

CANCER EPIDEMIOLOGY

Some life-style factors and the risk of invasive epithelial ovarian cancer in Swedish women

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Abstract. The objective of this nationwide case-control study was to examine body mass index (BMI), alcohol use, coffee consumption, cigarette smoking, and leisure-time physical activity in relation to epithelial ovarian cancer (EOC) risk. Subjects were 655 newly diagnosed EOC cases and 3899 population controls, all 50–74 years of age at recruitment between 1993 and 1995. Data were collected through mailed questionnaires. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression. Women with a BMI ≥ 30 kg/m² compared with those with a BMI < 22 kg/m² appeared to have an elevated EOC risk (OR = 1.37, 95% CI: 1.01–1.85), particularly of mucinous (OR = 2.76, 95% CI: 1.15–6.61) and clear-cell histologies (OR = 2.68, 95% CI: 0.96–7.48). The OR for EOC among coffee users reporting ≥ 6 daily cups compared with non-users was 0.68 (95% CI:

0.42–1.10). Alcohol consumption was unrelated to EOC risk. Compared to non-smokers the ORs of EOC among current smokers were 0.70 (95% CI: 0.52–0.94) for those who smoked 1–10 cigarettes/day and 0.74 (95% CI: 0.53–1.02) for heavier smokers, while former smokers were at an unaltered risk (OR = 0.83, 95% CI: 0.66–1.04). Reduced EOC risks were observed among women in the highest compared with the lowest physical activity levels both at age 18–30 years (OR = 0.67, 95% CI: 0.52–0.87) and during the last years preceding study enrollment (OR = 0.68, 95% CI: 0.53–0.87). We conclude that women may avoid an excess risk of EOC through maintaining a normal BMI and reduce their risk by participation in leisure-time physical activity. The use of coffee, alcohol, or cigarette smoking does not appear to increase the risk of EOC.

Key words: Alcohol use, Body mass index, Coffee consumption, Epithelial ovarian cancer, Physical activity, Smoking

Abbreviations: BMI = Body mass index; CI = confidence interval; EOC = epithelial ovarian cancer; OR = odds ratio

Introduction

Ovarian cancer is the sixth most common cancer among Swedish women, and the leading cause of mortality from gynecological malignancies [1]. Epidemiological studies indicate that parity, oral contraceptive use, tubal ligation, and hysterectomy protect against ovarian cancer, whereas nulliparity, infertility, hormone replacement therapy, and a family history of ovarian cancer appear to increase risk [2].

The effects of various life-style factors on the risk of ovarian cancer have not been established to the same extent. Most [3–9], but not all studies [10–14] indicate that there is a weak positive association between obesity and epithelial ovarian cancer (EOC) risk. Studies where coffee consumption [6, 15–21], alcohol

use [6, 16, 17, 21–25], cigarette smoking [6, 16, 21, 26–29], and physical activity [4, 11, 30–34] were addressed in relation to ovarian cancer risk reported conflicting results. In the context of a nationwide case-control study on risk factors for epithelial ovarian malignancies, we here examine the association between these life-style factors and the risk of EOC. As these factors are modifiable it is important to identify if preventive measures against EOC exist, recognizing the poor prognosis of the disease [2].

Subjects and methods

Methodological details of this case-control study have been reported previously [35]. Data on women

aged 50–74 years who were born and resident in Sweden, without any previous ovarian malignancy or bilateral oophorectomy, were collected through mailed self-administered questionnaires.

From October 1, 1993 to December 31, 1995 the regional tumor registries recorded 1205 case patients with newly detected ovarian malignancies. After approach by their physicians and signing informed consent forms, 914 (76%) case women were enrolled. Non-participation was due to patient refusal 181 (15%), and physicians' denial to contact the patients 110 (9%) mostly because of patient death or poor health. To verify the epithelial origin of tumors, our study pathologist (H. Nordlinder) reviewed tissue specimens. Of 878 tumors retrieved for review, 803 were classified epithelial. In addition, 25 of the 36 patients whose specimens we were unable to retrieve, were included. These had epithelial histologies according to the field pathology reports filed by local pathologists, which were used for classification of histological subtypes in our study. This work examines data on the 655 (79%) EOC cases, while borderline tumors are reported elsewhere [36].

Control women were randomly selected from a national population registry, and sampled simultaneously with cases. Of 4996 potential controls, 4148 (83%) agreed to participate. Mailed questionnaires were completed by 3596 (72%) controls, while 552 (11%) who initially failed to respond answered essential questionnaire parts in a telephone interview. Case women were not interviewed in this way, as 94% of those who agreed to participate completed the questionnaire. After excluding 249 women with previous bilateral oophorectomy, 3899 controls remained for analyses. To utilize resources controls were also subjects in parallel identically designed breast cancer [37] and endometrial cancer [38] studies. Until March 31, 1995, controls were frequency matched to the expected age distributions of breast cancer cases, and afterwards to ovarian and endometrial cancer cases respectively.

Information requested in the questionnaires covered anthropometrical, medical, reproductive, and life-style factors. For exposures that may change due to disease acquirement, subjects were asked to record what was applicable one year prior to questionnaire administration. Current body height and weight one year ago were used to calculate BMI (kg/m^2), and the cut-off points between categories (<22 , $22 < 25$, $25 < 27$, $27 < 30$, $\geq 30 \text{ kg}/\text{m}^2$) were chosen based upon the distribution of cases and controls. Coffee consumption was assessed in cups (150 ml) per day. Alcohol use in g/day was estimated from the monthly consumption of beer, wine, and liquor. In the algorithm defining total alcohol consumption the following glass volumes in milliliters and alcohol contents in grams were used: regular beer 200 ml–5.6 g, strong beer 200 ml–9.0 g, wine 100 ml–8.9 g, strong wine 40 ml–6.4 g, and hard liquor 40 ml–

12.8 g. The average total monthly consumption in grams was divided by 30 to obtain alcohol use in g/day. Cigarette smokers were categorized into never, former and current smokers, who were further divided by the number of daily smoked cigarettes (1–10, >10). Subjects were asked to specify how often they engaged in leisure time physical activity (never, <1 hour/week, 1–2 hours/week, >2 hours/week), in childhood, from 18–30 years of age, and during the last years prior to study enrollment.

Statistical analyses were conducted with the SAS statistical software [39]. Risk estimates for EOC were computed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs), using unconditional logistic regression models fit by the maximum likelihood method. All *p*-values and CIs were two-sided. Tests of statistical significance were performed using the likelihood ratio test of general heterogeneity. For a risk factor with 10% frequency among controls we had 88% power, at the 5% significance level, to detect an OR of 1.5. All results were adjusted for age (5-year categories), parity (0, 1, 2, 3, 4–13 births), age at menopause (premenopausal, <49 , $49 < 53$, ≥ 53 years), duration of oral contraceptive use (never, <1 year, ≥ 1 year), and ever use of hormone replacement therapy. When adding numerous other variables to the models, the risk estimates were not materially altered. Tests of interaction were conducted through the likelihood ratio test comparing models with and without interaction terms.

Ethics Committees of the University of Uppsala and the Karolinska Institute approved this study.

Results

Based on the histology reports of local field pathologists the 655 EOC cases were classified as follows: serous 337 (51%), mucinous 60 (9%), endometrioid 180 (27%), clear-cell 43 (7%), and undifferentiated or others 35 (5%). Details of the histological classifications according to the field pathologists and the centralized tumor specimen review by the study pathologist has been commented elsewhere [35]. Table 1 describes characteristics of the study participants. Ninety-two percent of the case women and 95% of controls were postmenopausal.

Table 2 shows the risk of EOC in relation to BMI one year prior to study enrollment. Women in the highest ($\geq 30 \text{ kg}/\text{m}^2$) compared with the lowest ($<22 \text{ kg}/\text{m}^2$) BMI category were at an increased risk of EOC overall (OR = 1.37, 95% CI: 1.01–1.85), and particularly mucinous cancers (OR = 2.76, 95% CI: 1.15–6.61). Likewise, elevated risks of clear-cell cancers and endometrioid cancers appeared, although these differences were not statistically significant.

Table 3 presents the risk of EOC according to coffee consumption, alcohol use, and cigarette smoking. Coffee users reporting six or more daily

Table 1. Characteristics of epithelial ovarian cancer cases and control women, Sweden 1993–1995

Characteristic	Serous N = 337		Mucinous N = 60		Endometrioid N = 180		Clear-cell N = 43		All invasive N = 655		Controls N = 3899	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age at diagnosis/ questionnaire (years)	62.6	7.3	62.5	7.8	61.6	7.6	61.2	7.2	62.4	7.4	63.4	7.1
Age at menarche (years)	13.5	1.3	13.4	1.2	13.6	1.4	13.3	1.3	13.5	1.3	13.6	1.4
Age at menopause (years) ^a	50.6	3.6	49.7	4.2	50.3	3.5	50.8	3.6	50.4	3.6	50.1	3.8
Parity	1.9	1.3	2.0	1.3	1.7	1.2	1.3	1.3	1.8	1.3	2.1	1.4
Body mass index (kg/m ²) ^b	25.2	4.4	26.2	4.0	26.0	5.7	27.0	5.5	25.7	4.9	25.4	4.2
	n	%	n	%	n	%	n	%	n	%	n	%
Nulliparous	62	18.4	9	15.0	33	18.3	16	37.2	126	19.2	435	11.2
Ever use of oral contraceptives	91	27.0	28	46.7	60	33.3	12	27.9	206	31.5	1351	34.7
Ever use of HRT ^c	89	26.4	15	25.0	44	24.7	8	18.6	169	25.9	796	20.6
Ever tubal ligation	6	1.8	2	3.3	4	2.2	2	4.7	15	2.3	148	3.8
Ever hysterectomy	20	5.9	4	6.7	13	7.2	1	2.3	38	5.8	296	7.6
Coffee users	319	94.7	57	95.0	172	96.1	40	93.0	621	95.0	3212	95.4
Alcohol users	171	51.2	431	51.7	91	52.0	21	48.8	333	51.5	1791	53.6
Ever smokers	113	33.7	426	43.3	77	42.8	11	26.2	239	36.7	1649	42.6

SD = standard deviation; HRT = hormone replacement therapy.

^a Postmenopausal women only.

^b One year prior to answering the questionnaire.

^c Hormone replacement therapy (medium potency estrogens with or without progestins).

cups compared with non-users, had statistically non-significantly reduced risks of EOC overall (OR = 0.68, 95% CI: 0.42–1.10), and of serous and mucinous histologies. Coffee use was weakly related to endometrioid EOC, however all these risk estimates were statistically non-significant. We observed no association between alcohol consumption and the risk of EOC. Current cigarette smokers compared with never smokers appeared to have a slightly reduced risk of EOC, with ORs of 0.70 (95% CI: 0.52–0.94) for those smoking up to 10 cigarettes/day and 0.74 (95% CI: 0.53–1.02) for those who smoked more than 10 cigarettes/day. Women who reported former cigarette smoking compared with never smokers, were not at an apparently altered risk of EOC overall (OR = 0.83, 95% CI: 0.66–1.04), although risk estimates below unity appeared for serous (OR = 0.72, 95% CI: 0.52–0.98) and clear-cell histologies (OR = 0.49, 95% CI: 0.19–1.29). Cigarette smoking was not associated with mucinous or endometrioid EOC.

Leisure-time physical activity and EOC risk is described in Table 4. A reduced risk of EOC was seen with leisure-time physical activity both at age 18–30 years and during the last years preceding study enrollment, with ORs in the highest compared with the lowest physical activity levels of 0.67 (95% CI: 0.52–0.87) and 0.68 (95% CI: 0.53–0.87), respectively. For all EOC combined a dose–response effect was seen with an augmented protection among women participating in weekly leisure-time physical activities of longer duration, and this appeared both at ages 18–30 years (p for trend = 0.002) and during the last

years preceding study enrollment (p for trend = 0.008). Histology specific risk estimates of EOC during the same time periods also generally indicated protective effects from leisure-time physical activity during adult time periods, except for physical activity at 18–30 years of age and mucinous cancers. No clear association was observed between physical activity during childhood and EOC risk, and no apparent dose–response effect appeared for this time period (p for trend = 0.06).

Because physical activity at different age intervals is correlated we also tried to assess at which adult age interval the protective effect of leisure-time physical activity is most important. When mutually adjusting for all the three age intervals of leisure-time physical activity by incorporating them in the same logistic regression model (last column of Table 4), there was some evidence that leisure-time physical activity at age 18–30 years conveys the most protection, however these results were statistically not significant.

Discussion

Principal findings of this study on the risk of EOC in women aged 50–74 include moderately positive associations with BMI, negative associations with cigarette smoking and leisure-time physical activity, and a lack of association with alcohol use.

Strengths of our study include the large size, the nationwide population-based design and fairly good participation rates, attenuating the concern of selection bias. As in all case–control studies, the

Table 2. Odds ratios and 95 confidence intervals of epithelial ovarian cancer in relation to body mass index, Sweden 1993–1995

Category	Cases ^a																				
	Serous						Odds ratios of EOC by histologic subgroup														
	Mucinous		Endometr.		Clear-cell		All		Controls ^a		Serous		Mucinous		Endometrioid		Clear-cell		All		
N	N	N	N	N	N	N	N	N	N	N	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	
Body mass index one year ago (kg/m ²) ^b																					
<22 ^c	71	9	32	7	122	725	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–	
22 < 25	111	13	56	9	197	1241	0.98	0.71–1.35	0.89	0.38–2.10	1.06	0.67–1.68	0.77	0.27–2.15	0.99	0.77–1.28	0.77	0.27–2.15	0.99	0.77–1.28	
25 < 27	61	17	35	7	127	755	0.87	0.60–1.26	1.91	0.83–4.40	1.15	0.70–1.91	1.17	0.40–3.40	1.06	0.40–3.40	1.17	0.40–3.40	1.06	0.80–1.40	
27 < 30	55	8	34	11	115	675	0.90	0.61–1.30	1.08	0.41–2.85	1.26	0.75–2.10	2.15	0.81–5.72	1.10	0.83–1.46	2.15	0.81–5.72	1.10	0.83–1.46	
≥30	38	13	23	9	93	453	0.94	0.62–1.43	2.76	1.15–6.61	1.34	0.76–2.35	2.68	0.96–7.48	1.37	1.01–1.85	2.68	0.96–7.48	1.37	1.01–1.85	
<i>p</i> -value ^d																					
	0.94																				
	0.03																				
	0.82																				
	0.06																				
	0.23																				

EOC = epithelial ovarian cancer; OR = odds ratio; CI = confidence interval.

^a The totals for the different variables do not always equal the total number of subjects in the case or control category due to missing observations.^b Adjusted for age, parity, and age at menopause as categorized variables, duration of oral contraceptive use, and ever use of hormone replacement therapy.^c Reference category.^d *p*-value for the likelihood ratio test of general heterogeneity.

possibility of recall bias must be considered. Potential limitations of our study are rather crude exposure data, with no information on type of obesity (i.e. waist–hip ratio), other intake of caffeine than coffee, alternate tobacco or nicotine use than cigarette smoking, and types of occupational or leisure-time physical activity. We were unable to validate any of the self-reported exposures by laboratory methods. When comparing our results with those of other studies it has to be considered that the women in our study were mostly postmenopausal and between 50 and 74 years of age. Finally, because some of the statistical analyses by different histologies were restrained by low power as a consequence of few cases across categories, the histology specific results should be interpreted cautiously.

The present findings may be evaluated according to the ‘incessant ovulation’ [40], gonadotropin excess [41], and retrograde transportation hypotheses [42], all of which have been connected to ovarian cancer etiology. Additional hypotheses focus on altered estrogen, androgen, and progestin levels [43], and on ovarian inflammation [33, 44].

Similar to our data a moderately increased risk of EOC among women with a high BMI has been observed in some studies [3–9], while elsewhere either inverse associations [10, 14] or no associations appeared [11–13]. In our study on mostly postmenopausal women we assessed EOC risk according to BMI reported one year prior to study enrollment and we did not take into account BMI from earlier age periods, although in our analyses we adjusted for both age and menopausal status. It has been suggested that the effect of BMI on EOC risk may be modified by age and some [7, 11, 13], but not other [21] studies have found that a high BMI at a younger age has a stronger impact on subsequent EOC risk. The endocrine consequences induced by obesity as reflected in a high BMI seem to differ depending on menopausal status. Obese premenopausal women may become anovulatory with a shift to androgen and unopposed estrogen excess and a progestin deficit, whereas postmenopausally a hormonal situation with unopposed estrogens prevails. Most of the studies where the association between BMI and EOC risk was examined by menopausal status indicate that a high BMI is a stronger risk factor before than after menopause [3, 13, 21], and an excellent systematic review regarding this issue is provided by Purdie et al. [3]. When assessing the effects of obesity on EOC risk various methodological problems such as accurate anthropometric measurements must be recognized. Further, because obesity is correlated with diet, physical activity level, and other life-style factors, all of which may be difficult to measure, it remains an intricate task to assess the separate effect of obesity in relation to EOC risk.

It has been speculated that there is an association between obesity and endometrioid EOC, however

Table 3. Odds ratios and 95% confidence intervals of epithelial ovarian cancer in relation to coffee, alcohol, and cigarette use, Sweden 1993–1995

Category	Cases ^a												Odds ratios of EOC by histologic subgroup																	
	Serous			Mucinous			Endometrioid			Clear-cell			All			Serous			Mucinous			Endometrioid			Clear-cell			All		
	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Coffee drinking (cups/day) ^b	Never ^c	18	3	7	3	33	157	1.0	–	1.0	–	1.0	–	1.0	–	1.0	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–	1.0	
	<2	38	3	18	7	71	299	1.02	0.56–1.87	0.47	0.09–2.37	1.47	0.56–3.86	1.20	0.30–4.90	1.06	0.66–1.70													
	2–4	155	23	91	15	297	1486	0.85	0.50–1.44	0.77	0.23–2.65	1.64	0.70–3.85	0.48	0.13–1.72	0.93	0.61–1.40													
	4–6	93	26	43	18	192	1015	0.76	0.44–1.31	1.25	0.37–4.25	1.09	0.45–2.64	0.85	0.24–3.03	0.87	0.57–1.33													
	≥6	33	5	20	.	61	412	0.64	0.35–1.19	0.64	0.15–2.77	1.29	0.50–3.32	0.68	0.42–1.10															
	<i>p</i> -value ^d							0.34		0.29		0.26		0.003		0.18														
Alcohol consumption (g/day) ^b	Non-user ^c	163	29	84	22	313	1549	1.0	–	1.0	–	1.0	–	1.0	–	1.0														
	<5	121	22	65	15	238	1315	0.90	0.70–1.17	0.98	0.55–1.77	0.91	0.64–1.30	0.93	0.46–1.86	0.94	0.77–1.14													
	≥5	50	9	26	6	95	476	1.02	0.72–1.45	1.04	0.47–2.29	0.91	0.55–1.50	1.07	0.41–2.79	0.99	0.75–1.29													
		<i>p</i> -value ^d							0.68		0.99		0.86		0.95		0.80													
	Smoking cigarettes/day ^b	Never ^c	222	34	103	31	412	2224	1.0	–	1.0	–	1.0	–	1.0	–	1.0													
Former		59	13	40	5	125	799	0.72	0.52–0.98	0.98	0.50–1.91	1.06	0.72–1.57	0.49	0.19–1.29	0.83	0.66–1.04													
1–10		35	6	14	4	60	483	0.72	0.49–1.06	0.98	0.40–2.41	0.67	0.37–1.19	0.68	0.23–2.02	0.70	0.52–0.94													
≥11		19	7	23	2	54	367	0.53	0.33–0.88	1.18	0.50–2.79	1.12	0.66–1.90	0.38	0.08–1.67	0.74	0.53–1.02													
		<i>p</i> -value ^d							0.01		0.98		0.43		0.27		0.03													

EOC = epithelial ovarian cancer; OR = odds ratio; CI = confidence interval.

^a The totals for the different variables do not always equal the total number of subjects in the case or control category due to missing observations.^b Adjusted for age, parity, body mass index, and age at menopause as categorized variables, duration of oral contraceptive use, and ever use of hormone replacement therapy.^c Reference category.^d *p*-value for the likelihood ratio test of general heterogeneity.

Table 4. Odds ratios and 95% confidence intervals of epithelial ovarian cancer in relation to leisure time physical activity, Sweden 1993–1995

Category	Odds ratios of EOC by histologic subgroup																				
	Cases ^a										Controls ^a										
	Serous		Mucinous		Endometr		Clear cell		All		Serous		Mucinous		Endometr		Clear cell		All		
N	N	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Physical activity during childhood (hours/week) ^c	Never ^d	49	9	28	7	98	534	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–
	<1	39	2	24	4	75	371	1.14	0.72–1.79	0.33	0.07–1.54	1.22	0.68–2.18	0.80	0.23–2.85	1.09	0.78–1.54	1.35	0.90–2.01		
	1–2	110	26	48	14	205	1057	1.10	0.77–1.58	1.40	0.64–3.08	0.88	0.54–1.44	1.04	0.41–2.67	1.05	0.80–1.38	1.36	0.95–1.94		
	>2	135	22	76	18	268	1755	0.84	0.59–1.19	0.81	0.37–1.78	0.83	0.52–1.32	0.79	0.32–1.96	0.83	0.64–1.08	1.20	0.82–1.75		
	<i>p</i> -value ^e							0.17	0.07		0.47		0.88		0.08		0.08		0.30		
Physical activity at age 18–30 years (hours/week) ^c	Never ^d	58	10	34	9	116	551	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–
	<1	54	8	28	6	103	513	0.91	0.61–1.36	0.72	0.27–1.95	0.82	0.48–1.41	0.64	0.22–1.87	0.88	0.65–1.19	0.82	0.55–1.22		
	1–2	111	18	61	15	217	1203	0.82	0.58–1.16	0.86	0.39–1.90	0.80	0.51–1.26	0.74	0.31–1.75	0.83	0.64–1.07	0.78	0.53–1.15		
	>2	112	23	52	13	211	1448	0.71	0.51–1.00	0.91	0.43–1.94	0.56	0.35–0.89	0.52	0.21–1.17	0.67	0.52–0.87	0.70	0.46–1.07		
	<i>p</i> -value ^e							0.22	0.93		0.07		0.55		0.01		0.01		0.45		
Physical activity during last year preceding study enrollment (hours/week) ^c	Never ^d	64	12	37	10	130	595	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–
	<1	56	8	26	6	99	598	0.83	0.56–1.23	0.61	0.23–1.58	0.71	0.42–1.23	0.61	0.21–1.75	0.74	0.55–1.00	0.76	0.54–1.08		
	1–2	103	22	60	13	212	1142	0.81	0.58–1.13	1.03	0.49–2.13	0.85	0.55–1.33	0.74	0.31–1.75	0.84	0.66–1.08	0.81	0.67–1.25		
	>2	109	17	56	14	207	1386	0.69	0.50–0.96	0.69	0.33–1.49	0.67	0.43–1.04	0.64	0.27–1.51	0.68	0.53–0.87	0.78	0.56–1.09		
	<i>p</i> -value ^e							0.18	0.46		0.29		0.74		0.02		0.02		0.24		

EOC = epithelial ovarian cancer; OR = Odds ratio; CI = confidence interval.

^a The total for the different variables do not always equal the total number of subject in the case or control category due to missing observations.^b Also adjusted for the other age categories of leisure time physical activity.^c Adjusted for age, parity, body mass index, and age at menopause as categorized variables, duration of oral contraceptive use, and ever use of hormone replacement therapy.^d Reference category.^e *p*-value for the likelihood ratio test of general heterogeneity.

this was not seen two recent case-control studies [3, 21] and our findings only give weak support for such an association. Rather surprisingly we found a higher risk of mucinous EOC among women in the highest compared to the lowest BMI category, and this finding is inconsistent with other reports [3, 21].

There are several suggestions how obesity may alter EOC risk in the context of etiologic hypotheses. As extensive obesity is known to induce anovulation 'the incessant ovulation' hypothesis would predict a reduced EOC risk [45] among obese compared with normal weight premenopausal women. Postmenopausal obesity increases the peripheral conversion of androgens to estrone and estradiol [46], with concomitant reduction in sexual hormone binding globulins (SHBGs) and additional negative feedback on gonadotropin secretion. This should reduce EOC risk according to the gonadotropin hypothesis. However, elevated estrogens and androgens, and a deficit of progestins may also directly increase the risk of EOC [43], and any effects of insulin resistance and hyperinsulinemia on EOC risk are as yet unresolved [11, 47–49].

In our study on mainly postmenopausal women, those in the highest coffee consumption category were at statistically non-significant reduced risks of EOC, compared with non-users. This is in line with one study reporting a reduced risk of EOC among postmenopausal but not premenopausal coffee consumers compared with never users [21]. In other studies either positive [15, 16, 19, 21], inverse [20], or no associations [6, 17, 18] between coffee consumption and EOC risk appeared. Caffeine intake has been shown to reduce endogenous androgen and increase estrone and SHBG levels [50], which may explain our findings if increased androgen levels elevate EOC risk [43]. Any toxic effects of coffee with regard to EOC risk have not been fully examined [15, 21], and our data do not support such effects although we did not examine other caffeine exposures than coffee.

Previous studies examining alcohol use observed increased [6], decreased [22–25], and unaltered [16, 17, 21] risks of ovarian cancer, among users compared with abstainers. Hypothetically, heavy alcohol consumption may either directly attenuate gonadotropin secretion or, through impaired metabolism of estrogens in the liver, lead to elevated estrogens and reduced gonadotropins [35]. We found no consistent association between alcohol consumption and EOC risk.

Current cigarette smokers compared with never smokers in our study were at reduced risks of EOC, which is in disagreement with previous reports where higher risks of EOC appeared among smokers than non-smokers [26–29], or no associations were seen [6, 16, 21]. In a recent Australian study reporting positive associations between cigarette smoking and EOC risk, particularly the risk of mucinous tumors was increased [26]. Cigarette smoking has been reported

to increase cervical cancer risk, and the histological similarity between the endocervical lining and mucinous EOC could explain the positive association between cigarette smoking and the risk of mucinous EOC seen in other studies [26, 51], possibly mediated by toxicological effects of cigarette smoking [26]. In the study by Kuper et al. [21] elevated risk of serous EOC and mucinous tumors were seen among cigarette smokers compared with non-smokers. Our data gives no support of a positive association between cigarette smoking and mucinous EOC. Overall, cigarette smoking may attenuate the risk of EOC by decreasing estrogen levels [26]. Further, smokers enter menopause earlier than non-smokers [52], and a late age at menopause was associated with an increased risk of EOC in several studies [2].

We found moderately reduced risks of EOC following leisure-time physical activity at age 18–30 and during the last years preceding study enrollment, while no clear associations were seen for childhood exposures. Most case-control studies evaluating physical activity and EOC risk reported inverse associations [17, 30, 33, 34]. Other studies indicate an increased risk of EOC among women with high levels of physical activity compared with women who are less active [31, 32], and this was also seen in two prospective investigations assessing EOC risk in relation to physical activity level [4, 11]. The divergent results among studies may be explained by different cut-off points between physical activity levels, difficulties in measuring physical activity, and also from methodological problems in defining the occupational and recreational contributions to the total amount of physical activity. Possible mechanisms explaining a reduced risk of EOC following physical exercise include less body fat, decreased estrogen levels, delayed menarche, and anovulation among those involved in vigorous physical activity [4, 17, 33, 53, 54]. An elevated risk of EOC with physical activity may be expected if ovulatory cycles are restored after weight reduction induced by physical activity, and by increased gonadotropins following estrogen reduction. Also, it has been proposed that increased androgens and reduced progesterone through physical activity may increase EOC risk [43].

We conclude that women may avoid an excess risk of EOC through maintaining a normal BMI and that the risk may be reduced by participation in leisure-time physical activity. The use of coffee, alcohol, or cigarette smoking does not appear to increase the risk of EOC. Otherwise, we identified no lifestyle interventions which could potentially protect against EOC.

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