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ORIGINAL ARTICLE

Coffee, tea, and caffeine consumption and risk of epithelial ovarian cancer and borderline ovarian tumors: Results from a Danish case-control study

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ABSTRACT

Background. Epidemiological studies that have investigated the association between coffee, tea and caffeine consumption and ovarian cancer risk have produced conflicting results. Furthermore, only few studies have examined the role of coffee and tea consumption separately for borderline ovarian tumors. By use of data from a large Danish population-based case-control study, we examined the risk of ovarian tumors associated with coffee, tea, and caffeine consumption with a particular focus on characterizing risks by tumor behavior and histology.

Material and methods. From 1995 through 1999, we included 267 women with ovarian cancer, 115 women with borderline ovarian tumors and 911 randomly selected control women. All women completed a beverage frequency questionnaire with detailed information on coffee and tea consumption. Analyses were performed using multiple logistic regression models.

Results. Both coffee (OR = 0.90; 95% CI 0.84–0.97 per cup/day) and total caffeine consumption from coffee and tea combined (OR = 0.93; 95% CI 0.88–0.98 per 100 mg/day) decreased the risk of ovarian cancer. These associations were significant only for the serous and "other" subtypes of ovarian cancer. No relation between tea consumption and ovarian cancer risk was observed. The risk estimates for borderline ovarian tumors resembled those observed for ovarian cancer, but did not reach statistical significance.

Conclusions. Our results indicate that coffee consumption and total caffeine consumption from coffee and tea combined is associated with a modest decreased risk of ovarian cancer. However, more biological studies are needed to identify bioactive chemical compounds in coffee that potentially could affect ovarian cancer development.

Ovarian cancer is the main cause of mortality from gynecological malignancies [1]. The highest incidence and mortality rates are found in Western countries, not least in Denmark, which has one of the world's highest incidence and mortality rates of ovarian cancer (respectively 11 and 7 cases per 100 000 women annually) [2]. Well confirmed risk modifiers of ovarian cancer include oral contraceptive use, tubal ligation and hysterectomy, which all protect against ovarian cancer, whereas nulliparity, hormone replacement therapy, and a family history of ovarian cancer increase the risk [3]. Furthermore, it has been suggested that dietary elements including coffee and tea could have an influence on ovarian cancer risk [4].

An array of compounds found in coffee or tea (e.g. caffeine, diterpenes and polyphenols) have potential anti-carcinogenic properties and may thus protect against ovarian cancer [5,6]. However, coffee and tea also contain various other compounds including ochratoxin, acrylamid and purine that are known to be potentially mutagenic and thereby carcinogenetic [7].

Epidemiological studies investigating the potential association between consumption of coffee and tea and risk of ovarian cancer have produced conflicting results. Concerning coffee consumption,

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results from two recent meta-analyses showed no convincing association with ovarian cancer [8,9]. With regard to tea consumption, the majority of earlier studies observed no association with ovarian cancer, but results from a few studies have shown a protective effect [10]. Only a few studies have investigated the association between the caffeine content in coffee and tea and ovarian cancer risk and the results have been inconsistent. One study found caffeine consumption to be inversely associated with ovarian cancer risk [11], three studies found no association [12–14], while two studies found an increasing risk of ovarian cancer [15,16]. Lastly, only few studies have examined the role of coffee and tea consumption separately for borderline ovarian tumors [11,12,17,18].

Hence, the available literature leaves the association of coffee and tea consumption in ovarian tumor development not fully solved. To further explore this association, we used data from a large Danish population-based case-control study. We examined whether the association between coffee and tea consumption and ovarian tumor risk differed among tumor subgroups by tumor behavior and histology.

Methods

The present study is based on data from the Danish MALOVA (MALignant OVArian cancer) study, which is a population-based case-control study on ovarian cancer. Methodological details of this study have been reported previously [19]. The study was approved by the Scientific Ethics Committee and the Danish Data Protection Agency, and informed written consent was obtained from all women before their inclusion in the study.

Cases

Briefly, cases consisted of women aged 35–79 who were scheduled for an explorative laparotomy or laparoscopy due to suspected ovarian tumor between January 1995 and May 1999. The study area consisted of 16 gynecological departments in Denmark. The women were invited to participate in the study which included a personal interview and blood and tissue samples. To ensure that all eligible cases in the study area were included, the study database was linked every second month to the Danish Cancer Registry. This registry contains nationwide information about all incident cases of cancer diagnosed in Denmark since 1943 and is supplemented by linkage to the Causes of Death Registry and the National Patient Registry to ensure complete data [20].

As soon as possible after the diagnosis of ovarian cancer, the women were invited to a personal interview conducted by trained personnel at the hospital. The interview covered family history of cancer and lifestyle factors as well as social, reproductive, medical, and gynecological history. In addition, all participants were given a beverage frequency questionnaire to be self-completed and returned to the study investigators.

By May 1999, a total of 1235 women with histologically verified ovarian tumors had been identified in the study area. A personal interview was completed by 756 women, but only the 382 women who completed the beverage frequency questionnaire were included for analyses. Of these, there were 267 women with ovarian cancer and 115 women with borderline ovarian tumors. Of the ovarian cancers, 157 were serous adenocarcinomas, 30 were mucinous adenocarcinomas, 41 were endometrioid adenocarcinomas, and 39 were other types of adenocarcinomas (including clear cell tumors, mixed cell tumors, undifferentiated tumors and tumors of unknown histology). Of the borderline ovarian tumors, 59 were serous, 51 were mucinous and five were of other histological subtypes. All inclusion and exclusion criteria are shown in Figure 1.

Controls

A random sample of control women aged 35–79 from the female population in the study area was selected using the unique Danish personal identification number as the key identifier. Controls were sampled simultaneously with the cases and frequency matched in five-year intervals using the age distribution of women with ovarian cancer registered in the Danish Cancer Registry from 1987 to 1992. In order to obtain sufficient statistical power for the analyses, we aimed to include at least two control women per case woman.

In all, 3839 women were invited as controls including a personal interview, a beverage frequency questionnaire and a blood sample. The inclusion and exclusion criteria for the control women are presented in Figure 1. If a woman did not give notice about her participation, she was contacted by telephone or by a second letter, inviting her to take part in the study including a personal interview, a beverage frequency questionnaire and a blood sample *or* by participating with a telephone interview only. The telephone interview was less comprehensive than the personal interview and women who participated with a telephone interview were not offered the beverage frequency questionnaire for which reason these control women were not included for analysis. Hence, for analysis, we included as controls a total of 911 women who participated with a personal interview and completed the beverage frequency questionnaire.

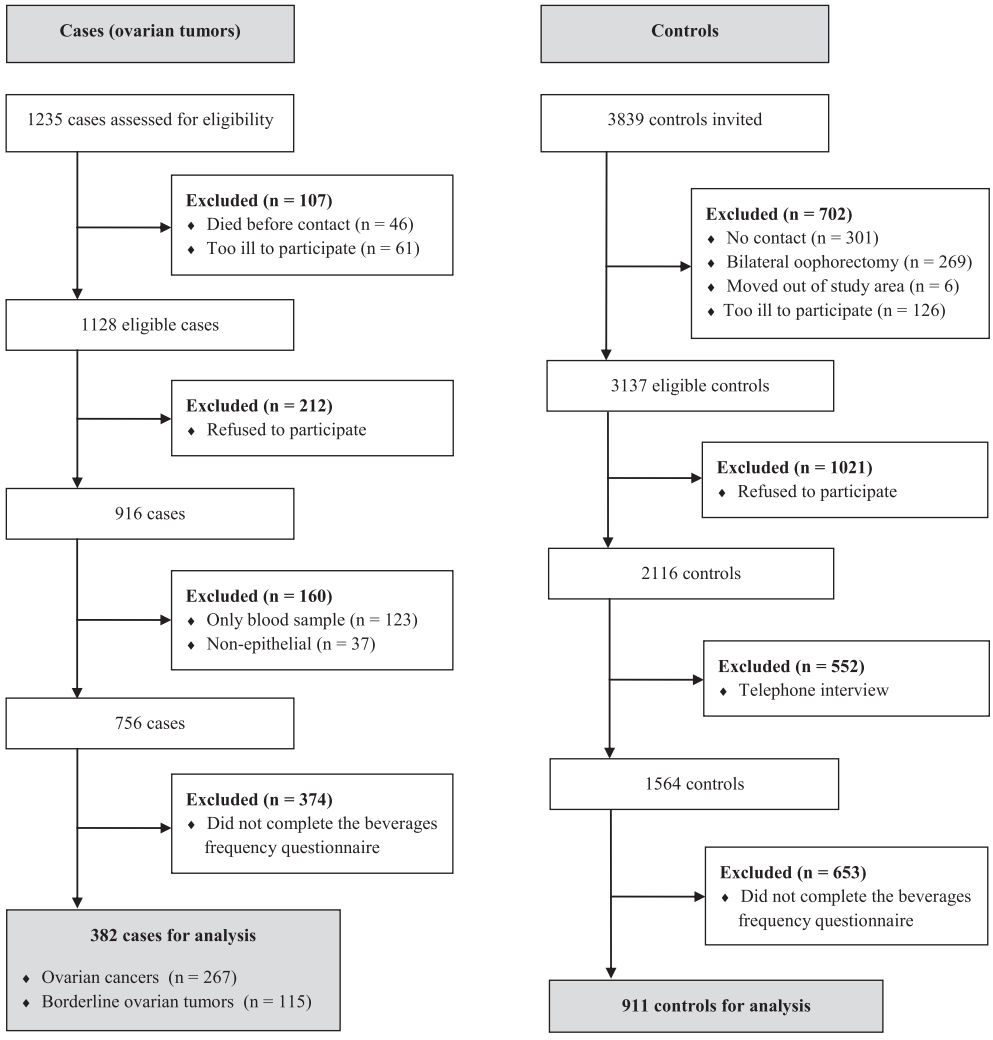

Figure 1. Inclusion and exclusion criteria for case and control women in the study.

Assessment of coffee, tea and caffeine consumption

In the beverage frequency questionnaire, coffee and tea consumption in the year prior to diagnosis (cases) or interview (controls) were recorded. Women indicated the frequency of consumption of tea and coffee on a scale of "never", "less than 1 cup per month", "1 cup per month", "2–3 cups per month", "1 cup per week", "2–4 cups per week", "5–6 cups per week", "1 cup per day", "2–3 cups per day", "4–5 cups per day", "6–7 cups per day", "8 or more cups per day". One cup was quantified as 200 ml (approx. 200 g). The questionnaire did not differentiate between filtered, unfiltered or instant coffee, between caffeinated or de-caffeinated coffee or between different types of tea (e.g. black versus green tea). However, at the time of the study (1995–1999) the vast majority of Danish women drank caffeinated, filtered coffee, and black tea. Hence, drawing on numbers from the Danish Veterinary and Food Administration [21], we estimated the caffeine content of coffee to 132 mg caffeine per 200 ml cup of coffee and to 52 mg caffeine per 200 ml cup of tea. Total daily consumption of caffeine was calculated as the sum of the weighted average caffeine content from coffee and tea.

Statistical analysis

We used multiple logistic regression analysis to estimate odds ratios (OR) and corresponding 95% confidence intervals (CI) for the association between total daily coffee, tea, and caffeine consumption and risk of ovarian cancer and borderline ovarian tumors. Subgroup analyses were conducted by histological type. Ovarian cancers were categorized as serous, mucinous, endometrioid, and "other" (including clear cell tumors, mixed cell tumors, undifferentiated tumors and tumors with unknown histology). Borderline ovarian tumors were categorized as either serous or mucinous tumors. Borderline endometrioid and clear cell tumors are uncommon and therefore these

tumor types were only included in the analyses for overall borderline ovarian tumors. Total daily caffeine consumption was categorized as quintiles of the distribution of caffeine in the entire study population.

In all analyses we adjusted for age in five-year categories corresponding to the sampling of controls. Furthermore, all analyses were adjusted for pregnancy (ever/never), number of pregnancies (linear), oral contraceptive use (ever/never) and duration of oral contraceptive use (linear). These potential confounders were based on a priori knowledge of their possible causal role in the development of ovarian cancer. Other potential confounding variables considered but not included in the final models, since they did not alter the fit of the models (i.e. did not alter the log of the effect estimate for epithelial ovarian cancer or borderline ovarian tumors risk by 10% or more), were: hormone replacement therapy use, educational level, smoking status, age at menarche, body mass index (BMI), breastfeeding, age at first and last pregnancy, hysterectomy, menopausal status, and a family history of breast and/or ovarian cancer.

Finally, linearity for all quantitative variables except age was tested by comparison with a model with spline effects with knots placed at the tertiles [22]. No significant deviations from linearity were found for any of the variables. All p-values were two-sided, and a significance level of 5% was used. Statistical analyses were performed using the PROC GENMOD procedure in the SAS software package (Version 9.2; SAS Institute, Cary, NC, USA).

Results

The mean age was 58.2 [standard deviation (SD) = 10.7] for ovarian cancer cases, 55.2 (SD = 11.0] for borderline ovarian tumors cases, and 57.6 (SD = 11.3) for controls. The vast majority of the women (90%) drank at least one cup of coffee per day and 83% drank at least one cup of tea per day. Coffee contributed 85% of total estimated caffeine intake in the study population while tea contributed only 15%.

Table I shows the associations between coffee, tea, and caffeine consumption and risk of ovarian cancer as well as of histological types of ovarian cancer. Adjustment for the selected potential confounders made virtually no changes to the estimates. We found that each extra cup of coffee per day among coffee drinkers was associated with a 10% decreased risk (95% CI 0.84–0.97). No convincing associations between daily tea consumption and risk of overall ovarian cancer or risk of any of the

Table I. Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for the associations between coffee, tea, and caffeine consumption and ovarian cancer, overall, and by histological type.

	Controls	Overall		Serous		Mucinous		Endometrioid		Other	
	n	n	OR (95% CI)*	n	OR (95% CI)*	n	OR (95% CI)*	n	OR (95% CI)*	n	OR (95% CI)*
Coffee consumption (cups/day)											
0	92	27	1.0	14	1.0	2	1.0	5	1.0	6	1.0
>0-<1	83	25	1.13 (0.59-2.15)	16	1.28 (0.57-2.89)	2	1.04 (0.14-7.80)	5	1.19 (0.32-4.12)	2	0.35 (0.07-1.85)
1-3	319	106	1.17 (0.70-1.94)	64	1.31 (0.68-2.52)	10	1.23 (0.26-5.84)	15	0.85 (0.29-2.44)	17	0.73 (0.27-1.98)
≥4	417	109	0.88 (0.53-1.45)	63	0.92 (0.48-1.78)	16	1.47 (0.33-6.69)	16	0.70 (0.24-2.03)	14	0.45 (0.16-1.30)
p-value for trend			<0.01		<0.01		0.45		0.20		0.14
Per cup coffee/day			0.90 (0.84-0.97)		0.89 (0.81-0.97)		1.07 (0.90-1.28)		0.90(0.77-1.06)		0.88 (0.74-1.05)
Tea consumption (cups/day)											
0	159	44	1.0	21	1.0	7	1.0	8	1.0	8	1.0
>0-<1	341	93	1.01 (0.66-1.54)	48	1.08 (0.61-1.91)	15	0.97 (0.37-2.49)	12	0.70 (0.27-1.77)	18	1.02 (0.42-2.47)
1-3	271	101	1.41 (0.93-2.15)	70	2.04(1.18-3.52)	6	0.51(0.17-1.56)	15	1.08(0.44-2.63)	10	0.73 (0.28-1.93)
≥4	140	29	0.81 (0.48-1.42)	18	1.05 (0.53-2.11)	2	0.34 (0.07-1.70)	6	0.97 (0.32-2.93)	3	0.47 (0.12-1.86)
p-value for trend			0.58		0.89		0.13		0.93		0.59
Per cup tea/day			0.98 (0.91-1.06)		1.01 (0.92-1.10)		0.83 (0.64-1.08)		1.01 (0.85-1.20)		0.95 (0.79-1.15)
Caffeine consumption† (mg/day)											
Q1 (≤262 mg)	177	65	1.0	41	1.0	4	1.0	10	1.0	10	1.0
Q2 (263-382 mg)	189	58	0.82 (0.53-1.26)	30	1.68 (0.40-1.16)	9	1.92 (0.57-6.49)	11	1.07 (0.43-2.64)	8	0.68 (0.41-2.97)
Q3 (383-595 mg)	184	50	0.74 (0.48-1.14)	30	0.70 (0.41-1.19)	3	0.66 (0.14-3.03)	7	0.70 (0.26-1.91)	10	0.92 (0.36-2.33)
Q4 (596-828 mg)	172	59	0.91 (0.59-1.40)	38	0.92 (0.55-1.54)	6	1.31 (0.36-4.84)	7	0.74 (0.27-2.05)	8	0.78 (0.29-2.12)
Q5 (>828 mg)	189	35	0.46 (0.29-0.75)	18	0.34 (0.20-0.68)	8	1.60 (0.46-5.61)	6	0.57 (0.20-1.66)	3	0.25 (0.07-0.96)
p-value for trend			<0.01		<0.05		0.52		0.08		<0.05
Per 100 mg/day			0.93 (0.88-0.98)		0.92 (0.86-0.99)		1.05 (0.91-1.20)		0.90 (0.80-1.02)		0.88 (0.77-1.00)

*Adjusted for pregnancy (ever/never), number of pregnancies (linear), oral contraceptive use (ever/never) and duration of oral contraceptive use (linear).

†Total caffeine consumption from both coffee and tea.

histological subtypes were observed. Concerning caffeine intake, women with daily caffeine consumption in the highest quintile (> 828 mg caffeine per day) had a statistically significantly lower risk of ovarian cancer than women in the reference group (quintile 1: ≤ 262 mg caffeine per day) (OR = 0.46; 95% CI 0.29–0.75). Furthermore, we found that each extra daily intake of 100 mg caffeine per day among women who drank coffee or tea was associated with a decreased risk of 7% (95% CI 0.88–0.98). When restricting the analyses to the histological subtypes of ovarian cancer, inverse associations between both coffee and caffeine and cancer risk were observed for serous, endometrioid and the group of "other" subtypes of ovarian cancer, but only the associations between coffee and caffeine consumption and serous ovarian cancer as well as the association between caffeine consumption and the group of "other" subtypes of ovarian cancer reached statistical significance. No associations between coffee and caffeine consumption and risk of mucinous ovarian cancer were observed.

Associations between coffee, tea, and caffeine consumption and risk of borderline ovarian tumors are presented in Table II. In general, the associations between coffee and caffeine consumption and risk of borderline ovarian tumors showed similar trends as those observed for ovarian cancer. However, the risk estimates did not reach statistical significance, most likely due to a smaller number of cases.

We also investigated whether the risk of ovarian cancer and borderline ovarian tumors associated with coffee and tea consumption (ever versus never use), respectively, varied according to pregnancy (ever/never), oral contraceptive use (ever/never), and menopausal status (pre/post). However, the risk of ovarian cancer and borderline ovarian tumors was not significantly affected by any of these potential risk factors, as none of these possible interaction factors were statistically significant (all p-values > 0.05; data not shown).

Discussion

In this population-based case-control study we investigated the association between coffee, tea, and caffeine consumption and risk of epithelial ovarian cancer and borderline ovarian tumors. The study's main strengths include the ability to examine risks among tumor subgroups by tumor behavior and histology, the population-based design and the ability to adjust for several known risk factors for ovarian cancer. Our results showed no convincing associations between tea consumption and risk of ovarian cancer whereas coffee and caffeine consumption decreased the risk of ovarian cancer. When the analyses were

Table II. Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for the associations between coffee, tea, and caffeine consumption and borderline ovarian tumours, overall, and by histological type.

	Controls	Overall		Serous		Mucinous	
	n	n	OR (95% CI)*	n	OR (95% CI)*	n	OR (95% CI)*
Coffee consumption (cups/day)							
0	92	10	1.0	4	1.0	5	1.0
>0-<1	83	18	1.70 (0.72-3.99)	7	1.78 (0.49-6.46)	11	2.03 (0.65-6.32)
1-3	319	42	1.16 (0.55-2.45)	25	1.68 (0.56-5.05)	16	0.90 (0.31-2.60)
≥4	417	45	0.86 (0.41-1.81)	23	1.06 (0.35-3.20)	19	0.62 (0.27-2.16)
p-value for trend			0.09		0.16		0.21
Per cup coffee/day			0.92 (0.83-1.01)		0.91 (0.80-1.04)		0.92 (0.80-1.05)
Tea consumption (cups/day)							
0	159	12	1.0	4	1.0	6	1.0
>0-<1	341	53	1.90 (0.97-3.71)	28	2.82 (0.96-8.29)	24	1.95 (0.76-5.00)
1-3	271	29	1.14 (0.69-2.84)	16	2.28 (0.74-7.00)	12	1.23 (0.44-3.38)
≥4	140	21	1.86 (0.87-3.98)	11	3.04 (0.93-9.95)	9	1.68 (0.57-4.94)
p-value for trend			0.97		0.65		0.47
Per cup tea/day			1.00 (0.91-1.10)		1.03 (0.91-1.17)		0.95 (0.82-1.10)
Caffeine consumption† (mg/day)							
Q1 (≤262 mg)	177	27	1.0	11	1.0	15	1.0
Q2 (263-382 mg)	189	28	0.90 (0.50-1.62)	13	0.93 (0.39-2.19)	14	0.85 (0.39-1.87)
Q3 (383-595 mg)	184	17	0.56 (0.29-1.08)	13	1.00 (0.43-2.34)	3	0.18 (0.05-0.65)
Q4 (596-828 mg)	172	22	0.76 (0.41-1.42)	12	0.94 (0.39-2.26)	9	0.62 (0.26-1.49)
Q5 (>828 mg)	189	21	0.63(0.33-1.18)	10	0.66 (0.27-1.64)	10	0.58 (0.25-1.37)
p-value for trend			0.13		0.27		0.16
Per 100 mg/day			0.95 (0.88-1.02)		0.95 (0.86-1.04)		0.93 (0.84-1.03)

*Adjusted for pregnancy (ever/never), number of pregnancies (linear), oral contraceptive use (ever/never) and duration of oral contraceptive use (linear).

†Total caffeine consumption from both coffee and tea.

restricted to histological subtypes of ovarian cancer, the inverse associations with coffee and caffeine were also observed for serous ovarian cancer and for the group of "other" ovarian cancer. Lastly, the risk estimates for borderline ovarian tumors resembled those observed for ovarian cancer, but did not reach statistical significance.

Results from two recent meta-analyses showed no convincing association between coffee consumption and ovarian cancer risk [8,9]. In addition, results from the largest prospective cohort study to date, including 330 849 women participating in the European Prospective Investigation into Cancer and Nutrition (EPIC), observed no association between coffee consumption and risk of ovarian cancer [9]. The inverse association between coffee consumption and risk of ovarian cancer observed in our study is in line with one previous study only. Using data from an Australian case-control study, Jordan et al. [11] found a 49% statistically significant decrease in ovarian cancer risk among women who consumed ≥ 4 cups of coffee per day compared to non-drinkers.

Our study showed no association between tea consumption and risk of ovarian cancer. This result concurs with results from a comprehensive recent review by Oppeneer et al. [10] of 16 separate studies. However, as a number of the reviewed studies found overall tea consumption to be associated with decreased ovarian cancer risk, Oppeneer et al. [10] noted that there is insufficient evidence at present to conclude that tea consumption is protective against ovarian cancer. Most recently, this was confirmed by the large prospective EPIC cohort study and meta-analysis performed by Bream et al. [9].

Previous studies of caffeine consumption in relation to ovarian cancer risk have shown conflicting results [11–16]. Three studies did not find evidence of an association [12–14] while two studies found an increased risk [15,16]. The inverse association between caffeine consumption and risk of ovarian cancer observed here has previously been observed only in the case-control study by Jordan et al. [11], which reported a 41% statistically significant decrease in ovarian cancer among women in the upper fifth quintile versus women in the lower fifth quintile of total caffeine consumption.

In the present study, the risk estimates for borderline ovarian tumors generally resembled those observed for ovarian cancer, but did not reach statistical significance. Jordan et al. [11] only observed an inverse association between coffee and caffeine consumption and risk of ovarian cancer but not for borderline ovarian tumors. Other studies investigating the associations between coffee, tea, and caffeine consumption and ovarian cancer or borderline ovarian tumors separately [8,11,12,14,17,18,23] have not found marked differences between these two tumor types and there is thus no major indication of a different risk profile between ovarian cancer and borderline ovarian tumors according to coffee, tea, and caffeine consumption.

When we performed separate analyses for histological subtypes of ovarian cancer, the inverse associations with coffee and caffeine were observed for serous ovarian cancer and for the group of "other" subtypes of ovarian cancer, but not for mucinous ovarian cancer. In contrast to our findings, most other studies on the associations between coffee, tea, and caffeine consumption by histological subtype of ovarian cancer found similar risk estimates for the various subtypes [9,12,14,15,17,18,22]. Our findings were supported only by Jordan et al. [11], whereas Goodman et al. [16] observed that coffee and caffeine consumption only increased the risk of mucinous ovarian cancer. Hence, even though the results from Goodman et al. [16] contrast to our results and those from Jordan et al. [11], these three papers in common support the growing body of evidence indicating that mucinous ovarian tumors may differ etiologically from non-mucinous ovarian cancer tumors [24]. However, most studies including the present are limited by their relatively low number of cases of some of the histological types, and further studies addressing associations between coffee and tea consumption and histological types of ovarian cancer are needed.

In our study, the inverse findings for caffeine consumption and ovarian cancer risk mirror the inverse findings for coffee consumption and ovarian cancer risk. As coffee was the primary contributor to the total estimated caffeine consumption (85%) while tea only contributed 15%, we find it possible that caffeine was the biological compound responsible for the decreased risk. Hence, the lower caffeine content in tea may explain the observed null associations between tea consumption and ovarian cancer risk. The observed inverse association between caffeine and ovarian cancer risk is potentially supported by results from biological studies, where caffeine has been found to be involved in modulation of tumor suppression through several endogenous pathways, e.g. the caspase-3 and p53 pathways; however the precise biological mechanisms remain unclear [25]. However, it is also possible that another component in coffee may be responsible for the decreased risk. Jordan et al. [11] argue that their finding of a decreased risk associated with coffee may not be due to its caffeine content, as they found no association between tea consumption and ovarian cancer risk despite the relatively high contribution of tea to the total caffeine consumption (49%). Furthermore, several other compounds found in coffee including

polyphenols, caffeic acid and diterpenes have potential anti-carcinogenic properties [5,6] and may explain why two small case-control studies found that consumption of decaffeinated coffee decreased the risk of ovarian cancer whereas no associations with caffeinated coffee were observed [17,26].

However, despite the fact that several biological hypotheses may explain the observed inverse association between coffee and caffeine consumption and risk of ovarian cancer, we cannot ignore that this risk pattern has not been observed in most previous studies. There are several possible explanations for this. First, methods of brewing, type of coffee, and roasting as well as grinding procedures vary among studies and may account for some of the observed differences. Second, a large variation in the choice of exposure categories between studies may potentially hamper comparisons of results from different studies. However, as the categories for coffee, tea and caffeine consumption used in the present study are virtually similar to the categories used in the vast majority of other studies, we do therefore not believe that this factor contributes markedly to the observed differences in results between studies. Third, our beverage frequency questionnaire did not provide information on specific types of coffee and tea or information on brewing method. The standard method of coffee brewing in Denmark in the mid-/late-1990s was drip brewing (filtered coffee) and the vast majority of tea consumption was black tea [27]. Consequently, the generalizability of our findings may be limited to these specific forms of consumption. Fourth, we had no information on other potential sources of caffeine (e.g. cola, cocoa or chocolate-containing food products). This exposure misclassification may slightly have biased our results. However, we are rather convinced that this misclassification may not be very large as coffee and tea have been shown to be by far the primary sources of caffeine in Denmark during the study period in the mid-1990s [28,29]. Fifth, the time period in which coffee and tea consumption has been measured vary among studies and may therefore partly explain some of the observed differences. In the present study, coffee and tea consumption was only assessed in the year preceding ovarian cancer diagnosis (or date of interview for controls). As the latency period for ovarian cancer (i.e. the time period from biological initiation of cancer until diagnosis) can last several decades and because consumption of coffee and tea may change over lifetime, we cannot entirely rule out that we have managed to capture consumption of coffee and tea during an etiologically relevant time period. For example, early ovarian cancer symptoms including symptoms of uneasiness may have induced coffee cessation among coffee drinkers and this scenario may partly explain the observed inverse association between coffee and ovarian cancer risk. Sixth, it is also possible that the observed inverse association reflects confounding characteristics of the women who drink coffee rather than a direct protective effect of coffee. For example, women who drink a lot of coffee may be different in terms of socioeconomic status, health-seeking behavior, etc. from women who consume less coffee. Hence we cannot rule out that our results may be influenced by unmeasured confounding. Further limitations of our study include the possibility of recall bias. However, the extensive personal interview shortly after diagnosis of ovarian cancer reduced the likelihood of severe recall bias. Finally, as a number of the eligible women did not complete the beverage frequency questionnaire, our results may have been affected by some degree of selection bias. However, as these women were not systematically different from the included women with regard to age and year at entry as well as potential confounders, we consider this potential bias to be of limited importance.

In conclusion, our results show that coffee consumption was associated with a modestly decreased risk of ovarian cancer. This pattern was also found for total caffeine consumption (including both coffee and tea), whereas we saw no effect on ovarian cancer risk for tea consumption alone. However, even though the existing literature is somewhat conflicting, our results are not supported by findings from most previous studies and should therefore be interpreted with caution. To further understand the potential role of coffee, tea, and caffeine consumption in ovarian cancer development, more well designed epidemiological studies with accurate assessment of type and brewing methods are needed. Furthermore, more biological studies are needed to identify bioactive chemical compounds in coffee that potentially could affect the development of ovarian cancer.

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