# Caffeine, Alcohol, Smoking, and the Risk of Incident Epithelial Ovarian Cancer

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**BACKGROUND.** Smoking, caffeine, and alcohol intake are all potentially modifiable factors that have an unclear association with ovarian cancer risk. Therefore, the associations between these exposures and ovarian cancer risk were prospectively examined among 110,454 women in the Nurses' Health Study (NHS) for the smoking analyses and 80,253 women for the dietary analyses.

**METHODS.** Women completed biennial questionnaires assessing ovarian cancer risk factors beginning in 1976, with food frequency questionnaires administered every 2 to 4 years starting in 1980. For the smoking analyses, 737 confirmed cases of epithelial ovarian cancer were identified and for the dietary aims, 507 cases were identified through June 1, 2004.

**RESULTS.** Compared with never-smokers, neither current nor past smoking was associated with ovarian cancer risk overall; however, both were associated with mucinous tumors (n = 69; rate ratio [RR], past = 2.02 [95% confidence interval (CI), 1.15–3.55]; RR, current = 2.22 [95% CI, 1.16–4.24]). A modest inverse association between caffeine intake and ovarian cancer risk was observed (RR, top vs bottom quintile = 0.80; 95% CI, 0.60–1.07 [$P = .03$]), which was strongest for women who had never used either oral contraceptives (RR = 0.65; 95% CI, 0.46–0.92 [$P$ for heterogeneity = .02]) or postmenopausal hormones (RR = 0.57; 95% CI, 0.36–0.91 [$P$ for heterogeneity = .13]). Alcohol was not associated with ovarian cancer risk.

**CONCLUSIONS.** The results of the current study suggest that cigarette smoking may only increase the risk for mucinous ovarian tumors, and alcohol intake was not associated with risk. However, an inverse association was observed between caffeine intake and ovarian cancer risk, particularly in women not using hormones; this finding merits further study. ***Cancer*** **2008;112:000–000.** © *2008 American Cancer Society.*

**KEYWORDS: ovarian cancer, caffeine, alcohol, smoking, coffee, tea, prospective.**

Increasing parity and oral contraceptive use have consistently been inversely associated with ovarian cancer[1]; however, these factors are not readily modifiable. The evidence supporting the role of more modifiable factors, such as smoking or caffeine and alcohol intake, in ovarian cancer etiology is unclear.

A recent meta-analysis of smoking and ovarian cancer, primarily consisting of retrospective case-control studies, reported no overall association between smoking and ovarian cancer risk.[2] However, current smokers had a 2-fold risk of mucinous tumors. Two small prospective studies ($\leq$40 cases) and 1 larger study (n = 454 cases) observed a suggestive positive association with all subtypes of invasive epithelial ovarian cancer incidence or mortality for current smoking of long duration.[3–5]


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Caffeine was found to be inversely associated with ovarian cancer risk in a large retrospective case-control study, with an approximately 40% decrease in risk in the top versus bottom quartile; this association was stronger in postmenopausal women and never oral contraceptive users.[6] Two other retrospective studies reported positive associations for caffeine, although this finding was restricted to premenopausal women.[7,8] Two major food contributors of caffeine—coffee and tea—have been studied more extensively, with inconsistent associations noted for both.[6,8–15] One prospective study reported no association for coffee,[16] but a significant inverse association for tea[17]; however a second smaller prospective study did not find a clear association with tea intake.[18]

The association between alcohol and ovarian cancer generally has been found to be modestly inverse[19–25] or null[8,14,15,26–31] in case-control studies. Similarly, prospective studies, including a large pooled analysis of 10 cohort studies,[32] have reported no clear associations with total alcohol.[33–36] Associations by alcohol type have been conflicting.

To help clarify these associations, we prospectively examined the association between caffeine, alcohol intake, cigarette smoking, and ovarian cancer risk, overall and by histologic subtype, in the Nurses' Health Study (NHS). We also assessed whether the associations varied by menopausal status, hormone use, and other participant characteristics.

## MATERIALS AND METHODS

The NHS cohort was established in 1976 when 121,701 U.S. female registered nurses ages 30 to 55 years completed and returned a questionnaire. The NHS cohort has been followed by questionnaire every 2 years since to update exposure variables and ascertain newly diagnosed disease. Smoking history was assessed at baseline and every questionnaire thereafter; follow-up was 95.3% of person-years through May 31, 2004. In 1980, we included a 61-item food frequency questionnaire (FFQ), which was expanded to 131 items in 1984, 1986, 1990, 1994, and 1998. We used the 1980 FFQ as the baseline for dietary analyses because the primary sources of caffeine and alcohol intake were included. Follow-up for those completing the 1980 FFQ was 97.8% of person-years through May 31, 2004. The racial/ethnic profile is 97% white, 2% African-American, and 1% Asian; 1% of women reported being of Hispanic origin. This study was approved by the Committee on the Use of Human Subjects in Research at the Brigham and Women's Hospital.

### Ascertainment of Cases

Incident cases of epithelial ovarian cancer were identified by biennial questionnaire through 2004. For women reporting a new ovarian cancer or cases identified via death certificate,[37] we obtained pathology reports and related medical records. A gynecologic pathologist, unaware of exposure status, reviewed the records to confirm the diagnosis and identify histologic type, subtype, morphology, and stage. We compared the histologic type from the pathology report with a standardized review of pathology slides for a subset of 215 cases. Overall, the concordance for invasiveness was 98% and that for histologic type was 83%; histologic type was used from the medical record review for all cases.

### Exclusions

For the smoking analysis, we used the 1976 baseline cohort after excluding those: reporting any diagnosis of cancer besides nonmelanoma skin cancer (n = 3359); with a history of bilateral oophorectomy (n = 7665); with a history of pelvic irradiation (n = 99); and missing year of birth (n = 124), leaving 110,454 women for this analysis. For the dietary analyses (1980 baseline) we excluded women who did not respond to the dietary questionnaire in 1980 or who had implausible dietary intakes (n = 29,233); other exclusions were as noted above (with 3661, 8439, 69, and 46 women excluded, respectively), leaving 80,253 women for analysis. Exclusions were updated biennially.

### Exposure

On each questionnaire, women were asked whether they were current or past smokers and the number of cigarettes smoked per day. In 1976, smokers were asked the age at which they commenced smoking. Pack-years were calculated by multiplying the number of packs smoked per day by the number of years smoked.

Information regarding caffeine and alcohol consumption was obtained from each FFQ. Intake of alcohol was recorded as average frequency of use of beer, wine, and liquor over the preceding year. The estimated alcohol content of each beverage was 13.2 g per bottle or can of beer, 10.8 g per glass of wine, and 15.1 g per standard drink of liquor. Total alcohol intake was recorded as the sum of these 3 beverages.

Caffeine consumption was calculated using U.S. Department of Agriculture food composition sources.[38–40] Respondents were asked the average frequency of use of caffeine-containing foods and beverages, including coffee (137 mg caffeine/cup), tea (47 mg caffeine/cup), soda (46 mg caffeine/can or bottle),

**TABLE 1**
**Distribution of Ovarian Cancer Risk Factors by Smoking, Caffeine, and Alcohol Intake in 1990, the Approximate Midpoint of the Study**

| | Smoking status | | | Caffeine intake, mg/Day* | | | Alcohol intake, g/Day | |
|---|---|---|---|---|---|---|---|---|
| | Never | Past | Current | ≤136 | >245–360 | >500 | <0.1 | ≥15 |
| Sample size | 42547 | 32677 | 15616 | 11865 | 13079 | 11155 | 12544 | 7684 |
| Mean age, y | 56.2 | 56.6 | 56.0 | 56.2 | 56.5 | 55.8 | 56.8 | 57.1 |
| Mean duration of OC use, mo | 22.6 | 24.1 | 25.4 | 24.1 | 25.4 | 24.6 | 21.3 | 30.1 |
| Mean current BMI | 25.8 | 26.0 | 24.8 | 26.0 | 25.8 | 25.4 | 26.8 | 24.4 |
| Current smoker, % | — | — | — | 7.8 | 14.5 | 34.4 | 11.6 | 28.9 |
| Parous, % | 91.9 | 92.7 | 92.2 | 92.5 | 92.8 | 92.9 | 93.0 | 91.0 |
| Mean parity† | 3.2 | 3.2 | 3.2 | 3.1 | 3.2 | 3.2 | 3.1 | 3.1 |
| Family history of ovarian cancer, %‡ | 2.2 | 2.2 | 2.1 | 2.7 | 2.5 | 2.4 | 2.7 | 2.5 |
| Tubal ligation, % | 16.2 | 17.1 | 18.3 | 17.3 | 17.6 | 19.0 | 17.5 | 18.4 |
| Postmenopausal, % | 60.9 | 62.7 | 66.6 | 63.9 | 64.2 | 66.0 | 64.2 | 65.8 |
| Current postmenopausal hormone use, %§ | 29.3 | 31.9 | 23.6 | 30.6 | 30.8 | 27.4 | 25.9 | 33.2 |

OC indicates oral contraceptive; BMI, body mass index.

* Categories presented are the first, third, and fifth quintiles of caffeine intake in this population.

† Among parous women.

‡ Asked in 1992.

§ Among postmenopausal women.

and chocolate (7 mg caffeine/serving), with choices ranging from never or almost never to 6 or more times per day. In 1980, the questionnaire asked about any tea consumption; however, subsequent FFQs asked only about nonherbal tea (ie, caffeinated).

Primary analyses of caffeine and alcohol used the cumulative average because this best represents overall long-term intake, and secondarily we used simple updating at each questionnaire. For cumulative updating, we used averaged caffeine or alcohol intake in 1980 and 1984 to predict ovarian cancer risk from 1984 to 1986; the averaged caffeine or alcohol intake in 1980, 1984, and 1986 to predict risk from 1986 through 1990, and so on. For simple updating, we used the amount consumed in 1980 to predict risk from 1980 through 1984, the amount consumed in 1984 to predict risk from 1984 through 1986, the amount consumed in 1986 to predict risk from 1986 through 1990, and so on.

### Other Covariates

Data regarding exposures and confounders, including body mass index (BMI), reproductive history, and postmenopausal hormone (PMH) use were obtained from the biennial questionnaires and updated every 2 years, where relevant. Oral contraceptive use was asked every 2 years from 1976 through 1982, by which time use was rare because of the age distribution of our cohort. Tubal ligation history was asked from 1976 through 1984 and in 1994. Family history of ovarian cancer was asked in 1992. Parity was defined as the number of pregnancies lasting ≥6 months and was asked through 1984.

### Statistical Analysis

We calculated person-years from the 1976 questionnaire return date for smoking or the 1980 questionnaire return date for the dietary factors to the date of ovarian cancer diagnosis, death, or June 1, 2004, whichever was sooner. Incidence rates for each category of exposure were calculated by dividing the number of incident ovarian cancer cases by the total person-time in that category. Cox regression analysis with time-dependent covariates was used to estimate rate ratios (RR) and 95% confidence intervals (95% CIs). For the smoking analyses, we adjusted for age (continuous), parity (continuous), oral contraceptive use (never, ≤3 years, >3–5 years, >5–8 years, and >8 years), PMH use (premenopausal, or postmenopausal never, past, or current), tubal ligation (yes or no), and BMI (<21 kg/m$^2$, 21 to <23 kg/m$^2$, 23 to <25 kg/m$^2$, 25 to <30 kg/m$^2$, and ≥30 kg/m$^2$). For the dietary analyses, we additionally adjusted for smoking status (never, past, current <15 cigarettes/day, current 15+ cigarettes/day). Additional adjustment for other potential confounders, including lactose intake, height, simple hysterectomy, and age at menarche did not appear to significantly alter estimates of ovarian cancer risk and thus were not included in the final models. Tests for trend were determined using continuous variables of intake via

**TABLE 2**
**Risk of Epithelial Ovarian Cancer Between 1976 and 2004, According to Cigarette Smoking Status, Duration, and Pack-Years**

| | | | All epithelial ovarian cancer | | Mucinous only* |
|---|---|---|---|---|---|
| | Cases | Person-years | Age-adjusted RR | Multivariate RR† (95% CI) | Multivariate RR† (95% CI) |
| Smoking status | | | | | |
| Never | 322 | 1,191,820 | 1.0 | 1.0 | 1.0 |
| Past | 274 | 826,185 | 1.07 | 1.05 (0.86–1.28) | 2.02 (1.15–3.55) |
| Current, 1–14/d | 45 | 160,610 | 1.07 | 1.08 (0.92–1.27) | 2.22 (1.16–4.24)‡ |
| Current, 15+/d | 96 | 353,389 | 1.05 | 1.06 (0.74–1.51) | |
| Smoking duration | | | | | |
| Never | 304 | 1,096,329 | 1.0 | 1.0 | 1.0 |
| 1–9 y | 77 | 239,045 | 1.34 | 1.34 (1.04–1.73) | |
| 10–19 y | 88 | 330,470 | 1.19 | 1.19 (0.93–1.51) | |
| 20–29 y | 98 | 372,571 | 1.09 | 1.10 (0.87–1.39) | — |
| 30–39 y | 96 | 314,410 | 0.95 | 0.98 (0.77–1.23) | |
| 40+ y | 67 | 152,178 | 0.99 | 1.04 (0.79–1.37) | |
| Per 20 y, *P* for trend | | | | 1.02 (0.93–1.11), .74 | 1.44 (1.07–1.96), .02 |
| Pack-years of smoking | | | | | |
| Never smokers | 305 | 1,100,461 | 1.0 | 1.0 | 1.0 |
| 1–19 | 210 | 725,800 | 1.16 | 1.16 (0.97–1.38) | — |
| 20–39 | 130 | 424,176 | 1.11 | 1.14 (0.92–1.40) | |
| ≥40 | 85 | 246,678 | 0.98 | 1.02 (0.80–1.31) | |
| Per 20 pack-years, *P* for trend | | | | 1.01 (0.93–1.09), .85 | 1.30 (1.05–1.62), .02 |

RR indicates rate ratios; 95% CI, 95% confidence interval.

* There were 69 mucinous cases in the analysis.

† Adjusted for age, parity, oral contraceptive use, postmenopausal hormone use, tubal ligation, and body mass index.

‡ Includes all current smokers.

the Wald test. We assessed whether the associations differed by menopausal status, ever oral contraceptive use, tubal ligation, current smoking, parity, and PMH use (among postmenopausal women) by comparing the slopes of the exposures across categories of the modifying variable via the Wald test. The results were similar when excluding borderline cancers; therefore, results are presented including invasive and borderline tumors.

## RESULTS

We identified 737 incident epithelial ovarian cancer cases (655 invasive and 82 borderline) between June 1, 1976 and June 1, 2004 among the total NHS cohort. Among eligible women who responded to the 1980 FFQ, we identified 507 cases (443 invasive and 64 borderline). In 1990, the approximate midpoint of the study, women in the top quintile of caffeine intake or those who drank ≥15 g/day of alcohol were more likely to be current smokers (34.4% and 28.9%, respectively) than women with a low intake of caffeine or alcohol (7.8% and 11.6%, respectively) (Table 1). The duration of oral contraceptive was longer among women who drank ≥15 g/day versus those who drank no alcohol. Furthermore, current smokers and nonalcohol drinkers were less likely to be current PMH users than never/past smokers and alcohol consumers, respectively. A family history of ovarian cancer was not associated with the exposures of interest.

There was no association between current or past smoking and ovarian cancer risk (Table 2); women who were current smokers of ≥15 cigarettes per day had an RR of 1.06 (95% CI, 0.74–1.51) versus never-smokers. Risk did not increase with increasing duration of smoking (*P* for trend = .74) or pack years (*P* for trend = .85). However, smoking was significantly associated with risk of mucinous tumors, with an RR of 2.22 (95% CI, 1.16–4.24) for all current smokers and 2.02 (95% CI, 1.15–3.55) for past smokers versus never-smokers. Furthermore, the risk of mucinous tumors was significantly associated with smoking duration (RR per 20 years of 1.44; *P* for = .02) and pack-years (RR per 20 pack-years of 1.30; *P* for trend = .02). Because we had only 69 mucinous cases, we were unable to conduct categorical analyses of smoking duration and pack-years. No association was observed for other ovarian cancer subtypes or borderline tumors (data not shown).

**TABLE 3**
**Risk of Epithelial Ovarian Cancer Between 1980 and 2004, According to Caffeine Intake and Coffee, Tea, and Cola Consumption**

| | Cases | Person-years | Age-adjusted RR | Multivariate RR* (95% CI) |
|---|---|---|---|---|
| Caffeine intake, mg/d | | | | |
| ≤136 | 111 | 290,927 | 1.0 | 1.0 |
| >136–245 | 100 | 286,338 | 0.91 | 0.89 (0.68–1.17) |
| >245–360 | 105 | 281,503 | 0.97 | 0.95 (0.72–1.24) |
| >360–500 | 100 | 297,861 | 0.93 | 0.90 (0.68–1.18) |
| >500 | 91 | 307,248 | 0.85 | 0.80 (0.60–1.07) |
| | | | | *P* for trend = .03 |
| Caffeinated coffee intake | | | | |
| None | 78 | 223,561 | 1.0 | 1.0 |
| >0–6 cups/wk | 93 | 266,751 | 0.85 | 0.84 (0.62–1.14) |
| 1 cup/d | 115 | 274,138 | 1.03 | 1.01 (0.75–1.36) |
| 2 cups/d | 124 | 368,766 | 0.90 | 0.87 (0.65–1.16) |
| 3+ cups/d | 97 | 327,470 | 0.79 | 0.75 (0.55–1.02) |
| | | | | *P* for trend = .03 |
| Tea intake | | | | |
| ≤1 cup/wk | 188 | 573,675 | 1.0 | 1.0 |
| 2–6 cups/wk | 195 | 469,808 | 1.17 | 1.19 (0.97–1.46) |
| 1 cup/day | 69 | 225,928 | 0.93 | 0.95 (0.72–1.25) |
| 2+ cups/day | 53 | 190,800 | 0.94 | 0.96 (0.70–1.30) |
| | | | | *P* for trend = .39 |
| Cola intake | | | | |
| None | 93 | 214,711 | 1.0 | 1.0 |
| >0–4/wk | 278 | 809,096 | 0.79 | 0.81 (0.63–1.03) |
| 5–6/wk | 67 | 189,204 | 0.90 | 0.91 (0.66–1.27) |
| 1+/day | 69 | 250,865 | 0.80 | 0.82 (0.59–1.13) |
| | | | | P for trend = .81 |
| Decaffeinated coffee intake† | | | | |
| None | 140 | 365,594 | 1.0 | 1.0 |
| >0–6 cups/wk | 147 | 421,752 | 0.81 | 0.81 (0.64–1.03) |
| 1 cup/d | 71 | 164,169 | 1.02 | 1.00 (0.75–1.34) |
| 2 cups/d | 36 | 91,198 | 0.93 | 0.90 (0.62–1.30) |
| 3+ cups/d | 14 | 38,982 | 0.90 | 0.86 (0.49–1.49) |
| | | | | *P* for trend = .97 |

RR indicates rate ratios; 95% CI, 95% confidence interval.

* Adjusted for age, parity, oral contraceptive use, postmenopausal hormone use, tubal ligation, smoking status, and body mass index.

† Analysis began in 1984 because this was the first time that decaffeinated coffee was asked on the food frequency questionnaire.

We observed a significant inverse trend of ovarian cancer risk with caffeine (*P* for trend = .03) and caffeinated coffee intake (*P* for trend = .03); however, no individual RRs were found to be statistically significant (Table 3). For example, the RR comparing the top versus bottom quintile of caffeine intake was 0.80 (95% CI, 0.60–1.07), and that comparing 3+ cups/day of coffee versus none was 0.75 (95% CI, 0.55–1.02). There was no association noted between decaffeinated coffee and risk (RR for 3+/day vs none of 0.86; 95% CI, 0.49–1.49 [*P* for trend = .97]); decaffeinated coffee was asked beginning in 1984. The results for the simple update of caffeine and coffee were similar to the cumulative update (data not shown). When we included a 4-year lag between exposure assessment and disease follow-up, the results for caffeine were slightly stronger (RR for highest vs lowest quintile of 0.71; 95% CI, 0.52–0.97). In addition, we did not observe an association between cumulatively updated tea intake and ovarian cancer risk (RR for 2+ cups/day vs ≤1 cup/week of 0.96; 95% CI, 0.70–1.30); however, there was a suggestive inverse association for the simple updated tea analysis (comparable RR of 0.75; 95% CI, 0.55–1.01). Because the question regarding tea differed on the 1980 FFQ, we conducted a secondary analysis beginning in 1984 when the question was standardized to "tea, nonherbal." Here, compared with the reference group of ≤1 cup/week, the RRs using cumulatively updated tea consumption were 1.06 for 2 to 6 cups/week, 0.95 for 1 cup/day, and 0.68 (95% CI, 0.45–1.02) for 2 + cups/day (*P* for trend = .05). Cola was not associated with risk of ovarian cancer. Results for caffeine and caffeine-containing beverages were similar when examining specific ovarian cancer subtypes or with borderline tumors (data not shown).

Total alcohol intake in g per day (g/day) or servings per week was not associated with ovarian cancer risk (Table 4). The RR comparing women consuming 15+ g/day of alcohol versus nondrinkers was 0.99 (95% CI, 0.72–1.36; *P* for trend = .91). There were no associations noted between individual alcoholic beverages (beer, total wine, red wine, white wine, and liquor) and ovarian cancer risk. The results were similar when using simple updating of intake, including a 4-year lag, when examining borderline tumors, or stratifying by ovarian cancer subtypes (data not shown).

In general, the associations of alcohol, caffeine, and smoking with ovarian cancer risk did not vary by relevant variables such as age, oral contraceptive use, parity, tubal ligation, BMI, and PMH use (Table 5; data not shown). However, we did observe suggestive interactions between caffeine intake and both oral contraceptive use (*P* for heterogeneity = .02) and PMH use (*P* for heterogeneity = .13). Specifically, the inverse association between caffeine and risk was observed among never-oral contraceptive users (RR for top vs bottom quintile of 0.65; 95% CI, 0.46–0.92 [*P* for trend = 0.002]), but not among ever-oral contraceptive users (comparable RR of 1.29; 95% CI, 0.78–2.14 [*P* for trend = .68]). We observed a similar interaction between coffee and oral contraceptive use (RR for never-users of 0.64; 95% CI, 0.44–0.93 [*P* for trend = .003, *P* for heterogeneity = .03]). Furthermore, among postmenopausal women, the caffeine association was stronger among never-PMH users (RR = 0.57; 95% CI, 0.36–0.91 [*P* for trend = .007])

**TABLE 4**
**Risk of Epithelial Ovarian Cancer Between 1980 and 2004, According to Alcohol and Related Beverage Intake**

| | Cases | Person-years | Age-adjusted RR | Multivariate RR* (95% CI) |
|---|---|---|---|---|
| Alcohol intake, g/d | | | | |
| <0.1 | 110 | 340,139 | 1.0 | 1.0 |
| 0.1–4.9 | 217 | 610,924 | 1.08 | 1.05 (0.83–1.33) |
| 5.0–14.9 | 114 | 330,391 | 1.04 | 0.99 (0.75–1.30) |
| 15+ | 66 | 182,422 | 1.06 | 0.99 (0.72–1.36) |
| | | | | *P* for trend = .91 |
| Alcohol intake | | | | |
| Never | 49 | 142,969 | 1.0 | 1.0 |
| >0–4 drinks/wk | 249 | 688,087 | 0.99 | 0.99 (0.72–1.35) |
| 5–6 drinks/wk | 80 | 232,175 | 0.95 | 0.93 (0.65–1.34) |
| 1+ drinks/d | 129 | 400,645 | 1.00 | 0.97 (0.69–1.35) |
| | | | | *P* for trend = .99 |
| Beer intake | | | | |
| Never | 339 | 1,003,278 | 1.0 | 1.0 |
| 1–4 drinks/wk | 152 | 402,630 | 1.10 | 1.08 (0.89–1.31) |
| 5–6 drinks/wk | 5 | 23,417 | 0.66 | 0.65 (0.27–1.58) |
| 1+ drinks/d | 9 | 29,559 | 0.89 | 0.86 (0.44–1.68) |
| | | | | *P* for trend = .69 |
| Wine intake | | | | |
| Never | 157 | 460,733 | 1.0 | 1.0 |
| 1–4 drinks/wk | 286 | 808,098 | 1.02 | 0.99 (0.81–1.21) |
| 5–6 drinks/wk | 36 | 96,614 | 1.04 | 1.00 (0.69–1.45) |
| 1+ drinks/d | 28 | 95,032 | 0.90 | 0.85 (0.56–1.27) |
| | | | | *P* for trend = .99 |
| Liquor intake | | | | |
| Never | 228 | 688,087 | 1.0 | 1.0 |
| 1–4 drinks/wk | 220 | 633,214 | 1.01 | 1.00 (0.82–1.21) |
| 5–6 drinks/wk | 23 | 58,471 | 1.09 | 1.03 (0.67–1.59) |
| 1+ drinks/d | 35 | 80,332 | 1.20 | 1.13 (0.78–1.63) |
| | | | | *P* for trend = .65 |

RR indicates rate ratio; 95% CI, 95% confidence interval.
* Adjusted for age, parity, oral contraceptive use, postmenopausal hormone use, tubal ligation, smoking status, and body mass index.

versus ever-users (RR = 0.89; 95% CI, 0.58–1.36 [*P* for trend = .41]). When stratifying PMH users as never/past versus current the results were similar (*P* for heterogeneity = .01). Caffeine was suggestively, inversely associated with postmenopausal ovarian cancer (RR range, all quintiles, of 0.71–0.75), but was positively associated with premenopausal ovarian cancer (RR range,1.42–2.87). However, this interaction was not statistically significant (*P* for heterogeneity = .48), likely because of the limited number of premenopausal cases.

## DISCUSSION

In this large prospective study of incident ovarian cancer, we did not observe an association with smoking; however, smoking status, duration, and pack-years were significantly associated with the risk of mucinous tumors. Furthermore, we observed suggestive inverse associations between ovarian cancer risk and caffeine, coffee, and tea intake, which, for caffeine and coffee, were stronger for women who had never used oral contraceptives or PMH. Finally, we did not observe any associations with alcohol intake.

In this study, we did not find strong evidence of an association between total ovarian cancer risk and smoking. This is consistent with the majority of previous studies,[2,8,41–44] although 2 small prospective studies reported an increased risk of ovarian cancer overall with current smoking.[3,5] It is biologically plausible that the association between smoking and ovarian cancer could differ by histologic subtype. Mucinous tumors may be etiologically different from other subtypes, because these tumors histologically resemble colonic epithelium,[45] a tissue susceptible to cigarette-induced carcinogenesis.[46,47] For example, oral contraceptives and reproductive risk factors may not confer significant protection for mucinous tumors.[48,49] A recent meta-analysis of 10 primarily retrospective studies observed a 2-fold increased risk of mucinous tumors for current versus never-smokers, with a significant trend for increasing pack-years.[2] This is consistent with our findings, although we only had 69 mucinous cases in the current analysis. Other individual studies have reported similar findings.[41–43] Overall, existing evidence suggests that smoking likely is only a risk factor for mucinous tumors.

With regard to caffeine and caffeine-containing beverages, we generally observed a lower risk of ovarian cancer with increasing intake. However, these results should be interpreted with caution for several reasons. First, for caffeine and coffee, although the *P* for trend was statistically significant, no individual RRs were significant. Second, we did not observe an association between tea and ovarian cancer risk when using the 1980 study population, although an inverse association was noted when beginning the analysis in 1984 or when using the simple update analysis. This latter difference may be in part because tea could have different effects early versus late in the carcinogenic process. The lack of association in the 1980 study population may be due, in part, to misclassification of tea intake on the 1980 FFQ, which asked about any tea consumption; subsequent questionnaires asked specifically about nonherbal tea intake. We used 1980 as the baseline in our caffeine analyses because tea only contributed modestly (≈16%) to total caffeine intake in our population.

To our knowledge, only 3 previous studies have examined caffeine intake and the risk of ovarian cancer; all were retrospective.[6–8] Two reported a suggestive

**TABLE 5**
**Caffeine Intake and Ovarian Cancer Risk, Stratified by OC Use Among All Women and PMH Use Among Postmenopausal Women**

| | Never OC user* | | Ever OC user | | Never PMH user† | | Ever PMH user | |
|---|---|---|---|---|---|---|---|---|
| | No. of cases | Multivariate‡ RR (95% CI) | No. of cases | Multivariate‡ RR (95%CI) | No. of cases | Multivariate§ RR (95% CI) | No. of cases | Multivariate§ RR (95% CI) |
| Caffeine, mg/d | | | | | | | | |
| ≤136 | 84 | 1.0 | 27 | 1.0 | 46 | 1.0 | 54 | 1.0 |
| >136–245 | 70 | 0.82 (0.60–1.14) | 30 | 1.11 (0.66–1.87) | 35 | 0.70 (0.45–1.10) | 44 | 0.79 (0.53–1.18) |
| >245–360 | 53 | 0.66 (0.46–0.93) | 52 | 1.83 (1.15–2.92) | 28 | 0.57 (0.36–0.92) | 52 | 0.92 (0.63–1.36) |
| >360–500 | 51 | 0.62 (0.43–0.88) | 49 | 1.76 (1.09–2.82) | 26 | 0.52 (0.32–0.84) | 44 | 0.86 (0.58–1.29) |
| >500 | 55 | 0.65 (0.46–0.92) | 36 | 1.29 (0.78–2.14) | 31 | 0.57 (0.36–0.91) | 39 | 0.89 (0.58–1.36) |
| *P* for trend | | .002 | | .68 | | .007 | | .41 |

OC indicates oral contraceptive; PMH, postmenopausal hormone; RR, rate ratio; 95% CI, 95% confidence interval.

* *P* for interaction between OC use and caffeine, .02.

† *P* for interaction between PMH use and caffeine, .13

‡ Adjusted for age, parity, OC use, PMH use, tubal ligation, smoking status, and body mass index.

§ Excluding premenopausal women and those with an unknown menopausal status. Adjusted for age, parity, OC use, PMH use, tubal ligation, smoking status, and body mass index.

increased risk with caffeine intake only among premenopausal women.[7,8] Interestingly, we also observed a suggestive positive association for premenopausal women, but a modest inverse association for postmenopausal women; however, this difference was not found to be statistically significant. Biologic data support this potential interaction because caffeine intake has been associated with increased estrogen concentrations in premenopausal women (perhaps only for black tea) and shorter menstrual cycles.[50–52] Conversely, in postmenopausal women, caffeine intake may be associated with higher sex hormone-binding globulin (SHBG) and lower free estrogen concentrations; this mechanism may act through an effect on the hepatic production of SHBG.[53,54] This potential interaction should be examined further in studies with larger numbers of premenopausal women.

It is interesting to note that a third case-control study[6] reported a significant inverse association between caffeine and ovarian cancer risk, with a 41% reduced risk comparing the top versus bottom quartile. This is similar to our results of a 20% decreased risk. Notably, both studies observed that the association with caffeine was strongest for women who never used oral contraceptives.[6] Furthermore, among postmenopausal women, we only observed an inverse association for women who had never used PMH. Although still preliminary, the observed interactions with oral contraceptive use and PMH use suggest that caffeine may only be associated with ovarian cancer risk among women not using exogenous hormones. This may be because hormones, particularly estradiol, can interfere with caffeine metabolism.[55,56] However, these results need to be replicated in other prospective studies.

The results for coffee and tea consumption are less clear. We observed an inverse association for caffeinated coffee, but no association with decaffeinated coffee. This suggests that if there is an association it may act through caffeine consumption; however, another prospective study did not observe an association with either coffee type.[16] Furthermore, retrospective studies have reported inconsistent results ranging from inverse[6,44] or null[10,15] to positive associations.[7,8] This may be related to the different types of coffee consumed among the various populations because these may differ in their chemical composition and caffeine levels.[6] Further research should examine specific kinds of coffee in relation to risk. For tea, 3 prospective studies (including our own) observed a significant or suggestive inverse association.[17,18] Mostly black tea was consumed in these populations; however, it is unclear whether the type of tea is important, or whether individual components of tea mediate the association. Interestingly, retrospective studies generally have reported a positive association for tea,[6,10,15,57] possibly because of recall bias in ovarian cancer cases. As women develop abdominal symptoms, they increase their tea consumption, increasing recent intake in cases versus controls. Accumulating evidence suggests that caffeine-containing beverages may play a role in ovarian cancer risk.

Epidemiologic studies have not demonstrated an increase in ovarian cancer risk among alcohol drinkers. In fact, data from 6 prospective studies[22,33–36] and a combined analysis of 10 prospective studies,[32] which both included the NHS, strongly suggest that neither total alcohol nor specific alcoholic drinks are associated with ovarian cancer risk or by histologic subtype. Despite this, several retrospective studies

have reported an inverse association[19–25]; these differences may be because of recall bias. One advantage of the current analysis was the ability to update alcohol exposure over time, rather than using just baseline exposure.

The strengths of the current study include the prospective and detailed assessment of diet and updating of dietary information approximately every 4 years. The relevant timing of dietary exposures with respect to the latency of ovarian cancer is unknown and likely to be long. However, our follow-up length of up to 30 years likely includes the relevant exposure period. In addition, analyses excluding the first 4 years of follow-up were similar to the primary results, suggesting that there is relatively little bias because of preclinical disease. Furthermore, we controlled for multiple potential confounding factors, with the exception of family history of ovarian cancer, because this variable was not assessed until 1992. However, family history was not found to be associated with the exposures of interest and thus was unlikely to be a confounder. The principal limitation is modest power in histologic subtype analyses. In addition, the NHS is comprised predominantly of white women and this may limit the generalizability to other populations.

The results of the current study suggest that reducing alcohol intake and the cessation of smoking is not likely to have a substantial impact on risk of ovarian cancer. The possibility that caffeine may reduce ovarian cancer risk, particularly for women who have not previously used exogenous hormones, is intriguing and warrants further study, including an evaluation of possible biologic mechanisms.

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## Caffeine, Alcohol, Smoking, and the Risk of Incident Epithelial Ovarian Cancer

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The modifiable risk factors for ovarian cancer were examined and it was found that cigarette smoking increased the risk only for mucinous ovarian tumors, whereas alcohol intake was not associated with risk. However, an inverse association was observed between caffeine intake and ovarian cancer risk, particularly in women not using hormones. This finding merits further study.