922 (0.957–3.860)	0.0664	3.166 (1.212–8.271)	0.0187	2.535 (1.135–5.663)	0.0233
Ever use birth control pills						
No	1	I	-	I	-	I
Yes	0.477 (0.261–0.872)	0.0162	0.242 (0.091–0.646)	0.0046	0.396 (0.171–0.915)	0.0303
Ever use female hormones						
No	1	I	-	I	-	I
Yes	1.036 (0.594–1.808)	0.9011	1.515 (0.476–2.782)	0.7547	1.057 (0.526–2.125)	0.8767
Smoking pack-year	0.996 (0.926–1.072)	0.9191	0.945 (0.801–1.114)	0.4979	0.986 (0.908–1.070)	0.7294
All results are weighted. All multivariabl energy intake, BMI, birth control use, fer	e regression adjusted for <i>a</i> male hormones use, and sr	ige, race, educ noking status.	ation level, marital status, fa ORs, odds ratio; CI, confider	mily poverty inco nce interval; BMI,	ome ratio, daily total sugars , body mass index.	intake, daily total

coffee daily: drinking >2 cups coffee daily was only 16 times more likely to have endometrial cancer than women who did not drink any coffee.

Some previous studies claimed that the risk of endometrial cancer appeared to be reduced by coffee consumption (20-24,32). However, some of them did not show strong evidence in regular population (20,22). Additionally, some of them found the inverse association was only between endometrial cancer and high coffee consumption. Gavrilyuk and colleagues reported endometrial cancer risk decreased in women consuming \geq 8 cups/day (21). In Friberg's (32) and Je's (24) studies, only \geq 4 cups of coffee per day were associated with a lower risk of endometrial cancer. And in both of those two studies, the reference group was women who drank one cup or less. In current NHANES study, there was not a sufficiently valid high coffee consumption record. This may blind us to further evidence. Moreover, the reference group in this study was post-menopausal women who did not drink coffee at all. The risk of endometrial cancer was extraordinarily lower among women who drank >2 cups coffee daily than among those who drank ≤ 2 cups. This study may obtain the same result as previous studies if the reference group is changed. Overall, there was significant evidence to show that coffee consumption is a risk factor of endometrial cancer compared to non-consumption.

The major difference between this study and previous studies, which made this study unique, is that this study directly investigated the association between caffeine intake and endometrial cancer. The NHANES dataset has recorded individual daily caffeine intake from all the selfreported food and beverage consumption. The estimated amount of caffeine intake is detailed and accurate. The association between caffeine intake and endometrial cancer was consistent with the results between coffee consumption and endometrial cancer. Compared to women who didn't have any caffeine intake, both of fewer caffeine intake (≤93 mg) or larger caffeine intake (>93 mg) were risk factor of endometrial cancer. And above all, the results also showed that the risk among women who intake more caffeine dropped down to 2/3 risk of fewer intake. It may suggest caffeine is the key component to the association between coffee consumption and endometrial cancer. The previous studies, which tried to inquire into what kind of role caffeine plays, grouped exposure as caffeinated coffee consumption and decaffeinated coffee consumption to investigate this association. Giri and his colleagues found the hazard ratios for women who drank ≥ 2 cups/day for

decaffeinated coffee were 0.67 (95% CI: 0.43–1.06) (22), which means no significant association existed. In Je's investigation, the inverse association they found among women who consumed ≥ 2 cups/day vs. <1 cup/month (RR =0.78; 95% CI: 0.57–1.08) was also not convincing (24). Besides caffeine, there were several other compounds in coffee, such as antioxidants, diterpenes, etc. that may impact the association between caffeine intake and endometrial cancer. Also, the impact may be related to the method of brewing or other substances such as sweeteners or creamer. However, in this NHANES study, caffeine intake was measured and calculated accurately. Caffeine intake had a significant association with the risk of endometrial cancer. In the further, etiological evidences needs to be found.

In addition, the result showed that excess obesity (BMI \geq 35) was a significant risk factor of endometrial cancer. Friedenreich and her colleagues had the same conclusion (33). Obese women tend to have higher circulating estrogen, hyperinsulinemia, and relatively low levels of SHBG (34,35). Those factors have been shown by many studies to increase the risk of endometrial cancer (4,36,37). Unlike estrogen-only hormone-replacement therapy (HRT), birth control pills are combined estrogen-progestogen medicine. Some studies concluded that combined estrogen-progestogen could decrease risk (38-40). In our study, birth control use was suggested as a beneficial factor of endometrial cancer. This observation is consistent with those studies.

Major strengths of this study include its national population-based design with relatively large sample sizes. NHANES oversampled minorities, thus providing adequate sample size for the stratified analyses with validated dietary interview data. Moreover, the dietary consumption records were obtained through 2 days 24-hour recall interview. The trained interviewer recorded detailed information about foods and beverages that participants reported what they consumed during the 24-hour prior to the interview. Participants used a set of standard measurements to estimate volume or amount of their foods or beverages consumption. This way of recording dietary consumption minimizes the recall bias. In addition, USDA provided professional nutrient guidelines to calculate nutrient intake of all exposure and potential confounders accurately. There are about 30 nutrient guidelines for different coffee types, such as instant coffee prepared with water, breakfast blend brewed coffee, restaurant-prepared brewed espresso, milk-based iced mocha, etc. And caffeine from all foods and beverages consumed, such as coffee cake, coca, or tea, has been included. Each type of coffee has a unique

Characteristics	Women with cancer	Women without cancer	P value
Daily coffee consumption (gm)			0.3373
Ν	931	4.902	
Mean ± SE	332.44±20.7470	311.15±8.9275	
Daily coffee consumption level (gm), N (%)			0.1860
0	402 (18.19)	2,146 (81.81)	
≤358	227 (15.73)	1,380 (84.27)	
> 358	302 (18.84)	1,377 (81.16)	
Daily total caffeine intake (mg)			0.2057
Ν	931	4,902	
Mean ± SE	176.44±8.7726	163.60±4.1936	
Daily total caffeine intake level (mg), N(%)			0.5410
0	44 (14.88)	308 (85.12)	
≤93	390 (18.35)	2,140 (81.65)	
>93	497 (17.75)	2,455 (82.25)	

nutrient guideline. It made the findings of this study more powerful and convincing. Furthermore, smoking and coffee consumption are highly correlated and cigarette smoking has been suggested to be associated with lower risk of endometrial cancer (7,8). This study has controlled smoking status to eliminate its impact on the association between coffee consumption and endometrial cancer.

However, the potential contribution of this paper is limited for several reasons. First, because coffee intake, cancer status, and other demographic characteristics used in this study were self-reported, measurement errors are inevitable. Second, the cross-sectional design in the NHANES limits conclusions about the causal relationship of risk factors and coffee consumption. Cancer may impact on life behaviors. To make sure having cancer would not change habit of drinking coffee significantly, coffee consumption and caffeine intake between postmenopausal women who have cancer and do not have cancer was investigated previously. As shown in Table 3, the results suggested that there is no difference between those two groups coffee drinking habit. Third, as NHANES records the cancer status as "uterine cancer" not "endometrial cancer", the total of endometrial cancer may be overestimated. However, nearly all of uterine cancers are endometrial carcinomas (1), resulting in limited bias in this study. Finally, although all analyses were weighted

to account for the complex sampling design applied in NHANES, our results may not represent the whole US population due to the survey limitations.

Conclusions

Despite the limitations, this study uses 10 years' national data to provide unique and valuable contributions in discussing the association between caffeine intake and endometrial cancer. The results showed that both caffeine intake and coffee consumption is associated with increased risk of endometrial cancer, but risks reduced when having higher intake. Birth control pills use is a factor for reduced risk of endometrial cancer, while excess obesity is significant risk factor.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the NHANES ERB.

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