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Cigarette smoking and risk of borderline and invasive epithelial ovarian cancer

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Studies regarding the association between smoking and risk of epithelial ovarian cancer (EOC) are inconsistent. The purpose of this study was to examine the association between smoking and EOC, overall and according to invasiveness and histological subtype in a cohort of women with a high proportion of smokers at enrolment. We followed 103,081 women, aged 30–50 years in 1991/1992, from the Norwegian-Swedish Women's Lifestyle and Health cohort. The women completed a questionnaire on personal characteristics and exposures at enrolment and were subsequently followed with linkages to national registers through December 31, 2004. We used Cox proportional hazard regression models to estimate hazard ratio (RR) of EOC with 95% confidence intervals (CIs) associated with different measures of smoking exposures adjusting for confounding variables. Altogether 343 [241 (70%) invasive and 102(30%) borderline] incident EOC cases were identified. Former [HR = 2.2(95% CI 1.0–4.7)] and current [HR = 2.7(95% CI 1.2–5.7)] smokers had a more than doubling in risk for borderline tumors compared to never smokers. Women who had smoked for more than 20 years had 3 times [HR = 3.1(95% CI 1.5–6.7)] the risk of borderline tumors compared to never smokers. A test for trend according to smoking status was almost significant for mucinous tumors (p-trend = 0.05). A significant dose response relationship was found according to smoking intensity [pack-years; (0–9, 0–14, ≥ 15)] and duration [number of years; (0–10, 11–20, ≥ 20)] for borderline and serous tumors (p-trends < 0.05). In conclusion, smoking may increase the risk of borderline EOC.
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Key words: epidemiology; women; smoking; prospective cohort; epithelial ovarian cancer; borderline tumors; Norway; Sweden

Relatively little is known about the causes of ovarian cancer. Established factors that increase the risk are age, nulliparity, infertility, family history of ovarian cancer, whereas increasing parity, oral contraceptive use, tubal ligation and hysterectomy reduce the risk.[1,2] Several other factors such as a late age at menarche, an early menopause, a late age at first and last birth, breast feeding and physical activity have been linked with decreased risk, while obesity, postmenopausal hormone therapy use, and alcohol consumption have been linked with increased risk. However, many studies did not find these associations. Several etiologic hypotheses; the incessant ovulation, the retrograde transport, the inflammation, exogenous carcinogens, and some related to specific hormones, have been postulated. None of the suggested hypotheses so far can explain all the epidemiological data.[1–3]

According to the latest Monograph on "Tobacco smoke and involuntary smoking" from the International Agency for Research on Cancer there is insufficient evidence to draw any conclusions regarding the possible effect of smoking on ovarian cancer risk.[4]

Risch *et al.* was the first to suggest that mucinous and nonmucinous ovarian cancer may have different etiology.[5] A recent systematic review, including a meta-analysis, about smoking and ovarian cancer lends support to this hypothesis. Jordan *et al.* found that there was a significant doubling in risk of mucinous, but not of serous, endometroid and clear cell ovarian cancers among current smokers compared to never smokers.[6] This meta-analyses included data from 1 cohort study,[7] 8 population based case-control studies[8–15] and 1 pooled analysis of 10 case-control studies from the US.[16]

Because the use of tobacco is rising sharply globally,[17] smoking may generate large numbers of ovarian cancers if a causal association exists. The purpose of this study was to examine the association between smoking and epithelial ovarian cancer (EOC), overall, according to invasiveness and histological subtype in a cohort of women with a high proportion of smokers at enrolment.

Material and methods

Study cohort

The Norwegian-Swedish Women's Lifestyle and Health Cohort Study was initiated in 1991/1992. In Norway, a nationwide random sample of 100,000 women, born between 1943 and 1957, was drawn from the National Population Register at Statistics Norway. In Sweden, a random sample of 96,000 women, born between 1942 and 1962 residing in the Uppsala Health Care Region (which comprises about one-sixth of the Swedish population), was drawn from the National Population Register at Statistics Sweden (Stockholm, Sweden).

All women received a letter inviting them to participate in the study. The letter requested the women to provide written informed consent, and contained a comprehensive questionnaire to be completed and returned in a prestamped envelope. The common set of questions included detailed assessment of smoking habits, alcohol consumption, contraceptive use, reproductive history, history of breast cancer in the mother and sister(s), height and current weight (allowing us to calculate BMI as weight in kilograms divided by the square of height in meters), and other aspects of lifestyle habits. In both countries, the national Data Inspection Boards and the regional Medical Ethical Committees approved the study.

Smoking assessment

The questionnaire elicited information on current and previous smoking history. Women who reported to be ever smokers were asked to fill in an 8 by 7 table with preset categories for number of cigarettes smoked daily at different age intervals. On the basis of this table, we further categorized ever smokers according to current and former smoking status, age of smoking initiation, smoking duration; average number of cigarettes smoked daily, and pack-years of smoking (i.e. number of cigarettes smoked per day,

divided by 20, multiplied by the number of years smoked). The women reported if they were living with a smoker or did as a child. We categorized women who had never smoked, but had been living with a smoker as 'passive smokers' and those reporting neither as 'never smokers'. The women in the cohort with missing information on the variables related to passive smoking (1,7%) were classified as never smokers. The smoking patterns in this cohort have been described in detail elsewhere.[18]

Other exposures

Women who reported a natural menopause at cohort enrolment were considered postmenopausal. All other women were considered premenopausal, regardless of age, hysterectomy or use of hormone therapy. We calculated average daily consumption of alcohol in grams based on the content of pure alcohol in the different sorts of beverages among drinkers.

Follow-up

In Norway, 57,584 (57.6%) and in Sweden 49,259 (51.3%) women returned completed questionnaires. The cohort data were linked to the national registries of cancer and statistics in Norway and Sweden, to identify all cancer cases and deaths/emigrations, respectively. In both countries, the national registries are both accurate and virtually complete.[19,20] The ovarian tumors had been coded according to a slightly modified version of the 7th edition of the International Classification of Diseases through 1992 and since 1993 the second edition of the International Classification of Diseases for Oncology. We excluded women with germ cell and sex cord-stromal tumors. Invasive and borderline surface epithelial-stromal ovarian tumors were referred to as EOC. They were further categorized according to histology as serous, mucinous, endometroid, clear cell and others including those with unspecified information. Woman-years were calculated from the start of follow-up to the date of diagnosis of EOC, the date of any incident cancer (except basal cell carcinoma) diagnosis, emigration, death, or the end of follow-up, *i.e.*, December 31, 2004, whichever occurred first.

Among the 106,841 women included, we excluded 1,689 women who were diagnosed with any invasive cancer before the start of follow-up, 13 women who had emigrated or died before the start of follow-up, 2 women with missing vital status, 465 women with bilateral oopheroctomy at baseline and 1,591 women with no information on smoking history, leaving 103,081 subjects in the analytical cohort.

Statistical analysis

Each of the following factors was evaluated as a potential confounder of the relation between cigarette smoking and EOC: age at enrolment, years of education, age at menarche, age at menopause, nulliparity (yes, no), infertility (yes, no), number of children, age at first birth, age at last birth, family history of breast cancer in first degree relatives (yes, no), ever hormonal contraceptive use(yes, no), duration of hormonal contraceptive use (years), ever postmenopausal hormone therapy(yes, no), alcohol consumption (g/day), mean physical activity score (1–5), body height (cm), body weight (kg) and BMI. The hazard ratio (HR) for each of these factors was estimated in both univariate and multivariate analyses. Factors changing the HR 5% or those previously shown to be related to risk of EOC in this cohort,[21,22] were included in the final multivariate models [age at enrolment (years, continuous), nulliparous (yes/no), duration of hormonal contraceptive use (years) and menopausal status at enrolment (pre/post)]. Women (N = 1,922) with missing values for any of the co-variates were excluded from the multivariate models.

We used the Cox proportional hazard model to estimate age and multivariate adjusted HR associated with different measures of smoking exposure for EOC overall, invasive, borderline, serous and mucinous tumors and the two latter also according to invasive status.[23] We first conducted the analyses with never smokers, and thereafter with both passive and never smokers in the reference group.

The Cox analyses were performed with the PHREG procedure in the SAS statistical package.[24] We entered multiplicative terms between smoking and possible confounders in the models to evaluate interaction. Tests for linear trend were obtained by creating an ordinal exposure variable with equally spaced scores and including it in the model. We tested for heterogeneity between the 2 countries and between 2 strata of the confounding variables with Wald χ^2 statistics. HR's are given with 95% confidence intervals (CI's).

Results

During the 1,324,000 woman years of follow-up, 343 [241 (70%) invasive and 102 (30%) borderline] incident EOC cases were identified. The proportion of borderline tumors was 30% in Norway and 29% in Sweden. The tumors were classified as 194 serous, 55 mucinous, 25 endometroid and 69 others (clear cell and unspecified). Altogether, 34% of the serous and 62% of the mucinous was classified as borderline tumors. Sixty-three percent of the women reported to be ever smokers. Among the 23,608 women classified as passive smokers 91% reported to be living with a smoker at the time of enrolment.

Table I shows the distribution of selected characteristics at enrolment among cases and noncases, and according to type of EOC. Cases were older, had fewer years of follow-up, had less education, were more likely to be postmenopausal, and if so older at menopause. Cases were more likely to have a history of breast cancer in the family, of infertility, of ever postmenopausal hormonal therapy use and they reported to be heavier and to consume more alcohol compared to noncases. Cases were younger at age of first birth and of last birth, were less likely to have a history of ever hormonal contraceptive use, duration of HC use was shorter among ever users and duration of smoking among current smokers was longer compared to noncases (all *p's* < 0.05). Women with borderline tumors were younger at diagnosis, had fewer years of follow-up, were older at menopause, fewer were teetotallers, and they were more likely to be current smokers compared to those with invasive cancers (all *p's* < 0.05). Women with mucinous tumors were younger at diagnosis, had fewer years of follow-up, had a longer duration of HC use among ever users, and had a lower BMI compared to those with serous tumors (all *p's* < 0.05) (Table I).

Table II shows that the multivariate HR's among passive smokers were above unity for the different tumor categories, but none was significantly different from never smokers. Ever smokers had a significantly increased HR of 40% (95% CI 1.0–2.0) for all tumors compared to never smokers. Both former [HR = 2.2(95% CI 1.0–4.7)] and current [HR = 2.7(95% CI 1.2–5.7)] smokers had a more than doubling in risk for borderline tumors compared to never smokers. Women who started to smoke before 20 years of age had more than twice [HR = 2.6(95% CI 1.2–5.5)] and those who had smoked for more than 20 years had 3 times [HR = 3.1(95% CI 1.5–6.7)] the risk of borderline tumors compared to never smokers. A test for trend was significant according to smoking status for all (*p*-trend = 0.02) and borderline (*p*-trend = 0.001) tumors and was borderline significant for mucinous tumors (*p*-trend = 0.05). A significant dose response relationship was found according to number of pack-years and number of years smoked for both borderline and serous tumors (all *p*-trends < 0.05) (Table II).

Table III shows the corresponding multivariate HR's compared to the reference group including both passive and never smokers. This table shows materially similar results as those displayed in Table II, but the estimates are somewhat lower, and the confidence intervals more narrow (Table III).

Table IV shows that ever smokers had a significant increased risk of serous borderline [HR = 2.5(95% CI 1.3–4.5)] and a non-significant increased risk for both invasive [HR = 1.2(95% CI 0.5–2.9)] and borderline [HR = 1.6(95% CI 0.7–3.4)] mucinous

TABLE I – DISTRIBUTION OF SELECTED CHARACTERISTICS OF STUDY POPULATION (N – 103,081) AT ENROLMENT, GIVEN AS MEAN[1] AND PERCENTAGES (%)[1], AMONG CASES, NONCASES AND ACCORDING TO TYPE OF EPITHELIAL OVARIAN CANCER, THE NORWEGIAN-SWEDISH WOMEN'S LIFESTYLE AND HEALTH COHORT STUDY, 1991–2004

Characteristics	Noncases $N = 102,738$	Cases $N = 343$	Invasive[2] $N = 241$	Borderline[2] $N = 102$	Serous[3] $N = 194$	Mucinous[3] $N = 55$
Age at enrolment (y)	40.3	42.5**	42.8	41.9	42.6	41.6
Age at diagnosis (y)	NA	49.8	50.5	48.1**	50.4	48.1**
Duration of follow-up (y)	12.9	7.3**	7.7	6.3**	7.8	6.5*
Education (y)	12.2	11.8*	11.8	11.8	11.7	11.6
BMI[4] at enrolment	23.2	23.6*	23.5	23.9	24.0	22.7*
Mean phys. activity score[5]	3.1	3.1	3.1	3.1	3.1	3.1
Age at menarche (y)	13.1	13.2	13.2	13.0	13.1	13.3
Age at first birth (y)	24.0	23.4**	23.3	23.4	23.1	23.8
Age at last birth (y)	29.0	28.1**	28.3	27.7	28.0	28.2
Number of children	2.0	1.9	2.0	1.8	2.0	1.8
Number of children (%)						
0	11.8	14.9	13.7	17.7	12.9	16.4
1–2	57.7	58.0	56.9	60.8	55.2	61.8
3+	30.6	27.1	29.5	21.6	32.0	21.8
Infertility(%)	3.7	5.9*	5.9	6.0	5.7	7.6
Ever horm. contracept. use (%)	73.1	61.0**	59.6	64.4	61.5	54.6
Duration of hormonal contraceptive use[6] (y)	5.9	4.6**	4.3	5.2	4.2	6.3*
Postmenopausal at enrolment (%)	3.8	7.8**	7.9	7.6	6.6	14.0
Age at menopause (y)[7]	42.4	44.9**	44.1	46.8**	44.8	45.2
Ever post-menop. ht use (%)	3.7	6.1*	5.0	8.8	5.7	12.7
Fam. hist. of breast ca. (%)[8]	4.8	7.3*	8.7	3.9	8.8	3.6
Hysterectomi (%)	2.5	2.8	2.9	3.0	2.6	1.9
Teetotallers (%)	9.0	10.0	12.1	4.9*	11.4	7.3
Alcohol consumption (g/day)[9]	3.9	4.0	3.9	4.3	4.2	3.9
Smoking status (%)						
Never	14.5	12.0	13.7	7.8*	10.3	10.9
Passive	22.5	20.1	22.8	13.8	22.2	18.2
Former	35.4	36.4	35.3	39.2	36.6	36.4
Current	27.6	31.5	28.2	39.2	30.9	34.5
Smoking duration						
Former	15.4	15.4	13.0	14.7	16.0	14.5
Current	25.2	27.4**	28.7	27.3	28.2	31.3

[5]T-Test or χ^1 test for differences between cases versus noncases, women with invasive versus borderline, and serous versus mucinous tumors; *p value < 0.05; **p value < 0.001.–[2]All histological types.–[3]Include invasive and borderline tumors.–[4]Body-mass-index; the weight in kilograms divided by the square of the heights in meters.–[5]Leisure time physical activity in the year preceding cohort enrolment (scored as 1–5, low to high level.–[6]Among ever hormonal contraceptive users.–[7]Among women that were postmenopausal at enrolment.–[8]Among mother or sister(s).–[9]Among drinkers.

TABLE II – MULTIVARIATE[1] ADJUSTED HAZARD RATIO (95% CONFIDENCE INTERVAL) OF EPITHELIAL OVARIAN CANCER OVERALL AND BY SUBTYPES ACCORDING TO VARIOUS MEASURES OF SMOKING EXPOSURE COMPARED WITH NEVER SMOKERS AMONG 101,159[2] WOMEN, NORWEGIAN-SWEDISH WOMEN'S LIFESTYLE AND HEALTH COHORT STUDY, 1991–2004

Smoking exposure	All tumors ($N = 337$)			Invasive[3] ($N = 238$)			Borderline[3] ($N = 99$)			Serous[4] ($N = 189$)			Mucinous[4] ($N = 54$)		
	Cases/Cohort	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI
Never	41/14,638	1.0	(ref.)	33	1.0	(ref.)	8	1.0	(ref.)	20	1.0	(ref.)	6	1.0	(ref.)
Passive	68/22,746	1.1	(0.7–1.6)	54	1.1	(0.7–1.7)	14	1.1	(0.5–2.7)	42	1.4	(0.8–2.3)	10	1.1	(0.4–3.0)
Former	124/35,873	1.4	(1.0–2.0)	85	1.2	(0.8–1.8)	39	2.2	(1.0–4.7)	70	1.6	(1.0–2.6)	20	1.4	(0.6–3.5)
Current	104/27,902	1.4	(1.0–2.1)	66	1.1	(0.8–1.7)	38	2.7	(1.2–5.7)	57	1.6	(1.0–2.7)	18	1.5	(0.6–3.9)
Trend test[4]	$p = 0.02$			$p = 0.47$			$p = 0.001$			$p = 0.26$			$p = 0.05$		
Ever smokers	228/63,775	1.4	(1.0–2.0)	151	1.2	(0.8–1.7)	77	2.4	(1.1–4.9)	127	1.6	(1.0–2.6)	38	1.5	(0.6–3.5)
Age (years) of smoking initiation															
≥20	78/18,431	1.4	(1.0–2.0)	58	1.3	(0.8–2.0)	20	1.9	(0.8–4.4)	37	1.4	(0.8–2.4)	16	2.0	(0.8–5.1)
<20	150/45,344	1.4	(1.0–2.0)	93	1.1	(0.7–1.6)	57	2.6	(1.2–5.5)	90	1.8	(1.1–2.9)	22	1.2	(0.5–3.0)
No of cigarettes per day															
1–9	125/32,290	1.5	(1.0–2.1)	85	1.3	(0.8–1.9)	40	2.4	(1.1–5.2)	62	1.5	(0.9–2.5)	22	1.7	(0.7–4.2)
≥10	103/31,485	1.3	(0.9–1.9)	66	1.1	(0.7–1.6)	37	2.3	(1.1–5.0)	65	1.8	(1.1–2.9)	16	1.2	(0.5–3.2)
No of pack-years															
0–9	115/33,943	1.4	(1.0–1.9)	83	1.2	(0.8–1.9)	32	1.9	(0.9–4.1)	55	1.3	(0.8–2.2)	21	1.6	(0.8–3.9)
10–14	54/13,416	1.7	(1.1–2.5)	27	1.1	(0.6–1.8)	27	4.1	(1.9–9.0)	38	2.5	(1.4–4.2)	8	1.5	(0.5–4.4)
≥15	59/16,416	1.3	(0.9–1.9)	41	1.1	(0.7–1.8)	18	2.0	(0.9–4.7)	34	1.6	(0.9–2.7)	9	1.2	(0.4–3.5)
Trend test[5]	$p = 0.21$			$p = 0.97$			$p = 0.03$			$p = 0.03$			$p = 0.90$		
No of years smoked															
0–10	90/29,462	1.3	(0.9–2.0)	70	1.2	(0.8–2.0)	20	1.6	(0.7–3.9)	43	1.3	(0.7–2.3)	18	2.0	(0.8–5.5)
11–20	67/22,965	1.3	(0.9–2.0)	45	1.2	(0.7–1.8)	22	2.0	(0.9–4.5)	37	1.5	(0.9–2.6)	8	0.9	(0.3–2.7)
>20	112/25,986	1.5	(1.0–2.1)	69	1.1	(0.7–1.7)	43	3.1	(1.5–6.7)	67	1.9	(1.1–3.1)	18	1.6	(0.6–4.1)
Trend test[5]	$p = 0.04$			$p = 0.76$			$p = 0.001$			$p = 0.007$			$p = 0.48$		

[1]Adjusted for age, nulliparous, menopausal status, and duration of hormonal contraceptive use, all at enrolment.–[2]Women ($N = 1,922$) with missing values for any of the co-variates were excluded from the multivariate model.–[3]All histological types.–[4]Include invasive and borderline tumors.–[5]Includes never smokers.

TABLE III – MULTIVARIATE[1] ADJUSTED HAZARD RATIO (95% CONFIDENCE INTERVAL) OF EPITHELIAL OVARIAN CANCER OVERALL AND BY SUBTYPES ACCORDING TO VARIOUS MEASURES OF SMOKING EXPOSURE COMPARED WITH REFERENCE GROUP[2] AMONG 101,159[3] WOMEN, NORWEGIAN-SWEDISH WOMEN'S LIFESTYLE AND HEALTH COHORT STUDY, 1991–2004

Smoking exposure	All tumors (N = 337)			Invasive[4] (N = 238)			Borderline[4] (N = 99)			Serous[5] (N = 189)			Mucinous[5] (N = 54)		
	Cases/Cohort	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI
Reference group[2]	109/37,384	1.0	(ref.)	87	1.0	(ref.)	22	1.0	(ref.)	62	1.0	(ref.)	16	1.0	(ref.)
Former	124/35,873	1.3	(1.0–1.7)	85	1.1	(0.8–1.5)	39	2.0	(1.2–3.3)	70	1.3	(0.9–1.8)	20	1.4	(0.7–2.6)
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Trend test[6]	*p = 0.02*			*p = 0.6*			*p = 0.001*			*p = 0.11*			*p = 0.26*		
Ever smokers	228/63,775	1.3	(1.1–1.7)	151	1.1	(0.9–1.5)	77	2.2	(1.3–3.5)	127	1.3	(1.0–1.8)	38	1.4	(0.8–2.5)
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Trend test[6]	*p = 0.08*			*p = 0.83*			*p = 0.004*			*p = 0.04*			*p = 0.63*		
No of years smoked															
0–10	158/52,208	1.3	(0.9–1.8)	82	1.2	(0.8–1.8)	34	1.5	(0.7–3.0)	60	1.0	(0.6–1.7)	20	2.0	(0.9–4.2)
11–20	67/22,965	1.3	(0.9–1.7)	69	1.1	(0.8–1.6)	43	1.9	(1.0–3.4)	67	1.2	(0.8–1.9)	18	0.9	(0.4–2.1)
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Trend test[6]	*p = 0.01*			*p = 0.65*			*p = 0.0001*			*p = 0.02*			*p= 0.36*		

[1]Adjusted for age, nulliparous, menopausal status, and duration of hormonal contraceptive use, all at enrolment.–[2]Reference group includes never and passive smokers.–[3]Women (N = 1,922) with missing values for any of the co-variates were excluded from the multivariate model. –[4]All histological types.–[5]Include invasive and borderline tumors.–[6]Includes reference group.

TABLE IV – MULTIVARIATE[1] ADJUSTED HAZARD RATIO (95% CONFIDENCE INTERVAL) OF SEROUS AND MUCINOUS EPITHELIAL OVARIAN CANCER BY INVASIVE STATUS AMONG EVER SMOKERS COMPARED WITH REFERENCE GROUP[2], NORWEGIAN-SWEDISH WOMEN'S LIFESTYLE AND HEALTH COHORT STUDY, 1991–2004

Smoking exposure	Invasive						Borderline					
	Serous (N = 125)			Mucinous (N = 21)			Serous (N = 64)			Mucinous (N = 33)		
	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI
Reference group[2]	49	1.0	(ref.)	7	1.0	(ref.)	13	1.0	(ref.)	9	1.0	(ref.)
Ever smokers	76	1.0	(0.7–1.5)	14	1.2	(0.5–2.9)	51	2.5	(1.3–4.5)	24	1.6	(0.7–3.4)

[1]Adjusted for age, nulliparous, menopausal status, and duration of hormonal contraceptive use, all at enrolment.–[2]Reference group includes never and passive smokers.

tumors compared to a reference group including both passive and never smokers.

Ever smokers had a similar increased risk of EOC compared to the reference group including passive and never smokers in Norway [HR = 1.3(95% CI 1.0–1.8)], and in Sweden [HR = 1.3(95% CI 0.9–1.9)] (*p* for heterogeneity = 0.95). The corresponding HR's did not differ significantly between 2 strata of the following confounding variables; age, menopausal status, parity and hormonal contraceptive use (all *p*'s for heterogeneity >0.05).

Discussion

Our study finds that both former and current smokers have an overall increased risk of EOC. After stratification the positive association is mostly confined to women with borderline tumors. Women who started to smoke before 20 years of age had more than twice and those who had smoked for more than 20 years had 3 times the risk of borderline tumors compared to never smokers. Furthermore, a borderline significant dose response relationship is revealed between smoking status and mucinous tumors. Our results show a dose response relationship with number of pack-years and number of years smoked for both borderline and serous tumors.

To our knowledge, our cohort study is the first to find significant overall associations between ever, current, and former smoking and risk of EOC. One likely explanation for the consistent findings is that this is also the first prospective study that includes borderline tumors. Our study has a high proportion of borderline tumors compared to previous studies.[6] It is reassuring that this proportion was similar in Norway and Sweden. Borderline tumors are more

likely to occur among younger than older women.[1,2] Almost all the women in our study were premenopausal and less than 50 years at enrolment. If there is a positive association between smoking and borderline, but not with invasive tumors, we would expect a large proportion of borderline tumors in populations where the smoking prevalence has been high for several decades.

The Canadian cohort study,[7] found that ever smokers had a small, nonsignificant increased risk of EOC compared to never smokers. This study also revealed a significant increased risk with smoking intensity (at least 30 pack years) and duration (at least 40 years) mostly associated with nonmucinous tumors. Current smoking was on the other hand associated with a significantly increased risk for mucinous, but not for nonmucinous tumors.[7] The other published cohort study till date focusing on smoking and risk of EOC,[25] included only 39 invasive cases. The Japanese study found a significant linear trend for number of pack years smoked and EOC. Our nonsignificant estimates and lack of dose response for invasive EOC are in agreement with the results from the Canadian study.

A previous Norwegian cohort study that examined the association with smoking habits and risk of all cancers did not find any overall association between smoking and the 140 ovarian cancer cases.[26] Two other cohort studies[27,28] found a positive association between cigarettes smoked per day and ovarian cancer mortality, which was significant in the former,[27] but not in the latter study.[28]

Some of the studies[7,8,11] in the review[6] support the notion that cigarette smoking may act as an initiator for serous/nonmucinous tumors because of the long period of time between the causal action of cigarette smoking and diagnosis. We find similar HR's

among former and current smokers for serous tumors. This is consistent with an initiator effect of smoking. Although we adjust for potentially confounding variables, we cannot exclude the possibility that our results are due to residual confounding.

Some studies[7–9,11,12,15] in the review[6] also suggest that smoking may have a promoting effect regarding the development of mucinous tumors because of the short period of smoking exposure before diagnosis. Furthermore, Jordan *et al*., discuss the possibility that the revealed increased risk may be due to misclassification of mucinous tumors from the gastrointestinal tract, pancreas or cervix that present clinically as primary ovarian cancer. However, they note that the studies with the strongest associations with smoking either were with borderline tumors where the diagnosis is more reliable, or with cases that were reviewed centrally by 3 pathologists.[6] In our study, all the HR's for the different measures of smoking exposure related to mucinous tumors were above unity, none were significant, but all have CI's that are compatible with a doubling in risk. We have few cases and our results should be interpreted with caution.

Benzo(a) pyrene [B(a)p] is a potent carcinogen present in cigarettes that acts locally.[29] B(a)p adducts have been found in ovarian follicular cells among women exposed to cigarette smoke. Presence of these adducts may increase the risk for DNA damage through a direct carcinogenic effect.[30] This supports the biological plausibility of a positive association between smoking and EOC.

Our study has several strengths including the prospective design, adjustment for potential confounders, virtually complete follow-up and classification according to both invasiveness and subtype. Another force is that a large proportion of women were ever smokers at enrolment. Furthermore, we were able to separate current and former smokers, and to run analyses with and without passive smokers included in the reference group. Also, the distribution of

risk factors for EOC differed between cases and noncases in the expected way suggesting a high internal validity of our cohort. The cumulative incidence rates during follow-up for all cancer sites are almost identical as those reported to the national cancer registries in Norway in the same period.[31] This indicates also a high external validity in spite of a mediocre response rate. The smoking habits among our Norwegian and Swedish women reflect known smoking patterns in the respective countries.[32,33]

Limitations of our study are that we have few cases and crude information about passive smoking. We therefore display the results showing that the results are materially the same when we include the passive smokers in the reference group. Another limitation is the lack of information on occasional smoking, an activity around 10% of the Norwegian female population report to do.[32] Moreover, we do not have updated information on changes in smoking habits during follow-up. Nevertheless, we find it likely that any misclassification of smoking exposure and of tumor histology will have attenuated the displayed associations.

In conclusion, smoking may increase the risk of borderline ovarian tumors. If our results are confirmed by other studies, it will have implications for public health, as smoking may be one of few potentially avoidable risk factors for ovarian cancer. The results from our study should give yet another incentive to curb the smoking epidemic spreading among women in the developing countries.

Acknowledgements

References

1. Gertig DM, Hunter D. Ovarian cancer. In: Adami HO, Hunter D, Trichopoulos D, eds. Textbook in cancer epidemiology. New York: Oxford University Press, 2002. 378–94.
2. Lukanova A, Kaaks R. Endogenous hormones and ovarian cancer: epidemiology and current hypotheses. Cancer Epidemiol Biomarkers Prev 2005;14:98–107.
3. Hanna L, Adams M. Prevention of ovarian cancer. Best Pract Res Clin Obstet Gynaecol 2006;20:339–62.
4. IARC. IARC monographs on the evaluation of carcinogenic risks to humans. Tobacco smoke and involuntary smoking. Lyon, France: IARC Press, 2004.
5. Risch HA, Marrett LD, Jain M, Howe GR. Differences in risk factors for epithelial ovarian cancer by histologic type. Results of a case-control study. Am J Epidemiol 1996;144:363–72.
6. Jordan SJ, Whiteman DC, Purdie DM, Green AC, Webb PM. Does smoking increase risk of ovarian cancer? A systematic review. Gynecol Oncol 2006;103:1122–9.
7. Terry PD, Miller AB, Jones JG, Rohan TE. Cigarette smoking and the risk of invasive epithelial ovarian cancer in a prospective cohort study. Eur J Cancer 2003;39:1157–64.
8. Kuper H, Titus-Ernstoff L, Harlow BL, Cramer DW. Population based study of coffee, alcohol and tobacco use and risk of ovarian cancer. Int J Cancer 2000;88:313–18.
9. Marchbanks PA, Wilson H, Bastos E, Cramer DW, Schildkraut JM, Peterson HB. Cigarette smoking and epithelial ovarian cancer by histologic type. Obstet Gynecol 2000;95:255–60.
10. Riman T, Dickman PW, Nilsson S, Correia N, Nordlinder H, Magnusson CM, Persson IR. Risk factors for epithelial borderline ovarian tumors: results of a Swedish case-control study. Gynecol Oncol 2001;83:575–85.
11. Green A, Purdie D, Bain C, Siskind V, Webb PM. Cigarette smoking and risk of epithelial ovarian cancer (Australia). Cancer Causes Control 2001;12:713–19.
12. Modugno F, Ness RB, Cottreau CM. Cigarette smoking and the risk of mucinous and nonmucinous epithelial ovarian cancer. Epidemiology 2002;13:467–71.
13. Goodman MT, Tung KH. Active and passive tobacco smoking and the risk of borderline and invasive ovarian cancer (United States). Cancer Causes Control 2003;14:569–77.
14. Riman T, Dickman PW, Nilsson S, Nordlinder H, Magnusson CM, Persson IR. Some life-style factors and the risk of invasive epithelial ovarian cancer in Swedish women. Eur J Epidemiol 2004;19:1011–19.
15. Pan SY, Ugnat AM, Mao Y, Wen SW, Johnson KC. Association of cigarette smoking with the risk of ovarian cancer. Int J Cancer 2004;111:124–30.
16. Kurian AW, Balise RR, McGuire V, Whittemore AS. Histologic types of epithelial ovarian cancer: have they different risk factors? Gynecol Oncol 2005;96:520–30.
17. World Health Organization. Women and the tobacco epidemic: challenges for the 21st Century. Geneva: The World Health Organization, 2001.
18. Gram IT, Braaten T, Terry PD, Sasco AJ, Adami HO, Lund E, Weiderpass E. Breast cancer risk among women who start smoking as teenagers. Cancer Epidemiol Biomarkers Prev 2005;14:61–6.
19. Lund E. Pilot study for the evaluation of completeness of reporting to the cancer registry. Incidence of cancer in Norway, 1978. Oslo, Norway: The Cancer Registry of Norway, 1981. 11–14.
20. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. Acta Radiol Oncol 1984;23:305–13.
21. Kumle M, Weiderpass E, Braaten T, Adami HO, Lund E. Risk for invasive and borderline epithelial ovarian neoplasias following use of hormonal contraceptives: the Norwegian-Swedish Women's Lifestyle and Health Cohort Study. Br J Cancer 2004;90:1386–91.
22. Weiderpass E, Margolis KL, Sandin S, Braaten T, Kumle M, Adami HO, Lund E. Prospective study of physical activity in different periods of life and the risk of ovarian cancer. Int J Cancer 2006;118:3153–60.
23. Cox DR. Regression models and life-tables. J Roy Stat Soc Ser B 1972;34:187–220.
24. SAS Institute. SAS/STAT User's Guide. Cary, NC: SAS Institute Inc., 1999.
25. Niwa Y, Wakai K, Suzuki S, Tamakoshi K, Lin Y, Yatsuya H, Kondo T, Nishio K, Yamamoto A, Tokudome S, Hamajima N, Toyoshima H, et al. Cigarette smoking and the risk of ovarian cancer in the Japanese population: findings from the Japanese Collaborate Cohort study. J Obstet Gynaecol Res 2005;31:144–51.

26. Engeland A, Andersen A, Haldorsen T, Tretli S. Smoking habits and risk of cancers other than lung cancer: 28 years' follow-up of 26,000 Norwegian men and women. Cancer Causes Control 1996;7:497–506.

27. Doll R, Gray R, Hafner B, Peto R. Mortality in relation to smoking: 22 years' observations on female British doctors. Br Med J 1980;280:967–71.

28. Tverdal A, Thelle D, Stensvold I, Leren P, Bjartveit K. Mortality in relation to smoking history: 13 years' follow-up of 68,000 Norwegian men and women 35–49 years. J Clin Epidemiol 1993;46:475–87.

29. Hecht SS. Cigarette smoking: cancer risks, carcinogens, and mechanisms. Langenbecks Arch Surg 2006;391:603–13.

30. Zenzes MT, Puy LA, Bielecki R. Immunodetection of benzo[a]pyrene adducts in ovarian cells of women exposed to cigarette smoke. Mol Hum Reprod 1998;4:159–65.

31. Lund E, Kumle M, Braaten T, Hjartaker A, Bakken K, Eggen E, Gram IT. External validity in a population-based national prospective study—the Norwegian Women and Cancer Study (NOWAC). Cancer Causes Control 2003;14:1001–8.

32. Lindbak R. Tall om tobakk 1973-98. Oslo, Norway: Statens tobakkskaderåd, 1999.

33. SBU-rapport nr 138. Metoder för rökavvänjning. Stockholm: Statens beredning för utvärdering av medicinsk metodik, 1998.