Risk Factors for Epithelial Borderline Ovarian Tumors: Results of a Swedish Case–Control Study

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Objective. **Borderline ovarian tumors have a favorable prognosis. Previous epidemiological studies indicate common risk factors for invasive epithelial ovarian cancers and borderline tumors, but it remains unresolved whether these tumors are precursors of invasive cancers or a separate disease entity. The objective of this population-based case–control study conducted in 1993–1995 was to examine reproductive and other factors in relation to the risk of borderline ovarian tumors.**

Methods. **Subjects were 193 histologically verified incident epithelial borderline tumor cases and 3899 randomly selected controls aged 50–74 years, whose data were collected through mailed questionnaires. Risk estimates were calculated by unconditional logistic regression.**

Results. **Ever parous women were at reduced risk, with odds ratios of 0.44 (95% confidence interval (CI) 0.26–0.75) for serous and 0.63 (95% CI 0.34–1.19) for mucinous tumors. No clear trends emerged for age at first birth, at menarche, and at menopause. Lactation reduced tumor risk. Oral contraceptive ever use conferred no protection, with odds ratios of 1.40 (95% CI 0.87–2.26) for serous and 1.04 (95% CI 0.61–1.79) for mucinous tumors. The odds ratio for serous tumors following unopposed estrogen ever use was 2.07 (95% CI 1.08–3.95), whereas no risk increase appeared with estrogens supplemented by cyclic or continuous progestins. Mucinous tumors were not associated with hormone replacement therapy. The odds ratio for serous tumors in the highest category of body mass index was 6.47 (95% CI 3.09–13.5).**

Conclusions. **Increasing parity and lactation reduce the risk of borderline ovarian tumors in women aged 50–74, while no protection follows oral contraceptive use. Hormonal situations such as unopposed estrogen use and obesity, where estrogens are not counteracted by progestins, may increase the risk of serous tumors.** © 2001 Academic Press

Key Words: **case–control studies; borderline ovarian tumors; epidemiology; risk factors.**

INTRODUCTION

Epithelial ovarian tumors of low malignant potential constitute a subgroup of ovarian malignancies and are also called borderline ovarian tumors. These tumors are mostly of serous or mucinous histology, display mitotic and nuclear abnormalities, show cellular multilayering, and are capable of metastasis, but respect the ovarian stroma [1–3]. Compared to invasive epithelial ovarian cancers, borderline tumors occur in younger women, present at an earlier stage, and have a favorable prognosis [4–9]. The incidence rate of borderline tumors is lower than that for invasive cancers [10–11], with proportions of borderline tumors ranging from 12 to 33% in epithelial ovarian tumor series [11].

Most of the published epidemiological data on epithelial ovarian cancer risk consider either invasive cancers or invasive and borderline tumors combined. Increasing parity, lactation, oral contraceptive use, tubal ligation, and hysterectomy seem protective, while a positive family history and infertility may be associated with higher risk [12–15]. Results from the relatively few epidemiological studies evaluating borderline tumors separately indicate that most of the risk factors for invasive cancers also pertain to borderline tumors [14, 16–19], but it remains unresolved whether borderline tumors are precursors of invasive cancers or a separate disease entity.

We have conducted a nationwide case–control study designed to investigate the effects of reproductive and some other factors on the risk of epithelial ovarian malignancies of different histologic subtypes in peri- and postmenopausal women. Here we report how reproductive events, oral contraceptives, hormone replacement therapy (HRT), gynecological surgery, family history, body mass index, and certain lifestyle factors relate to the risk of epithelial borderline ovarian tumors.

MATERIALS AND METHODS

Women in this population-based case–control study were aged 50–74, born and resident in Sweden, and recruited from

October 1, 1993, to December 31, 1995. Eligible cases were those diagnosed with an incident, histologically confirmed, borderline or invasive epithelial ovarian tumor. The cases were identified through the six regional cancer registries, which provide an almost complete cancer registration in Sweden [20]. After being approached by their physicians, case subjects signed an informed consent form before entering the study. Data were collected through mailed self-administered questionnaires.

In total, 1208 women with newly detected ovarian tumors of any histology were reported to the regional cancer registries, and 917 (76%) agreed to participate. Reasons for nonparticipation among cases included patient refusal in 181 (15%) and physicians' disapproval to contact the patients in 110 (9%), mostly due to death or poor health. One of us (HN) reviewed 881 of the 917 tumor specimens, and in all 806 cases were classified as epithelial [21]. Also included among cases were 25 of 36 patients whose specimens we were unable to retrieve, with epithelial histology according to the original pathology report. There was a close agreement (94%) between original reports and the review with respect to epithelial and nonepithelial subtypes. After excluding 2 cases with previous bilateral oophorectomy and 1 with recurrent disease, 828 cases of epithelial ovarian tumors remained. Of those, 635 (77%) were classified as invasive cancers and 193 (23%) as borderline tumors. This report considers epithelial borderline ovarian tumors.

Control women were randomly selected from a continuously updated population register covering all residents in Sweden and sampled simultaneously with the cases. Among 4996 controls, 4148 (83%) accepted participation, 811 (16%) refused, and 37 (1%) didn't respond due to poor health. Questionnaires were completed by 3596 (72%) controls, while 552 (11%) who initially failed to respond agreed to answer essential parts of the questionnaire in a telephone interview. Case women were not interviewed in this way as 94% of those who had given consent to be approached completed the questionnaire. After exclusion of 249 controls who reported previous bilateral oophorectomy, 3899 controls without a history of borderline ovarian tumor or invasive ovarian cancer were included in the data set. To improve cost effectiveness most of the controls were also subjects in parallel case–control studies on breast [22] (recruitment period October 1, 1993, to March 31, 1995) and endometrial cancers [23] (recruitment period January 1, 1994, to December 31, 1995), where similar study designs were used. Until March 31, 1995, the controls were frequency matched to the expected age distribution of breast cancer cases and afterward to endometrial and ovarian cancer cases, respectively.

In the questionnaire, extensive information was requested on body build, smoking, alcohol consumption, physical exercise, hereditary factors, medical history, gynecological surgery, reproductive events, use of oral contraceptives, menopausal symptoms, and use of HRT. To facilitate recall of oral contraceptives and HRT, subjects were shown charts picturing all brands commercially available in Sweden from 1950 onward. For each episode of exogenous hormone use, the brand, dose, and starting and stopping dates were recorded. For case women the mean interval from diagnosis to arrival of the questionnaire was 4.5 months (standard deviation 2.0 months). Approximately 50% of cases and controls were further contacted by telephone interviewers to clarify important missing or inconsistent details in the mailed questionnaires. The telephone interviewers were blinded to the study hypotheses.

Use of HRT was categorized as follows: (1) medium potency estrogens (i.e., conjugated estrogen, estradiol, and other synthetic estrogens) without added progestins; (2) medium potency estrogens cyclically combined with progestins (<16 days/cycle, most commonly 10 days/cycle); (3) medium potency estrogens continuously combined with progestins (≥ 19 days/cycle, most commonly 28 days/cycle); (4) low potency estrogens (mainly oral or topical estriol used to alleviate vaginal atrophy and urogenital symptoms). All exposures were censored after an index date, for cases 3.0 months before the date of diagnosis and for controls 7.5 months before the date of questionnaire arrival (equaling the mean time of 4.5 months from diagnosis to questionnaire arrival in cases plus 3.0 months).

For women with natural menopause, age at menopause was defined as age at cessation of natural bleedings. Women with hysterectomy, with bleedings due to HRT, or with missing information on age at menopause were classified as postmenopausal and assigned an age at menopause if they had reached the age when natural menopause had occurred in 90% of the subjects (current smokers: cases 54 years and controls 55 years; nonsmokers: cases and controls 55 years) and otherwise as unknown. The assigned age at menopause of 50 years equaled the mean age at menopause for subjects in all of the case and smoking strata in our study. Premenopausal women were included as a separate category in the variable defining age at menopause to allow comparisons with postmenopausal subjects. Menopausal symptoms were categorized as ever having hot flushes, sweating, or palpitations 1 year ago or earlier.

Statistical analyses were performed with the SAS statistical package [24]. Risk estimates for borderline tumors were computed as odds ratios with corresponding 95% confidence intervals (CI), using unconditional logistic regression models fit by the maximum likelihood method. All P values and confidence intervals were two-sided. Tests of statistical significance were performed using the likelihood ratio test for general heterogeneity. For a categorical variable with k levels, this tests the null hypothesis that the effect is the same for all levels versus the alternative hypothesis that the effect is different for at least one level. Under the null hypothesis, the test statistic has a χ^2 distribution with $(k - 1)$ degrees of freedom. For most of the analyses a multivariate statistical model was developed including age (5-year categories), parity (0, 1, 2, 3, 4, 5–13 births), age at menopause (premenopausal, <49, $49 < 53$, ≥ 53 years),

TABLE 1
Descriptive Characteristics of Epithelial Borderline Ovarian Tumor Cases and Control Women, Sweden, 1993–1995

| | Cases | | | | | | Controls ($N = 3899$) | |
| | Serous ($N = 110$) | | Mucinous ($N = 81$) | | All borderline ($N = 193$) | | | |
Characteristic	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age at diagnosis/interview (years)[a]	61.6	8.0	62.0	7.7	61.8	7.8	63.4	7.1
Age at menarche (years)	13.7	1.4	13.2	1.4	13.5	1.4	13.6	1.4
Age at menopause (years)[b]	50.4	3.6	49.7	3.3	50.1	3.4	50.1	3.8
Parity	1.8	1.3	1.8	1.2	1.8	1.2	2.1	1.4
Age at first birth (years)[c]	24.7	5.9	25.1	5.2	24.8	5.6	24.6	4.6
Age at last birth (years)[c]	29.5	5.9	29.8	6.1	29.6	5.9	30.4	5.4
Breastfeeding duration (months)[c]	9.4	8.0	6.0	4.3	8.0	6.9	11.2	10.3
Abortions (number of)	0.2	0.5	0.2	0.5	0.2	0.5	0.3	0.6
Body mass index (kg/m^2)[d]	27.5	4.6	25.3	3.8	26.5	4.4	25.4	4.2
	No.	%	No.	%	No.	%	No.	%
Nulliparous	20	18.2	12	14.8	33	17.1	435	11.2
Ever evaluated for infertility	6	5.5	4	4.9	10	5.2	102	2.6
Ever use of oral contraceptives	47	42.7	33	40.7	81	42.0	1351	34.7
Ever use of HRT[e]	27	24.5	13	16.0	41	21.2	796	20.6
Ever use of low potency estrogens	17	15.5	17	21.3	34	17.7	782	20.2
Ever tubal ligation	2	1.8	1	1.2	3	1.6	148	3.8
Ever hysterectomy	7	6.4	7	8.6	15	7.8	296	7.6
Ever unilateral oophorectomy	2	1.8	3	3.7	6	3.1	167	4.3
Ever smoking	53	48.1	39	48.1	91	47.6	1649	32.6
Family history of ovarian cancer	2	1.9	4	5.3	6	3.3	80	2.5
Family history of breast cancer	10	9.3	5	6.3	15	8.0	315	9.5

[a] Age at diagnosis of cases and interview of controls.

[b] Postmenopausal women only.

[c] Parous women only.

[d] One year ago.

[e] Hormone replacement therapy (medium potency estrogens with or without progestins).

body mass index (BMI)($<22, 22 < 25, 25 < 27, 27 < 30, \geq 30$ kg/m^2), and ever use of oral contraceptives, unopposed estrogens, medium potency estrogens cyclically combined with progestins, and medium potency estrogens continuously combined with progestins. No substantial changes in risk estimates were induced by adding numerous other variables to the model. Also, as there generally was a good agreement between age-adjusted and multivariate results, only the latter will be reported. Tests of interaction were conducted through the log-likelihood ratio test comparing models with and without interaction terms.

The study was approved by the Ethics Committees of the University of Uppsala and the Karolinska Institute in Stockholm.

RESULTS

The histologic distribution of the 193 borderline ovarian tumors cases was as follows: serous, 110 (57%); mucinous, 81 (42%); and endometrioid, 2 (1%). After reviewing tumor spec-

imens a shift of 25 cases from invasive to borderline tumors occurred compared to the original pathology classification. Table 1 shows descriptive characteristics of subjects regarding age, reproductive factors, body mass indices, exogenous hormone use, prior gynecological surgery, smoking, and family history of ovarian and breast cancer. Cases had a slightly younger mean age than controls. Fewer cases ($n = 160$, 83%) than controls ($n = 3462$, 89%) were parous.

Reproductive History

Table 2 presents odds ratios for borderline ovarian tumors according to reproductive factors. Parous women were at lower risk of borderline tumors, and the protection increased with the number of child births. The risk was less than 44% in women who had given birth to three or more children. A reduced risk appeared for both serous and mucinous tumors, with odds ratios of 0.44 (95% CI 0.26–0.75) for serous and 0.63 (95% CI 0.34–1.19) for mucinous tumors among ever parous women. We were unable to find any clear association between age at

TABLE 2
Odds Ratios and 95% Confidence Intervals for Epithelial Borderline Ovarian Tumors According to Reproductive Factors, Sweden, 1993–1995

| | Cases (N) | | | Controls (N) | Histologic subgroup | | | | | |
| | | | | | Serous | | Mucinous | | All | |
Category	Serous	Mucinous	All		OR[a,b]	95% CI[c]	OR[b]	95% CI	OR[b]	95% CI
Parity										
0[d]	20	12	33	435	1.0		1.0		1.0	
1	24	15	39	688	0.66	0.35–1.23	0.76	0.35–1.65	0.68	0.42–1.12
2	33	38	72	1443	0.39	0.21–0.70	0.79	0.40–1.55	0.53	0.34–0.83
3	27	8	35	846	0.52	0.28–0.97	0.31	0.12–0.77	0.44	0.26–0.73
4	3	6	9	316	0.14	0.04–0.49	0.55	0.19–1.60	0.27	0.12–0.61
≥5	3	2	5	169	0.29	0.08–1.00	0.44	0.10–2.02	0.33	0.12–0.87
P value[e]					0.002		0.10		0.003	
Age at first birth (years)[f]										
<20[d]	16	10	26	393	1.0		1.0		1.0	
20–24	34	24	58	1471	0.58	0.30–1.10	0.68	0.31–1.50	0.60	0.36–0.99
25–29	27	21	49	1126	0.68	0.34–1.32	0.69	0.30–1.57	0.67	0.40–1.13
30–34	5	11	16	352	0.38	0.13–1.09	1.16	0.46–2.97	0.68	0.35–1.34
≥35	8	3	11	120	1.49	0.56–3.97	0.94	0.24–3.77	1.25	0.56–2.78
P value[e]					0.08		0.60		0.16	
Breastfeeding duration (months)[f]										
0[d]	9	7	16	161	1.0		1.0		1.0	
1–5	22	20	42	612	0.74	0.32–1.76	0.68	0.27–1.68	0.72	0.38–1.36
6–11	22	20	42	840	0.58	0.24–1.37	0.46	0.18–1.15	0.52	0.28–1.00
≥12	26	9	35	1024	0.72	0.29–1.77	0.22	0.08–0.65	0.47	0.24–0.94
P value[e]					0.64		0.02		0.12	
Abortions (number of)										
0[d]	88	67	157	3072	1.0		1.0		1.0	
1	18	10	28	646	0.99	0.57–1.71	0.67	0.33–1.37	0.84	0.54–1.29
≥2	4	4	8	181	0.80	0.28–2.28	0.78	0.24–2.56	0.78	0.35–1.71
P value[e]					0.91		0.50		0.61	
Age at menarche (years)										
<12	5	5	10	219	0.77	0.30–1.97	1.03	0.40–2.63	0.88	0.45–1.71
12–14[d]	68	56	124	2543	1.0		1.0		1.0	
≥15	21	13	35	793	1.15	0.69–1.91	0.82	0.44–1.51	1.02	0.69–1.51
P value[e]					0.71		0.80		0.91	
Age at menopause (years)										
Premenopausal	10	9	19	184	0.66	0.28–1.51	1.59	0.59–4.29	0.93	0.49–1.77
<49	28	23	51	1202	0.66	0.39–1.11	0.86	0.49–1.52	0.71	0.50–1.09
49–52[d]	37	28	66	1210	1.0		1.0		1.0	
≥53	32	19	52	1209	0.98	0.60–1.61	0.74	0.41–1.36	0.88	0.60–1.30
P value[e]					0.34		0.51		0.50	

[a] OR, odds ratio.

[b] Adjusted for age, parity, body mass index, and age at menopause as categorized variables and ever use of oral contraceptives, unopposed estrogens with cyclic progestins, and estrogens with continuous progestins (medium potency estrogens only).

[c] CI, confidence interval.

[d] Reference category.

[e] P value for the likelihood ratio test of general heterogeneity.

[f] Parous women only.

first birth and risk of borderline tumors, and this also applied for age at last birth (data not shown). Overall, a 48% risk reduction was seen among parous women with a history of breastfeeding for at least 6 months, an effect which seemed stronger for mucinous tumors. A lower proportion of cases than controls reported a history of spontaneous or induced abortions, indicating a slight risk reduction which was not statistically significant. Only 10 case women reported infertility evaluation and the odds ratio for borderline tumors associated with this procedure was 1.64 (95% CI 0.81–3.29), with similar odds ratios for all tumor types.

Table 2 also shows menstrual history. Neither age at men-

TABLE 3
Odds Ratios and 95% Confidence Intervals for Epithelial Borderline Ovarian Tumors According to Oral Contraceptive Use, Sweden, 1993–1995

| | Cases (N) | | | Controls (N) | Histologic subgroup | | | | | |
| | | | | | Serous | | Mucinous | | All | |
Category	Serous	Mucinous	All		OR[a,b]	95% CI[c]	OR[b]	95% CI	OR[b]	95% CI
Ever use of oral contraceptives										
No[d]	63	48	112	2538	1.0		1.0		1.0	
Yes	47	33	81	1351	1.40	0.87–2.26	1.04	0.61–1.79	1.23	0.86–1.76
P value[e]					0.17		0.88		0.26	
Duration of oral contraceptive use (years)										
Never[d]	63	48	112	2538	1.0		1.0		1.0	
<2	11	7	19	422	1.00	0.48–2.11	0.82	0.35–1.92	0.96	0.55–1.66
2–4	12	6	18	248	1.87	0.90–3.87	0.80	0.27–2.33	1.34	0.73–2.43
5–9	9	6	15	227	1.49	0.65–3.40	1.01	0.41–2.88	1.29	0.68–2.43
≥10	5	9	14	246	0.91	0.34–2.41	1.45	0.63–3.30	1.16	0.61–2.18
P value[e]					0.48		0.84		0.82	
Time since last use of oral contraceptives (years)[f]										
Never[d]	63	48	112	2538	1.0		1.0		1.0	
<15	4	7	12	204	0.86	0.22–3.39	0.93	0.22–3.90	1.16	0.45–3.02
15–19	11	7	18	219	2.07	0.73–5.89	0.96	0.25–3.71	1.67	0.74–3.80
20–24	11	5	16	347	1.29	0.51–3.25	0.44	0.12–1.65	0.92	0.43–1.94
≥25	11	9	20	375	1.20	0.54–2.70	1.00	0.39–2.56	1.14	0.62–2.10
P value[e]					0.48		0.49		0.49	

[a] OR, odds ratio.

[b] Adjusted for age, parity, body mass index, and age at menopause as categorized variables and ever use of unopposed estrogens, estrogens with cyclic progestins, and estrogens with continuous progestins (medium potency estrogens only).

[c] CI, confidence interval.

[d] Reference category.

[e] P value for the likelihood ratio test of general heterogeneity.

[f] Also adjusted for duration categories of oral contraceptive use.

arche nor age at menopause seemed to be related to the risk of borderline tumors, with the possible exception of a weakly reduced risk for serous tumors among women with an early age at menopause. Case women reported a higher frequency of irregular menstrual cycles than controls, yielding an odds ratio of 1.38 (95% CI 0.84–2.28), with only minor inconsistencies of odds ratios between tumor types. The odds ratios for borderline tumors among women who ever had experienced menopausal symptoms were 1.17 (95% CI 0.84–1.64) overall, 0.88 (95% CI 0.56–1.37) for serous, and 1.75 (95% CI 1.06–2.91) for mucinous tumors.

Only three cases reported tubal ligation. Overall, the odds ratios for borderline tumors associated with gynecological surgery were 0.39 (95% CI 0.12–1.28) for tubal ligation, 0.81 (95% CI 0.41–1.60) for hysterectomy, and 0.72 (95% CI 0.31–1.67) for unilateral oophorectomy.

Exogenous Hormone Use

Table 3 gives odds ratios for borderline tumors according to oral contraceptive exposure. The proportions of ever users of oral contraceptives were 42% for case women and 35% for controls. We were unable to demonstrate a reduced risk of serous borderline tumors with use of oral contraceptives, with an odds ratio of 1.40 (95% CI 0.87–2.26) for ever users. The duration and time since last use of oral contraceptives and the risk of borderline tumors reflected no clear associations. Generally, the risk of mucinous tumors seemed unaltered by oral contraceptives, with an odds ratio close to unity for ever users. When analyzing postmenopausal women separately the odds ratio for serous tumors was 1.69 (95% CI 1.02–2.79) with ever use of oral contraceptives.

Table 4 presents odds ratios for borderline tumors according to the use of HRT. Ever use of any HRT (low potency estrogens excluded) was reported by 21% of cases and 20% of controls, and the odds ratio of borderline tumors following ever compared to never use was 0.98 (95% CI 0.67–1.43). The risk of serous tumors was increased among ever users of unopposed estrogens with an odds ratio of 2.07 (95% CI 1.08–3.95), whereas no risk increase was seen

TABLE 4
Odds Ratios and 95% Confidence Intervals for Epithelial Borderline Ovarian Tumors According to Use of Medium Potency Hormone Replacement Therapy, Sweden, 1993–1995

| | Cases (N) | | | Controls (N) | Histologic subgroup | | | | | |
| | | | | | Serous | | Mucinous | | All | |
Category	Serous	Mucinous	All		OR[a]	95% CI[b]	OR	95% CI	OR	95% CI
Ever use of estrogens only[c]										
No[d]	95	75	172	3531	1.0		1.0		1.0	
Yes	13	6	19	259	2.07	1.08–3.95	1.16	0.45–2.96	1.63	0.95–2.79
P value[e]					0.04		0.76		0.09	
Duration of use estrogens only (years)[f]										
Never[d]	95	75	172	3531	1.0		1.0		1.0	
<2	6	2	8	108	2.4	0.98–5.85	1.21	0.29–5.11	1.85	0.86–3.96
≥2	6	2	8	132	1.84	0.71–4.76	0.96	0.23–4.05	1.42	0.64–3.15
P value[e]					0.12		0.97		0.25	
Ever use of estrogens and cyclic progestins[c]										
No[d]	96	74	171	3434	1.0		1.0		1.0	
Yes	12	6	19	348	1.15	0.59–2.24	0.64	0.25–1.66	0.98	0.57–1.68
P value[e]					0.69		0.33		0.94	
Duration of use estrogens and cyclic progestins (years)[f]										
Never[d]	96	74	171	3434	1.0		1.0		1.0	
<2	5	2	8	135	1.03	0.39–2.73	0.56	0.13–2.37	0.94	0.43–1.96
≥2	7	2	9	178	1.47	0.63–3.42	0.26	0.04–1.92	0.91	0.44–2.03
P value[e]					0.69		0.20		0.96	
Ever use of estrogens and continuous progestins[c]										
No[d]	103	73	177	3494	1.0		1.0		1.0	
Yes	6	6	13	280	0.59	0.23–1.53	1.15	0.47–2.80	0.87	0.46–1.63
P value[e]					0.25		0.76		0.66	
Duration of use of estrogens and continuous progestins (years)[f]										
Never[d]	103	73	177	3494	1.0		1.0		1.0	
<2	3	2	6	125	0.71	0.21–2.36	0.86	0.20–3.67	0.90	0.38–2.12
≥2	2	3	5	127	0.61	0.14–2.64	1.39	0.42–4.68	0.89	0.35–2.28
P value[e]					0.69		0.85		0.94	

[a] OR, odds ratio.

[b] CI, confidence interval.

[c] Adjusted for categories of age, parity, body mass index, age at menopause, and ever use of oral contraceptives, low potency estrogens, and the other hormone replacement therapy types in this table.

[d] Reference category.

[e] P value for the likelihood ratio test of general heterogeneity.

[f] Adjusted for age, parity, body mass index, age at menopause, and ever use of oral contraceptives as categorized variables and for duration (never, <2, ≥2 years) of low potency estrogens and the other hormone replacement types in this table.

when progestins were added to the estrogens, with odds ratios of 1.15 (95% CI 0.59–2.24) for cyclic and 0.59 (95% CI 0.23–1.53) for continuous progestins. As there were only few exposures, no clear patterns emerged regarding duration of HRT and tumor risk. We found no associations between HRT and the risk of mucinous tumors. When stratifying by body mass index, lean women (BMI <25 kg/m^2) had an odds ratio for serous tumors of 3.39 (95% CI 1.37–8.38), with ever use of unopposed estrogens, while the risk estimate was close to unity for obese women (BMI ≥27 kg/m^2). Low potency estrogens were unrelated to borderline tumor risk (data not shown).

Lifestyle Factors and Family History

Table 5 provides odds ratios for borderline tumors in relation to certain lifestyle factors. The risk of serous tumors was strongly associated with increasing body mass index, whereas no clear associations were found for mucinous tumors. Women who engaged in physical activity at ages 18–30 years (proxy for lifelong physical activity) had lower risk estimates of borderline tumors than sedentary women, but the results were not statistically significant and no clear trends with increasing levels of physical activity were detected. Current smokers appeared to have an increased risk of mucinous tumors, while

TABLE 5
Odds Ratios and 95% Confidence Intervals for Epithelial Borderline Ovarian Tumors According to Body Mass Index, Physical Exercise, Smoking, and Alcohol Consumption, Sweden, 1993–1995

	Cases (N)			Controls (N)	Histologic subgroup					
					Serous		Mucinous		All	
Category	Serous	Mucinous	All		OR[a,b]	95% CI[c]	OR[b]	95% CI	OR[b]	95% CI
Body mass index 1 year ago (kg/m^2)										
<22[d]	11	14	26	725	1.0		1.0		1.0	
22–24	26	28	54	1241	1.57	0.74–3.32	1.44	0.72–2.86	1.43	0.86–2.37
25–26	22	19	42	755	2.40	1.11–5.17	1.70	0.82–3.56	1.97	1.16–3.34
27–29	18	13	31	675	2.44	1.10–5.38	1.30	0.58–2.88	1.71	0.98–2.99
≥30	32	7	39	453	6.47	3.09–13.5	0.79	0.28–2.29	3.10	1.79–5.36
P value[e]					<0.001		0.44		0.001	
Physical activity at age 18–30 years (h/week)										
Never[d]	20	16	37	551	1.0	1.0	1.0		1.0	
<1	14	11	26	513	0.60	0.28–1.30	0.60	0.27–1.37	0.61	0.35–1.06
1–2	38	27	65	1203	0.94	0.52–1.70	0.69	0.36–1.32	0.78	0.51–1.21
>2	38	27	65	1448	0.82	0.46–1.45	0.57	0.30–1.09	0.67	0.44–1.03
P value[e]					0.52		0.41		0.23	
Smoking (cigarettes/day)										
Never[d]	56	42	100	2224	1.0		1.0		1.0	
Former	28	9	37	799	1.23	0.75–2.02	0.54	0.25–1.18	0.92	0.61–1.38
1–10	9	15	24	483	0.72	0.33–1.57	1.88	1.01–3.51	1.20	0.74–1.95
>10	15	15	30	367	1.26	0.66–2.43	2.31	1.22–4.40	1.66	1.04–2.63
P value[e]					0.52		0.002		0.14	
Alcohol consumption (g/day)										
Nonuser[d]	42	37	81	1549	1.0		1.0		1.0	
<5	50	25	75	1315	1.57	1.00–2.46	0.81	0.47–1.40	1.17	0.83–1.65
≥5	17	17	34	476	1.44	0.76–2.72	1.45	0.78–2.71	1.39	0.88–2.18
P value[e]					0.13		0.23		0.35	

[a] OR, odds ratio.

[b] Adjusted for age, parity, body mass index, and age at menopause as categorized variables and ever use of oral contraceptives, unopposed estrogens, estrogens with cyclic progestins, and estrogens with continuous progestins (medium potency estrogens only).

[c] CI, confidence interval.

[d] Reference category.

[e] P value for the likelihood ratio test of general heterogeneity.

the risk of serous tumors was not affected by smoking status. Women who reported alcohol consumption had a slight excess in risk of serous tumors compared to nonusers, whereas the findings for mucinous tumors were inconsistent.

Relatively more cases than controls stated that their mothers or sisters were diagnosed with ovarian cancer. The odds ratio for borderline tumors with an affected mother or sister was 1.53 (95% CI 0.65–3.62). The odds ratio for mucinous tumors was 2.63 (95% CI 0.92–7.52) and no effects could be seen for serous tumors.

DISCUSSION

The main findings of this nationwide case–control study on women aged 50–74 indicate a reduced risk of borderline ovarian tumors with increasing parity and lactation, while elevated risks of serous tumors appeared with a high body mass index

and ever use of unopposed estrogens. In contrast to previous investigators [14, 16–18, 25, 26] we found no protection from borderline tumors in women exposed to oral contraceptives.

Strengths of our study include the population-based design, the reliable national tumor registry enabling a complete catchment of cases with short delay [20], a consistent review of tumor specimens, and detailed information on oral contraceptive and HRT exposures. Although this study to our knowledge is the largest case–control study reported on borderline tumors, it is limited by a relatively small number of cases leading to low statistical power, especially when analyzing effect modification and infrequent exposures. Although fairly high participation rates should diminish the influence of selection bias, we have no data on nonparticipants. The telephone interview due to nonresponse in a subset of controls (11%) raises the concern of information bias, but assuming that these controls would

report more frequent use of oral contraceptives and HRT our findings on exogenous hormone use would be attenuated. Recall bias is unlikely to explain the associations appearing in our analyses as the results for serous and mucinous tumors seem to diverge. The introduction of covariates to the multivariate statistical models induced no substantial changes in risk estimates, suggesting that confounding is not a major problem, although a possible effect of unknown confounders must be recognized. It was unpractical to corroborate data in the questionnaires with hospital records, but a high correlation between self-reporting and patient records of hormonal exposure data has been found in validity studies [27, 28].

In contrast to earlier studies [14, 16–18, 25, 26] our data showed no reduced risk of borderline tumors among oral contraceptive users, and we found no consistency in odds ratios according to duration and time since last use. In most [14, 17, 18], but not all, studies [16] an increasing duration of oral contraceptive use appeared to further decrease the risk of borderline tumors, an association present only for serous tumors in one of the studies [14]. We believe that a plausible explanation to our results may be the differences in age distributions between this and other studies. The risk estimates in our study apply to older and mostly (90% of cases) postmenopausal women with a mean age of 61.8 years for cases, compared to the mean ages of 44 and 52 years reported by Harris *et al.* [18] and Risch *et al.* [14], respectively. Also in other studies of borderline tumors, 59 [16] and 65% [17] of cases were younger than 50.

Our data do not allow us to determine the reason for the absent protection from borderline tumors following oral contraceptive use, but at least two possible interpretations exist. First, it is suggested that the latency of borderline tumors may be 10 to 15 years, as inferred from studies on the Hiroshima cohort [29] and the younger ages of women with borderline compared to invasive epithelial tumors [18, 19, 30], where the protection from oral contraceptives still persists up to 15–20 years after last use [31]. Assuming that borderline tumors are precursors of invasive cancers and a progression time of 10 years between these stages, women who are in their fifties to seventies may have passed the period when a decreased risk of borderline tumors following oral contraceptives is expected, as only few women use oral contraceptives after the age of 40. Second, a subset of borderline ovarian tumors among postmenopausal women may be positively associated with oral contraceptive use. For postmenopausal women in our study the odds ratio of serous borderline tumors following ever use of oral contraceptives was 1.69 (95% CI 1.06–2.79). We advocate caution in interpreting this association, as no consistent trend appeared with duration of oral contraceptive use, and also as our results are the first to challenge those reported earlier. The risk increase may appear only after a long latency period as indicated by the odds ratio of 2.07 (95% CI 0.73–5.89) present in the category reporting last oral contraceptive use 15–19 years ago. Additional data supporting an elevated risk of

some borderline tumors with oral contraceptive use are derived from recent Norwegian [10] and Finnish [11] reports of increasing incidence rates of borderline tumors, possibly coinciding with more frequent prior oral contraceptive exposure. On the contrary, the risk of borderline tumors was elevated in ever users of oral contraceptives younger than 40 with an odds ratio of 1.98 (95% CI 0.74–5.27), but reduced in those who were older [32]. The concern of recall bias to explain our findings on oral contraceptives and the risk of borderline tumors is offset by parallel analyses on invasive epithelial ovarian cancers (submitted), showing a 32% risk reduction among oral contraceptive ever users.

In previous studies examining HRT and the risk of borderline tumors no associations were seen [14, 16, 18], and this is also supported by our overall risk estimate for any HRT. In HRT estrogens can be used unopposed or supplemented with cyclic or continuous progestins, to prevent endometrial hyperplasia and cancer. To our knowledge this study is the first to present the risk of borderline tumors according to different HRT regimens. An increased risk of serous tumors appeared among ever users of unopposed estrogens, while no elevated risk was detected for estrogens combined with progestins. The risk of mucinous tumors seemed unaffected by the use of HRT. Sparse exposures disallowed detailed analyses of HRT duration and tumor risk and also warrant caution in interpreting the associations for ever use of HRT.

An elevated risk of borderline tumors was noted among women in the highest category of usual body mass index in one study [18], while no association was evident in another [14]. In this study the risk of serous tumors was positively associated with high body mass index, but for mucinous tumors no clear effects were seen. Obese women have higher endogenous serum levels of estrogens than lean women. We found an increased risk of serous borderline tumors following unopposed estrogen use in lean but not obese women. Assuming a dose–response relationship between estrogen exposure and tumor risk, the risk should be higher in obese subjects. However, if there is a threshold estrogen level when the risk of borderline tumors appears, the endogenous level of estrogens in lean women may be below that threshold when not on unopposed estrogen therapy, whereas among estrogen users the estrogen levels rise enough to increase tumor risk. The findings of excessive risks of serous tumors with high body mass index and with the use of unopposed estrogens suggest that hormonal situations where estrogens are not balanced by progestins may be associated with an increased risk of these tumors. The mitogenic potential of estrogens [33] and progestin-induced apoptosis [34] in ovarian epithelial cells has been described previously.

In agreement with previous studies [14, 16–18, 26, 35], we found a reduced risk of borderline tumors in parous women, an effect which was statistically significant for serous tumors only. Risch *et al.* [14] reported a decreased risk of serous borderline tumors with increasing parity, whereas no associa-

tion appeared for mucinous borderline tumors. No clear association between age at first birth and risk of borderline tumors appeared in our data, corresponding with some [14, 16], but not all, studies [17, 18, 36]. We found a reduced risk of borderline tumors associated with breastfeeding, supporting the findings of others [14, 16, 18, 25].

Age at menarche was unrelated to the risk of borderline tumors in our data, similar to other reports [16–18]. A later age at menopause was associated with an increased risk in some [17, 35], but not all, studies [16, 18]. We found no consistent association between the age at menopause and the risk of borderline tumors, with the possible exception of a slightly reduced risk of serous tumors with an early age at menopause.

Central issues to epithelial ovarian tumor research are whether borderline lesions are precursors of invasive cancers or a distinct disease and whether nonmucinous and mucinous tumors have different risk factors. Several research groups [17–19] conclude that borderline and invasive tumors share the same epidemiological risk profile, but two of these studies [17, 18] did not report risk estimates according to histologic subtype and the third study [19] was hampered by few subjects and low participation rates. Similar risk factors for nonmucinous borderline and invasive tumors were also present in a large Canadian case–control study [14]. We interpret our findings of an absent protection from borderline tumors following oral contraceptive use to give some support to the idea that at least some borderline tumors may constitute a distinct disease, considering the established protective effect from oral contraceptives on epithelial ovarian cancer risk [31]. Other epidemiological data also support borderline tumors as a distinct disease. For instance, most studies of familial ovarian tumors show that familial and BRCA1-related tumors are less common in borderline than in invasive categories [15, 37–43]. In the pooled case–control study [18] the protection from oral contraceptives on tumor risk was weaker for borderline than for invasive lesions. Additional support for borderline tumors constituting a distinct disease is derived from molecular biogenetic studies of ovarian tumors, even if the evidence of causality of the investigated molecular aberrations is circumstantial. Mutations in the p53 tumor suppressor gene were detected in microscopically benign-appearing cysts adjacent to invasive but not borderline tumors [44], and p53 mutations also seemed less prevalent in borderline tumors [45–47]. Loss of heterozygosity [44] and K-ras oncogenes were more common in invasive cancers than borderline tumors in some studies [30, 49] but not in others [50, 51]. Expression of cyclin D1, which is involved in cell cycle progression and regulated by steroids, was more frequent in borderline tumors [49]. Other molecular studies consider borderline tumors precursors of invasive cancers [19, 51–58]. The main differences between serous and mucinous tumors in our data were lack of associations for mucinous tumors with oral contraceptives, HRT, and no clear association with a high body mass index. Also, an increased risk of mucinous but not serous tumors appeared for current smokers.

In conclusion, the lack of protection from oral contraceptive use on the risk of borderline ovarian tumors in this study gives some epidemiological support to a subset of these tumors in peri- and postmenopausal women, being etiologically different from invasive epithelial ovarian cancers. Serous and mucinous borderline tumors seem to have partly divergent risk factor profiles. In epidemiological studies separate analyses of borderline tumors and invasive epithelial ovarian cancers may assist in resolving whether borderline tumors are precursors of invasive lesions or a distinct disease entity.

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