

Short Communication

Coffee, Tea, Colas, and Risk of Epithelial Ovarian Cancer

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Abstract

Associations of coffee, tea, and other caffeinated beverages with ovarian cancer risk remain uncertain. In a population-based study in Washington State, 781 women with epithelial ovarian cancer diagnosed in 2002 to 2005 and 1,263 controls completed self-administered questionnaires detailing consumption of caffeinated and noncaffeinated coffee, teas, and colas and in-person interviews regarding reproductive and hormonal exposures. We assessed risk associated with coffee, tea, and cola drinking and with total caffeine consumption using logistic regression to calculate odds ratios and 95% confidence intervals. Neither caffeinated nor decaffeinated coffees were associated with ovarian cancer risk; also, we observed

no association of total caffeine with risk using a combined index that summed intake from coffee, tea, and carbonated soft drinks. Among teas, neither herbal/decaffeinated nor black teas were associated with risk; however, women who reported drinking ≥ 1 cup/d of green tea had a 54% reduction in risk ($P_{\text{trend}} = 0.01$). Associations of green tea with risk were similar when invasive and borderline cases were considered separately and when Asian women were excluded from analysis. Green tea, which is commonly consumed in countries with low ovarian cancer incidence, should be further investigated for its cancer prevention properties. (Cancer Epidemiol Biomarkers Prev 2008;17(3):712–6)

Introduction

Associations of coffee, tea, and other caffeinated beverages with ovarian cancer risk remain uncertain. Caffeine is a biologically active compound that could affect many aspects of carcinogenesis: *in vivo*, it induces CYP1A2, which may increase metabolic activation of procarcinogens; *in vitro*, it affects both cell cycle regulation and DNA repair (1-3). Coffee and tea also contain phytochemicals, including polyphenol flavonoids and catechins, which could affect cancer risk. A meta-analysis based on studies published through 1990 found a 30% increased risk of ovarian cancer among coffee drinkers compared with nondrinkers (4). Since that time, numerous additional studies have examined the relation of risk with intake of caffeinated beverages, including coffee, tea, and carbonated soft drinks, as well as total caffeine intake and have reported positive, inverse, and null results (5-15). The reasons for these inconsistent results are unclear but may be related to incomplete or nonspecific assessment

of multiple caffeine-containing beverages as well as differences in beverage consumption patterns across study populations.

We describe here the results of a population-based case-control study of ovarian cancer conducted in western Washington State from 2002 to 2005. Using an instrument specifically designed to capture intake of caffeine-containing beverages, we distinguished between preparation methods (brewed, instant, and espresso coffee drinks) and formulations (caffeinated and non-caffeinated coffees and teas; diet, regular, highly caffeinated, caffeinated, and caffeine-free colas and root beers) of these drinks. The question of whether these very commonly consumed beverages affect ovarian cancer risk is important because, lacking both a screening test and an effective treatment for nonlocalized disease, primary prevention remains the only feasible approach to reduce ovarian cancer mortality.

Materials and Methods

The study population and methods have been described (16). In brief, female residents of a 13-county area of western Washington State, ages 35 to 74 years, diagnosed with a primary invasive or borderline epithelial ovarian tumor from 2002 through 2005 were identified through a population-based registry that is part of the Surveillance, Epidemiology, and End Results program of the National Cancer Institute. We restricted our study

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to English-speaking women who had residential telephones at the time of cancer diagnosis, because random-digit dialing was used to select controls. Of 1,058 eligible women identified, 812 (76.6%) were interviewed; of the interviewed cases, 595 had invasive disease. Reasons for not obtaining an interview included physician refusal ($n = 23$), inability to locate the patient ($n = 10$), patient refusal ($n = 110$), and death ($n = 103$).

Controls were selected by random-digit dialing (17) using stratified sampling in 5-year age categories, 1-year calendar intervals, and two county strata in a 2:1 ratio to women with invasive disease. For 14,561 (82.0%) of the 17,768 telephone numbers belonging to a residence, we determined whether an eligible (that is, age- and county-eligible and able to communicate in English and, if so, with at least one ovary and no prior history of ovarian cancer) woman resided there. Of the 1,561 eligible women identified, 1,313 (84.1%) were interviewed, yielding a control response proportion (screening response \times interview response) of 69.0%.

The study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center, and all women provided signed informed consent before participating. In-person interviews pertained to the time before diagnosis (for cases) or before an assigned, comparable reference date (for controls) and included demographic and lifestyle characteristics, medical history, family history of cancer, and reproductive history. Participants reported their beverage consumption ~ 5 years before the diagnosis/reference date using a one-page self-administered questionnaire, which was completed by 781 cases and 1,263 controls.

Caffeine-containing beverages were ascertained as brewed coffee, instant coffee, espresso/espresso drinks, green tea, black tea, regular colas and root beer, diet colas and root beer, and highly caffeinated soft drinks. Decaffeinated forms of those beverages and herbal teas were reported as separate items. The frequency of consumption was reported in nine categories ranging from "never or less than once per month" to "six or more

Table 1. Associations of caffeinated and noncaffeinated beverages with epithelial ovarian cancer risk

	Controls ($n = 1,263$), n (%)	Cases ($n = 781$), n (%)	OR* (95% CI)
Coffee (instant, brewed, or espresso)			
Caffeine containing			
Nondrinkers	341 (27.0)	216 (27.7)	1.00
<1 cup/d	249 (19.7)	155 (19.9)	1.05 (0.79-1.40)
1 to <2 cups/d	200 (15.9)	137 (17.6)	1.10 (0.82-1.48)
2 to <3 cups/d	265 (21.0)	148 (19.0)	0.90 (0.67-1.19)
≥ 3 cups/d	207 (16.4)	123 (15.8)	0.87 (0.64-1.19)
Missing	1	2	$P_{\text{trend}} = 0.27$
Decaffeinated			
Nondrinkers	808 (64.2)	532 (68.1)	1.00
<1 cup/d	292 (23.2)	169 (21.6)	1.06 (0.84-1.35)
1 to <2 cups/d	65 (5.2)	42 (5.4)	1.19 (0.77-1.85)
2 to <3 cups/d	64 (5.1)	26 (3.3)	0.81 (0.49-1.33)
≥ 3 cups/d	30 (2.4)	12 (1.5)	0.70 (0.35-1.43)
Missing	4	0	$P_{\text{trend}} = 0.54$
Tea			
Herbal or decaffeinated tea			
Nondrinkers	633 (50.2)	430 (55.1)	1.00
<1 cup/d	528 (41.8)	291 (37.3)	0.87 (0.71-1.07)
≥ 1 cup/d	101 (8.0)	60 (7.7)	0.92 (0.63-1.33)
Missing	1	0	$P_{\text{trend}} = 0.28$
Green tea			
Nondrinkers	893 (70.8)	589 (75.4)	1.00
<1 cup/d	316 (25.0)	171 (21.9)	0.82 (0.66-1.04)
≥ 1 cup/d	53 (4.2)	21 (2.7)	0.46 (0.26-0.84)
Missing	1	0	$P_{\text{trend}} = 0.01$
Black tea			
Nondrinkers	623 (49.3)	414 (53.0)	1.00
<1 cup/d	509 (40.3)	293 (37.5)	0.93 (0.76-1.14)
≥ 1 cup/d	131 (10.4)	74 (9.5)	0.91 (0.65-1.27)
Colas and root beers			
Caffeine containing			
Nondrinkers	489 (38.9)	287 (36.8)	1.00
<1 can/d	594 (47.2)	337 (43.2)	0.94 (0.76-1.16)
1 to <2 cans/d	102 (8.1)	77 (9.9)	1.14 (0.80-1.63)
≥ 2 cans/d	73 (5.8)	79 (10.1)	1.51 (1.03-2.22)
Missing	5	1	$P_{\text{trend}} = 0.07$
Caffeine free			
Nondrinkers	903 (71.6)	558 (71.5)	1.00
<1 can/d	305 (24.2)	182 (23.3)	1.05 (0.84-1.32)
1 to <2 cans/d	37 (2.9)	20 (2.6)	0.91 (0.51-1.62)
≥ 2 cans/d	16 (1.3)	20 (2.6)	2.60 (1.25-5.39)
Missing	2	1	$P_{\text{trend}} = 0.116$

*ORs and 95% CIs adjusted for age, county, year of diagnosis/reference date, race/ethnicity, number of full-term pregnancies, duration of hormonal contraception, education, body mass index, smoking, tubal ligation/hysterectomy, and family history of breast/ovarian cancer.

Table 2. Association of total caffeine from coffee, tea, and soft drinks with epithelial ovarian cancer risk

	Controls (<i>n</i> = 1,263), <i>n</i> (%)	Cases (<i>n</i> = 781), <i>n</i> (%)	OR* (95% CI)
Daily caffeine equivalents [†]			
None	50 (4.0)	33 (4.2)	1.00
>0 to <0.5	347 (27.7)	213 (27.4)	1.05 (0.63-1.74)
0.5 to <1	168 (13.4)	117 (15.0)	1.21 (0.71-2.07)
1 to <2	239 (19.1)	152 (19.5)	1.06 (0.63-1.79)
2 to <3	243 (19.4)	131 (16.8)	0.89 (0.52-1.51)
≥3	207 (16.5)	132 (17.0)	0.99 (0.58-1.70)
Missing	9	3	<i>P</i> _{trend} = 0.38

*ORs and 95% CIs adjusted for age, county, year of diagnosis/reference date, race/ethnicity, number of full-term pregnancies, duration of hormonal contraception, education, body mass index, smoking, tubal ligation/hysterectomy, and family history of breast/ovarian cancer.

[†] Index of caffeine consumption, where 1.0 is equivalent to caffeine contained in 1 cup of brewed coffee.

per day." A medium serving size was defined as 8 ounces of brewed/instant coffee or tea, 1 shot of espresso, or a 12-ounce can of soda, and based on these guidelines, women reported their usual serving size as small, medium, or large.

For analysis, nondrinkers were defined as women in the lowest consumption level. Consumption was calculated as the product of frequency times serving size, where a large serving was considered 50% larger, and a small serving 50% smaller, than a medium serving. An index of caffeine intake was created by linking consumption of each type of beverage to the amount of caffeine contained in that beverage based on data from the University of Minnesota Nutrition Data System for Research (version 36; 2005) and the caffeine content of one cup of brewed coffee (137 mg) was used to report total intake as coffee serving equivalents. (Caffeine contents for a single serving of other commonly consumed beverages were generally lower, e.g., 75 mg for instant coffee and 52 mg for espresso drinks.)

Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using unconditional logistic regression. All analyses were adjusted for the matching variables of age, county of residence, and year of diagnosis/reference date as well as number of full-term births, duration of hormonal contraception, race/ethnicity, education, history of tubal ligation and/or hysterectomy, family history of ovarian and/or breast cancer, body mass index at age 30, and smoking. Polytomous logistic regression was used for analyses that separated case women according to the degree of invasiveness of the tumor. Statistical Analysis System (SAS Institute) was used for analysis. Tests for linear trend across categories were done by using an ordinal variable corresponding to rank from lowest to highest category (18).

Results

Roughly 90% of cases and controls were non-Hispanic whites. Compared with controls, fewer cases had completed college (33% versus 40%), used hormonal contraception (71% versus 80%), or had a tubal ligation (18% versus 22%). More cases than controls were nulliparous (25% versus 14%) and had a family history of ovarian cancer (12% versus 7%).

Coffee that contained caffeine was frequently drunk by cases and controls, with more than half of both groups

reporting at least 1 cup/d (Table 1). Consumption of other caffeinated beverages and decaffeinated beverages was less common (e.g., ≤10% controls reported drinking ≥1 cup/d of black or green tea). Neither caffeinated nor decaffeinated coffees were associated with ovarian cancer risk, and results were similar when instant, brewed, and espresso coffee formulations were considered separately. Among teas, neither herbal/decaffeinated nor black teas were associated with risk; however, women who reported drinking ≥1 cup/d of green tea had a 54% reduction in risk (*P*_{trend} = 0.01). In contrast, women who reported very frequent (≥2 cans/d) consumption of colas or root beer, whether or not these drinks contained caffeine, were at increased risk. In a combined index that summed caffeine intake from coffee, tea, and carbonated soft drinks, we observed no association of caffeine with risk (Table 2).

The green tea finding changed little when Asian women (28 controls and 32 cases) were excluded from analysis (OR, 0.81 and 0.41 for <1 and ≥1 cup/d, respectively; *P*_{trend} = 0.003). Also, our results were similar in analyses of histologic subgroups of tumors (that is, serous, mucinous, and other epithelial tumors) and within borderline and invasive subtypes. When women were subdivided according to age (<50 versus ≥50 years) or menopausal status, we observed no clear differences within subgroups of these variables. Associations of soda consumption with cancer risk were similar for total soda (OR, 1.60; 95% CI, 1.12-2.28 for ≥2 cans/d) and for sodas stratified by type of sweetening (artificial versus caloric).

Discussion

Epidemiologic evidence linking coffee drinking to ovarian cancer risk is inconclusive. Among studies published since 2000, positive (5, 8, 14), inverse (10), and null (6, 9, 11, 15) findings have been reported. Of studies reporting an increased risk, one reported an increase only among premenopausal women (5), another reported an overall increase in a predominantly postmenopausal population (8), and the third observed an increased risk in a cohort of whom roughly half of participants were postmenopausal (14). The single study that reported an inverse association with coffee appears unique in that >95% of coffee consumed in that Australian population was likely instant (10).

Fewer studies have examined total caffeine, with both increased (5, 8) and decreased (10) risks reported. Coffee is generally the primary contributor to total caffeine intake; thus, it is not surprising that the relation of caffeine to risk in these studies mirrors the findings for coffee.

The current study included a detailed assessment of multiple caffeine-containing beverages as well as their decaffeinated formulations. Some prior studies did not distinguish between caffeinated and decaffeinated forms of coffee (9-11, 14) or between brewed and instant preparation methods (5, 8-11, 15). Although the frequency of coffee drinking varied between populations, most studies were able to assess risk among women with substantial daily exposure, with the upper exposure category ranging from ≥ 1 in the study of Goodman et al. (8) to ≥ 3 in the current study to ≥ 4 in most other studies.

Studies on tea have also been inconsistent (5-8, 10, 12-15), reporting either null or inverse associations. Most of these studies did not distinguish between types of tea, which differ markedly in polyphenol content (19). One study conducted in China that examined green tea found a strong inverse association with weekly or more frequent consumption but no evidence of dose-response with increasing frequency (7). Our finding that green tea was associated with reduced risk is consistent with that study and with studies reporting risk reductions associated with green tea for a variety of other cancers (1, 19). However, no association of ovarian cancer risk with green tea was noted in a study conducted in Hawaii (8).

Green tea contains relatively high levels of the catechin epigallocatechin-3-gallate (20, 21), which has growth-inhibitory effects on ovarian cancer *in vitro* (22, 23). Additional processing required in the production of black tea converts some of the naturally occurring catechins and gallic catechins to other polyphenols (19). Populations outside Asia consume predominantly black tea (19). Some studies, including ours, that observed no association with black tea were conducted in western populations where tea drinking was relatively uncommon (6); others did not examine risk separately among frequent consumers (5, 8). Reductions in risk associated with black tea have generally been observed in populations where frequent (≥ 2 cups/d) drinking was assessed (12, 13, 15); however, null associations have also been observed in populations in which tea drinking is common and frequent consumption was assessed (10, 14).

Similar to the current study, the three prior studies (5, 8, 10) that assessed total caffeine intake included colas in their assessment. Jordan et al. (10) reported that colas accounted for $< 10\%$ of caffeine intake and that cola consumption was not associated with risk. Kuper et al. (5) reported no association of colas with risk among women with weekly or greater consumption but noted risk appeared elevated in those at the highest level of caffeinated cola consumption. Goodman et al. (8) reported no association with soda overall or with caffeinated soda, and a nonsignificant 50% reduction in risk among women with weekly consumption of at least 1.5 cups of noncaffeinated soda. Our observation that high consumption (≥ 2 cans/d) of colas and root beers was associated with a moderate increase in risk thus

contributes additional inconsistency to the available data; conceivably, chance or residual confounding in some or all of these studies (including our own) may be involved.

Strengths of this study include its population-based design, relatively large size, and the use of a beverage questionnaire specifically designed to capture caffeine intake. Nevertheless, we cannot discount the possibility of incomplete or differential recall by cases and controls nor can we exclude the possibility that characteristics associated with study participation resulted in a nonrepresentative sample of cases or controls. Consumption of caffeine-containing and decaffeinated beverages may change over the lifetime, and it is possible that we failed to capture consumption of beverages during an etiologically relevant time. Also, relative to prior studies, black tea was notably less commonly consumed in our study population; thus, our study lacked power to detect an association associated with its frequent consumption.

Although we observed no association of total caffeine, caffeinated or decaffeinated coffee, or herbal/decaffeinated or black tea with ovarian cancer risk, green tea was associated with a substantial decrease in risk. Green tea, which is commonly consumed in countries with low ovarian cancer incidence, should be further investigated for its cancer prevention properties.

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