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Risk Factors for Invasive Epithelial Ovarian Cancer: Results from a Swedish Case-Control Study

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This case-control study evaluated reproductive and other factors in relation to epithelial ovarian cancer (EOC) risk. Between 1993 and 1995, the authors recruited 655 EOC cases and 3,899 population controls aged 50–74 years who were born in and residents of Sweden. Data were collected through mailed questionnaires. Odds ratios were estimated by unconditional logistic regression. Parity reduced EOC risk (odds ratio = 0.61, 95% confidence interval (CI): 0.46, 0.81) for uniparous compared with nulliparous women. The risk of EOC decreased with incomplete pregnancies, early menopausal age, late age at first birth, and unilateral oophorectomy; increased with family history of ovarian cancer; and was not associated with menarcheal age, lactation, irregular menses, and menopausal symptoms. Histology-specific odds ratios of EOC for ever compared with never users of oral contraceptives were: serous, 0.56 (95% CI: 0.42, 0.74); mucinous, 1.96 (95% CI: 1.04, 3.68); endometrioid, 0.71 (95% CI: 0.49, 1.03); clear cell, 0.66 (95% CI: 0.31, 1.43); and all EOCs, 0.73 (95% CI: 0.59, 0.90). Prolonged oral contraceptive use reduced EOC risk, with persistent protection up to 25 years after the last use. Ever use of hormone replacement therapy increased EOC risk (odds ratio = 1.41, 95% CI: 1.15, 1.72). Among etiologic hypotheses, the retrograde transportation hypothesis accommodates most epidemiologic findings concerning EOC risk. *Am J Epidemiol* 2002;156:363–73.

case-control studies; contraceptives, oral; histology; hormone replacement therapy; ovarian neoplasms; reproductive history; sterilization

Abbreviations: CI, confidence interval; EOC, epithelial ovarian cancer; HRT, hormone replacement therapy.

Most cases of epithelial ovarian cancer (EOC), which constitute 80–90 percent of ovarian malignancies, are detected at an advanced stage, and the prognosis is poor, with 5-year survival rates of about 40 percent (1). The annual incidence rates, age standardized to the world population, are high in Scandinavia (15/100,000), intermediate in the Western world (10/100,000), and low in the developing countries and Japan (3/100,000) (2). In high-incidence areas, the lifetime risk of developing ovarian cancer is 1 to 2 percent. Therapeutic progress has been limited, and successful screening programs for the general public do not exist (3).

A consistent finding of epidemiologic studies on EOC is a reduced risk with increasing parity (4–9) and duration of oral contraceptive use (6, 8–11). A number of studies also indicate that incomplete pregnancies (4–6, 12, 13) and breast-feeding (4, 6, 8, 14, 15) reduce risk. Infertility adds to risk among nulliparous women, while temporary fertility problems among parous women do not seem to increase risk (4, 6, 8, 12, 14). Several studies found an increased risk after use of fertility drugs, but it has been difficult to separate the effects of fertility drugs from those of infertility (4, 6, 8). In most studies (4, 5, 9, 11, 12), age at menarche was a weak predictor of EOC risk. Late age at menopause increased

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EOC risk modestly in some (4, 12), but not all (5, 6, 11, 16–18), studies. A majority of studies found a protective effect after tubal ligation (4, 6, 8–10, 12, 14, 19–21) and hysterectomy (4, 6, 8–10, 14, 19–21). No association between hormone replacement therapy (HRT) and EOC emerged in some studies (6, 9, 16, 22), while others showed a modest risk increase (4, 12, 17, 23, 24), and three found a protective effect (14, 25, 26). Family history of ovarian cancer seems to increase risk (23, 27). Some (5, 23, 28, 29), but not all (17, 30, 31), studies in which histologic types of EOC were analyzed separately indicate that mucinous tumors may have a different risk factor profile than other epithelial ovarian tumors.

For decades, the "incessant ovulation" (32) and gonadotropin hypotheses (33) have been central to the discussion of ovarian carcinogenesis and have been supported by both epidemiologic findings and recent advance in molecular biology (34). Still, the cause of EOC remains obscure, and the hypotheses are not consistent with all epidemiologic findings. Other hypotheses examine the retrograde transportation through the fallopian tubes of contaminants or endogenous carcinogens (35), possibly mediating carcinogenesis through an inflammatory response in the ovarian epithelium (36). More recent hypotheses suggest a pregnancy-dependent clearance of transformed malignant cells from the ovaries (7) or a hormonal situation with androgen excess and progesterone deficiency (37).

We conducted a nationwide case-control study to investigate the effects of reproductive and other factors on the risk of epithelial ovarian malignancies in peri- and postmenopausal women. The focus of this paper is how reproductive events, oral contraceptives, HRT, gynecologic surgery, and family history relate to the risk of EOC by histologic type. Another intention is to discuss the epidemiologic associations with regard to etiologic hypotheses.

MATERIALS AND METHODS

Women in this population-based case-control study were aged 50–74 years, born and resident in Sweden, and without any previous ovarian malignancy or bilateral oophorectomy. Subjects were recruited from October 1, 1993, to December 31, 1995. Eligible cases were diagnosed with an incident, histologically confirmed EOC and were identified through six regional cancer registries, which provide an almost complete cancer registration in Sweden (38). After being approached by their physicians, cases signed an informed consent form before entering the study. Data were collected through mailed, self-administered questionnaires.

A total of 1,205 patients with newly detected ovarian tumors of any histology were reported to the regional cancer registries. Of these, 914 (76 percent) agreed to participate, 181 (15 percent) refused, and 110 (9 percent) were not approached because of physicians' refusal to contact the them, mostly because of death or poor health. To confirm the epithelial origin of the ovarian malignancies, one of the authors (H. N.) reviewed tumor specimens. Of the 914 tumors, 878 were retrievable for review, and 803 were classified as epithelial. Also included in the final data set of 828 cases were 25 of the 36 patients whose specimens we were unable to retrieve, with epithelial histology in the original histology report. The agreement between original reports and the review concerning epithelial and nonepithelial subtypes was 94 percent. Tumor histologies were classified according to the original histology reports of local pathologists. This paper presents data on 655 (79 percent) cases with EOC, while data on borderline tumors are published elsewhere (39).

Controls were randomly selected from a continuously updated population register covering all residents of Sweden and were sampled simultaneously with the cases. Among 4,996 controls, 4,148 (83 percent) agreed to participate, 811 (16 percent) refused, and 37 (1 percent) did not respond due to poor health. Questionnaires were completed by 3,596 (72 percent) controls, while 552 (11 percent) who initially failed to respond agreed to answer essential parts of the questionnaire in a telephone interview. Cases were not interviewed in this way because 94 percent of those who had given consent to be approached completed the questionnaire. After exclusion of 249 controls who reported previous bilateral oophorectomy, 3,899 remained for analyses. For improvement of cost-effectiveness, most of the controls were also subjects in parallel case-control studies on breast cancers (40) (recruitment period, October 1, 1993, to March 31, 1995) and endometrial cancers (41) (recruitment period, January 1, 1994, to December 31, 1995), in which similar study designs were used. Until March 31, 1995, the controls were frequency matched to the expected age distribution of breast cancer cases and afterwards to endometrial and ovarian cancer cases, respectively.

On the questionnaire, extensive information was requested on social, medical, reproductive, hereditary, lifestyle, and other factors. To facilitate recall of oral contraceptive and HRT use, subjects were shown charts picturing all the brands that were commercially available in Sweden from 1950 onward. In HRT, medium-potency estrogens (mainly estradiol or conjugated estrogens) were taken either unopposed or combined with progestins. For each episode of exogenous hormone use, the brand, dose, and starting and stopping dates were recorded. For cases, the mean interval from diagnosis to arrival of the questionnaire was 4.5 months (standard deviation, 2.0 months). All HRT 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 arrival of the questionnaire (equaling the mean time of 4.5 months from diagnosis to arrival of the questionnaire in cases plus 3.0 months). Approximately 50 percent of the cases and controls were contacted further by telephone interviewers to clarify important missing or inconsistent details on the mailed questionnaires. The telephone interviewers were blinded to the study hypotheses.

For women with natural menopause, age at menopause was defined as age at cessation of natural bleeding. We classified women with hysterectomy, with bleeding due to HRT, or with missing information on age at menopause as postmenopausal and assigned an age at menopause if they had reached the age when natural menopause had occurred in 90 percent of the subjects, stratified by smoking and case-control status (current smokers: cases, age 54 years, and controls, age 55 years; nonsmokers: cases and controls, age 55 years) and

TABLE 1. Descriptive characteristics of epithelial ovarian cancer cases and control women, Sweden, 1993–1995

Characteristic	Cases										Controls (n = 3,899)	
	Serous (n = 337)		Mucinous (n = 60)		Endometrioid (n = 180)		Clear cell (n = 43)		All invasive (n = 655)			
	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)†	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)
Age at first birth (years)‡	24.8	(4.6)	25.0	(4.0)	25.0	(4.4)	24.5	(4.3)	24.8	(4.4)	24.6	(4.6)
Age at last birth (years)‡	29.9	(5.3)	30.0	(4.9)	29.1	(5.0)	29.0	(4.4)	29.6	(5.2)	30.4	(5.4)
Breastfeeding duration (months)‡	10.0	(8.0)	8.3	(6.8)	8.8	(7.1)	8.5	(9.6)	9.5	(7.8)	11.2	(10.3)
No. of abortions	0.2	(0.5)	0.2	(0.4)	0.2	(0.5)	0.2	(0.6)	0.2	(0.5)	0.3	(0.6)
Body mass index (kg/m^2)§	25.2	(4.4)	26.2	(4.0)	26.0	(5.7)	27.0	(5.5)	25.7	(4.9)	25.4	(4.2)
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Nulliparous	62	18.4	9	15.0	33	18.3	16	37.2	126	19.2	435	11.2
Ever evaluated for infertility	14	4.2	1	1.7	8	4.4	2	4.7	29	4.4	102	2.6
Ever use of oral contraceptives	91	27.0	28	46.7	60	33.3	12	27.9	206	31.5	1,351	34.7
Ever use of HRT*	89	26.4	15	25.0	44	24.7	8	18.6	169	25.9	796	20.6
Tubal ligation	6	1.8	2	3.3	4	2.2	2	4.7	15	2.3	148	3.8
Hysterectomy	20	5.9	4	6.7	13	7.2	1	2.3	38	5.8	296	7.6
Unilateral oophorectomy	7	2.1			2	1.1	1	2.3	12	1.8	167	4.3
Ever smoking regularly	113	33.7	26	43.3	77	42.8	11	26.2	239	36.7	1,649	42.6
Family history of ovarian cancer	26	8.3	2	3.4	10	6.0			38	6.2	80	2.5
Family history of breast cancer	44	13.3	3	5.0	17	9.6	6	14.0	77	11.9	315	9.5

* SD, standard deviation; HRT, hormone replacement therapy (medium-potency estrogens with or without progestins).
† Postmenopausal women only.
‡ Parous women only.
§ One year prior to answering the questionnaire.

otherwise as unknown. The assigned age at menopause of 50 years equaled the mean age at menopause for subjects in all four case/control and smoking/nonsmoking 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 before or earlier.

Statistical analyses were performed with the SAS statistical package (SAS Institute, Inc., Cary, North Carolina). Relative risks were estimated as odds ratios with corresponding 95 percent confidence intervals by using unconditional logistic regression models fitted using the maximum likelihood method. All p values and confidence intervals were two sided. Tests of statistical significance of individual parameters in the models were made by using the likelihood ratio test for general heterogeneity. For most analyses, the fitted model included age (5-year categories), parity (0, 1, 2, 3, 4, and 5–13 full-term pregnancies), age at menopause (premenopausal, <49, 49–<53, and ≥53 years), body mass index (<22, 22–<25, 25–<27, 27–<30, and ≥30 kg/m^2), duration of oral contraceptive use (never, <1, and ≥1 year), and ever use of HRT. No substantial changes in risk estimates were induced by adding numerous other variables to the models. Tests of interaction were conducted by using the likelihood ratio test comparing models with and without interaction terms.

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

RESULTS

On the basis of the original histology reports of local pathologists, the 655 cases of EOC were distributed as follows: serous, 337 cases (51 percent); mucinous, 60 cases (9 percent); endometrioid, 180 cases (27 percent); clear cell, 43 cases (7 percent); and undifferentiated or others, 35 cases (5 percent). Table 1 presents descriptive characteristics of the subjects. Cases had a slightly younger mean age than did controls, and fewer cases (n = 529, 81 percent) than controls (n = 3,464, 89 percent) were parous.

Reproductive history

Table 2 shows odds ratios for EOC according to reproductive factors. For all histologic types, parous women were consistently at a lower risk of EOC compared with nulliparous women. For all EOCs combined, the level of protection increased with the number of childbirths. Overall, age at first birth of 35 years or older reduced the risk of EOC, but no clear associations appeared in younger categories of age at first birth or by different histologies. We found no association with age at last birth and cancer risk (data not shown). Breastfeeding conferred a strong protection against clear cell cancers, whereas this effect was not seen for other histologies or overall. Incomplete pregnancies (spontaneous and induced abortions) modestly decreased the risk of EOC. Only 29 cases were evaluated for infertility, and the odds ratio of EOC in women who had such a history was 1.23 (95 percent confidence interval (CI): 0.79, 1.94) compared with the risk in women without such a history. Difficulties in recall of infertility cause and treatment precluded further analyses of these factors.

Table 3 gives odds ratios according to menstrual factors. Moderately decreased risks appeared with older age at menarche for clear cell cancers and with a younger age at menopause for serous and clear cell cancers, although most of these results were not statistically significant. Overall, a weak negative association was observed between a young age at menopause and EOC risk. Irregular menstrual cycles were positively associated with endometrioid EOC and unrelated to EOC risk overall. Menopausal symptoms appeared to increase the risk of mucinous cancers, while the opposite was seen for clear cell cancers.

Exogenous hormone use

Table 4 presents odds ratios for EOC according to oral contraceptive use. Ever use of oral contraceptives was reported by 31 percent of the cases and 35 percent of the controls. Compared with risk for never users, a 27 percent reduced risk of EOC appeared among ever users of oral contraceptives. We found similar risk estimates for all histologies of EOC except for mucinous cancers, for which the odds ratio for ever use was 1.96 (95 percent CI: 1.04, 3.68). An increasing duration of oral contraceptive use further decreased the risk of serous, endometrioid, and all EOCs, whereas no clear association with duration and the risk of mucinous and clear cell cancers appeared. The protective effect of oral contraceptives on the risk of nonmucinous EOC was observed up to 25 years after cessation of use.

Table 5 shows odds ratios for EOC according to HRT, as reported by 26 percent of the cases and 21 percent of the controls. Ever users of HRT compared with never users had an increased risk of serous, endometrioid, and all EOCs combined, and the increase in risk was most pronounced among those who had used HRT for longer than 10 years. No evident association between HRT use and mucinous EOC risk appeared. Recency of HRT use was unrelated to EOC risk (data not shown).

Gynecologic surgery

Table 6 gives the odds ratios for EOC according to gynecologic surgery. Among cases, 2 percent reported tubal ligation, 6 percent reported hysterectomy, and 2 percent reported unilateral oophorectomy. All of these surgical procedures were slightly more common in controls and seemed to reduce the risk of EOC. In particular, unilateral oophorectomy reduced the risk of EOC, while lack of statistical power precluded a detailed assessment of tubal ligation and hysterectomy in relation to EOC risk.

Family history

Family history of ovarian cancer in a mother or sister increased the risk of EOC overall, with an odds ratio of 2.90 (95 percent CI: 1.92, 4.36). Odds ratios for serous, mucinous, and endometrioid cancers were 3.84 (95 percent CI: 2.39, 6.16), 1.45 (95 percent CI: 0.34, 6.19), and 2.90 (95 percent CI: 1.44, 5.82), respectively. No cases with clear cell histology reported a family history of ovarian cancer. Those with a family history of breast cancer in a mother or sister also had an elevated risk of EOC, with an odds ratio of 1.35 (95 percent CI: 1.03, 1.78).

DISCUSSION

Strengths of our study include the population-based design, a reliable national tumor registry enabling a complete ascertainment of cases, and detailed information on oral contraceptive and HRT use. The study was large but was still limited by few cases in some of the histologic groups, leading to low statistical power, especially when infrequent exposures were studied. The concern of selection bias should be averted by relatively high participation rates, although we have no data on nonparticipants. We believe that recall bias does not seriously influence our risk estimates, since variables such as parity and gynecologic surgery are unlikely to be recorded differently by cases and controls. Further, among the general public, the awareness of the protective effect of oral contraceptives on the risk of EOC is low (42), and a good correlation between self-reported exposures to oral contraceptives (43) and HRT (44) and those verified by clinical records has been reported. We saw no substantial changes in risk estimates by introduction of additional covariates in the statistical models, implying that confounding is unlikely to distort our results.

The protection of increasing parity on EOC risk in this study is consistent with previous research (4, 6–9). We found decreased risks of EOC for all histologies, including mucinous cancers, among parous compared with nulliparous women, which supports some reports (17, 31) but disagrees with others (5, 23). Our finding of a reduced risk of EOC in those older than age 35 years at first birth agrees with several population-based studies (4, 6, 7, 9) but opposes the positive associations seen in hospital-based case-control studies (4, 6, 12) or the absence of associations in other studies (4, 8, 11, 14). Overall, breastfeeding did not give protection from EOC in our data, similarly to the results of some studies (9, 17) but inconsistent with others in which protection was seen (4, 6,

TABLE 2. Odds ratios and 95% confidence intervals of epithelial ovarian cancers according to reproductive factors, Sweden, 1993–1995

Category	No. of cases*					No. of controls*	Odds ratios of EOC† by histologic subgroup									
							Serous		Mucinous		Endometrioid		Clear cell		All	
	Serous	Mucinous	Endometrioid	Clear cell	All		OR†,‡	95% CI†	OR‡	95% CI	OR‡	95% CI	OR‡	95% CI	OR‡	95% CI
Parity																
0	62	9	33	16	126	435	1.0§		1.0 §		1.0§		1.0§		1.0§	
1	59	10	45	4	128	688	0.60	0.41, 0.88	0.63	0.25, 1.58	0.76	0.47, 1.23	0.16	0.05, 0.49	0.61	0.46, 0.81
2	118	25	69	19	239	1,443	0.57	0.41, 0.80	0.65	0.29, 1.44	0.59	0.38, 0.92	0.34	0.17, 0.69	0.55	0.43, 0.70
3	72	10	19	3	112	846	0.60	0.42, 0.87	0.39	0.15, 1.01	0.28	0.16, 0.51	0.09	0.03, 0.32	0.44	0.33, 0.58
4	19	4	9		34	316	0.43	0.25, 0.74	0.44	0.13, 1.49	0.32	0.14, 0.71			0.35	0.23, 0.53
≥5	7	2	5	1	16	169	0.30	0.14, 0.68	0.42	0.09, 2.01	0.37	0.14, 0.98	0.16	0.02, 1.21	0.32	0.18, 0.56
Age at first birth (years)¶																
<20	30	4	16	5	59	393	1.0§		1.0§		1.0§		1.0§		1.0§	
20–24	111	20	53	8	208	1,471	0.87	0.57, 1.33	1.29	0.43, 3.88	0.82	0.45, 1.49	0.41	0.13, 1.29	0.86	0.63, 1.19
25–29	94	19	59	11	189	1,126	0.91	0.59, 1.42	1.74	0.56, 5.35	1.12	0.62, 2.04	0.64	0.21, 1.96	0.98	0.71, 1.37
30–34	32	8	15	3	61	352	1.00	0.58, 1.73	2.32	0.65, 8.29	0.81	0.38, 1.73	0.54	0.12, 2.41	0.96	0.64, 1.45
≥35	8		4		12	120	0.67	0.29, 1.54			0.52	0.16, 1.66			0.49	0.25, 0.96
Breastfeeding duration (months)¶																
<1	18	2	8	4	33	161	1.0§		1.0§		1.0§		1.0§		1.0§	
1–5	65	15	38	9	134	612	0.87	0.50, 1.53	2.19	0.49, 9.87	1.05	0.47, 2.34	0.54	0.16, 1.87	0.99	0.64, 1.52
6–11	62	17	43	6	134	840	0.61	0.35, 1.09	1.75	0.39, 7.87	1.10	0.50, 2.46	0.23	0.06, 0.88	0.77	0.50, 1.19
≥12	95	10	37	6	158	1,024	0.87	0.49, 1.54	0.83	0.17, 4.14	1.02	0.44, 2.37	0.24	0.06, 0.97	0.87	0.56, 1.35
No. of spontaneous or induced abortions																
0	278	49	149	38	547	3,072	1.0§		1.0§		1.0§		1.0§		1.0§	
1	45	11	26	3	86	646	0.84	0.60, 1.17	0.89	0.44, 1.80	0.78	0.50, 1.24	0.42	0.13, 1.39	0.76	0.59, 0.98
≥2	14		5	2	22	181	0.87	0.49, 1.53			0.60	0.24, 1.49	1.17	0.27, 5.08	0.70	0.44, 1.12

* The totals for the different variables do not always equal the total number of subjects in the case or the control category because of missing observations.
† EOC, epithelial ovarian cancer; OR, odds ratio; CI, confidence interval.
‡ Adjusted for age, parity, body mass index, age at menopause, and duration of oral contraceptive use as categorized variables and for ever use of HRT.
§ Reference category.
¶ Parous women only.

TABLE 3. Odds ratios and 95% confidence intervals of epithelial ovarian cancers according to menstrual factors, Sweden, 1993–1995

Category	No. of cases*					No. of controls*	Odds ratios of EOC† by histologic subgroup									
							Serous		Mucinous		Endometrioid		Clear cell		All	
	Serous	Mucinous	Endometrioid	Clear cell	All		OR†,‡	95% CI†	OR‡	95% CI	OR‡	95% CI	OR‡	95% CI	OR‡	95% CI
Age at menarche (years)																
<12	18	3	11	4	40	219	0.97	0.58, 1.62	0.75	0.23, 2.47	0.87	0.44, 1.70	1.38	0.48, 4.06	0.99	0.69, 1.43
12–14	211	45	123	31	431	2,543	1.0§		1.0§		1.0§		1.0§		1.0§	
≥15	64	9	31	3	113	793	0.96	0.71, 1.29	0.74	0.35, 1.53	0.84	0.56, 1.26	0.34	0.10, 1.13	0.87	0.69, 1.09
Age at menopause (years)																
Premenopausal	26	7	16	2	51	184	1.11	0.63, 1.93	2.47	0.74, 8.24	1.08	0.54, 2.17	0.41	0.08, 2.13	1.10	0.72, 1.66
<49	81	16	46	9	164	1,202	0.69	0.51, 0.93	0.79	0.40, 1.54	0.81	0.54, 1.22	0.62	0.26, 1.48	0.77	0.61, 0.96
49–52	116	20	54	13	210	1,210	1.0§		1.0§		1.0§		1.0§		1.0§	
≥53	110	16	59	18	218	1,209	1.00	0.75, 1.32	0.81	0.42, 1.59	1.19	0.81, 1.75	1.52	0.73, 3.18	1.10	0.89, 1.36
Irregular menstrual cycles																
No	302	55	158	41	589	3,589	1.0§		1.0§		1.0§		1.0§		1.0§	
Yes	35	5	22	2	66	310	1.28	0.87, 1.87	1.03	0.41, 2.61	1.61	1.00, 2.61	0.58	0.14, 2.46	1.24	0.92, 1.65
Menopausal symptoms (earlier than 1 year prior to questionnaire)																
No	139	15	80	24	266	1,445	1.0§		1.0§		1.0§		1.0§		1.0§	
Yes	194	44	98	19	382	1,876	1.04	0.81, 1.33	2.86	1.50, 5.46	0.86	0.61, 1.21	0.49	0.25, 0.96	1.05	0.87, 1.27

* The totals for the different variables do not always equal the total number of subjects in the case or the control category because of missing observations.
† EOC, epithelial ovarian cancer; OR, odds ratio; CI, confidence interval.
‡ Adjusted for age, parity, body mass index, age at menopause, and duration of oral contraceptive use as categorized variables and for ever use of HRT.
§ Reference category.

TABLE 4. Odds ratios and 95% confidence intervals of epithelial ovarian cancers according to oral contraceptive use, Sweden, 1993–1995

Category	No. of cases*					No. of controls*	Odds ratios of EOC† by histologic subgroup									
							Serous		Mucinous		Endometrioid		Clear cell		All	
	Serous	Mucinous	Endometrioid	Clear cell	All		OR†,‡	95% CI†	OR‡	95% CI	OR‡	95% CI	OR‡	95% CI	OR‡	95% CI
Ever use of OC†																
No	246	32	120	31	449	2,538	1.0§		1.0§		1.0§		1.0§		1.0§	
Yes	91	28	60	12	206	1,351	0.56	0.42, 0.74	1.96	1.04, 3.68	0.71	0.49, 1.03	0.66	0.31, 1.43	0.73	0.59, 0.90
Duration of OC use (years)																
Never	246	32	120	31	449	2,538	1.0§		1.0§		1.0§		1.0§		1.0§	
<2	38	7	29	4	84	422	0.72	0.49, 1.08	1.41	0.56, 3.54	1.11	0.69, 1.79	0.75	0.25, 2.30	0.95	0.71, 1.26
2–4	17	6	12	5	45	248	0.58	0.34, 0.98	2.05	0.78, 5.41	0.85	0.45, 1.60	1.50	0.53, 4.28	0.88	0.61, 1.25
5–9	13	3	5	1	24	227	0.49	0.27, 0.88	1.27	0.36, 4.44	0.31	0.11, 0.87	0.35	0.05, 2.72	0.50	0.32, 0.80
≥10	9	5	3	1	19	246	0.29	0.14, 0.58	1.79	0.62, 5.17	0.19	0.06, 0.62	0.26	0.03, 2.04	0.36	0.22, 0.59
Time since last use of OC (years)																
Never	246	32	120	31	449	2,538	1.0§		1.0§		1.0§		1.0§		1.0§	
<15	9	3	7	1	21	204	0.32	0.16, 0.65	1.23	0.33, 4.55	0.49	0.22, 1.11	0.32	0.04, 2.53	0.45	0.27, 0.73
15–19	15	4	6	4	31	219	0.58	0.33, 1.01	1.66	0.54, 5.10	0.40	0.16, 1.00	1.27	0.41, 3.99	0.66	0.43, 0.99
20–24	27	6	12	2	51	347	0.65	0.42, 1.00	1.49	0.57, 3.92	0.58	0.30, 1.09	0.41	0.09, 1.84	0.71	0.51, 0.99
≥25	26	8	25	4	70	375	0.57	0.36, 0.89	1.83	0.77, 4.35	1.12	0.68, 1.84	0.92	0.30, 2.81	0.90	0.27, 1.22

* The totals for the different variables do not always equal the total number of subjects in the case or the control category because of missing observations.
† EOC, epithelial ovarian cancer; OR, odds ratio; CI, confidence interval; OC, oral contraceptives.
‡ Adjusted for age, parity, body mass index, and age at menopause as categorized variables and for ever use of HRT.
§ Reference category.

TABLE 5. Odds ratios and 95% confidence intervals of epithelial ovarian cancers according to hormone replacement therapy, Sweden, 1993–1995

Category	No. of cases*					No. of controls*	Odds ratios of EOC† by histologic subgroup									
							Serous		Mucinous		Endometrioid		Clear cell		All	
	Serous	Mucinous	Endometrioid	Clear cell	All		OR†	95% CI†	OR	95% CI	OR	95% CI	OR	95% CI	OR‡	95% CI
Ever use of HRT†,‡																
No	248	45	134	35	484	3,074	1.0§		1.0§		1.0§		1.0§		1.0§	
Yes	89	15	44	8	169	796	1.48	1.13, 1.95	1.21	0.65, 2.25	1.39	0.96, 2.01	0.73	0.31, 1.71	1.41	1.15, 1.72
Duration of OC use (years)¶																
Never	248	45	134	35	484	3,074	1.0§		1.0§		1.0§		1.0§		1.0§	
<2	36	5	17	6	69	338	1.37	0.93, 2.01	0.91	0.35, 2.37	1.20	0.70, 2.04	1.13	0.42, 3.02	1.28	0.96, 1.72
2–<5	20	5	10	2	40	183	1.53	0.93, 2.51	1.98	0.75, 5.25	1.27	0.64, 2.53	0.94	0.22, 4.10	1.47	1.01, 2.14
5–<10	16	2	4		24	137	1.38	0.78, 2.43	0.91	0.21, 3.97	0.72	0.26, 2.01			1.07	0.67, 1.70
≥10	14	1	11		28	108	1.91	1.06, 3.45	0.74	0.10, 5.58	3.26	1.66, 6.39			2.03	1.30, 3.17

* The totals for the different variables do not always equal the total number of subjects in the case or control category because of missing observations.
† EOC, epithelial ovarian cancer; OR, odds ratio; CI, confidence interval; HRT, hormone replacement therapy (medium-potency estrogens with or without progestins).
‡ Adjusted for age, parity, body mass index, age at menopause, and duration of oral contraceptive use (never, <1, and ≥1 year) as categorized variables.
§ Reference category.
¶ Adjusted for age, parity, body mass index, age at menopause, and duration of oral contraceptive use (never, <2, 2–<5, 5–<10, and ≥10 years) as categorized variables.

8, 14, 15). We found a weakly reduced risk of EOC after incomplete pregnancies, as reported elsewhere (4–6, 12, 13), but not by others in which risk was unaffected (8, 9, 14, 17). A younger age at menarche increased the risk of EOC in several studies (9, 11, 12), whereas we and others (4, 5) found no association. A young age at menopause slightly reduced the risk of EOC, supporting some studies (4, 12), but not others in which no association between age at meno-

TABLE 6. Odds ratios and 95% confidence intervals of epithelial ovarian cancers according to gynecologic surgery, Sweden, 1993–1995

Category	No. of cases*					No. of controls*	Odds rats of EOC† by histologic subgroup									
							Serous		Mucinous		Endometrioid		Clear cell		All	
	Serous	Mucinous	Endometrioid	Clear cell	All		OR†,‡	95% CI†	OR‡	95% CI	OR‡	95% CI	OR‡	95% CI	OR‡	95% CI
Tubal ligation																
No	331	58	176	41	640	3,571	1.0§		1.0§		1.0§		1.0§		1.0§	
Yes	6	2	4	2	15	148	0.44	0.18, 1.10	0.79	0.18, 3.42	0.74	0.27, 2.09	1.85	0.41, 8.44	0.65	0.37, 1.16
Hysterectomy																
No	317	56	167	42	617	3,603	1.0§		1.0§		1.0§		1.0§		1.0§	
Yes	20	4	13	1	38	296	0.75	0.45, 1.26	0.68	0.20, 2.28	0.94	0.47, 1.88			0.71	0.47, 1.06
Unilateral oophorectomy																
No	330	60	178	42	643	3,732	1.0§		1.0§		1.0§		1.0§		1.0§	
Yes	7		2	1	12	167	0.39	0.17, 0.90			0.26	0.06, 1.06	0.60	0.08, 4.51	0.39	0.21, 0.72

* The totals for the different variables do not always equal the total number of subjects in the case or the control category because of missing observations.
† EOC, epithelial ovarian cancer; OR, odds ratio; CI, confidence interval.
‡ Adjusted for age, parity, body mass index, age at menopause, and duration of oral contraceptive use as categorized variables and for ever use of HRT.
§ Reference category.

TABLE 7. Expected change in epithelial ovarian cancer risk according to carcinogenic hypotheses versus observed risk change in epidemiologic studies

Characteristic	Observed risk change in epidemiologic studies	Expected risk change according to hypotheses			
		Incessant ovulation	Elevated gonadotropins	Retrograde bleeding	Progesterone deficiency
Parity	↓*	↓	↓	↓	↓
Breastfeeding	↓ →*	↓	↓	↓	↓
Oral contraceptive use	↓	↓	↓	↓	↓ †
HRT‡	↑ →*	↓	↓	↑ →§	↑ →¶
Tubal ligation/hysterectomy	↓	↓ →#	↑ →**	↓	↑ →††
Early age at menarche	↑ →	↑	↑	↑	↓‡‡
Late age at menopause	↑ →	↑	↓	↑	↓§§
Talc use	↑ →	→	→	↑	→

* ↓, reduced risk; →, unchanged risk; ↑, increased risk.
† Due to the progestin component in oral contraceptives.
‡ HRT, hormone replacement therapy.
§ Many hormone replacement regimens induce bleeding.
¶ Depending on the different contents of estrogens and progestins.
# Depending on whether these surgeries impair ovulatory function.
** Depending on whether these surgeries impair luteal-phase progesterone synthesis and feedback to gonadotropin secretion.
†† Depending on whether these surgeries impair luteal-phase progesterone synthesis.
‡‡ Assuming that earlier age at menarche leads to earlier progesterone synthesis.
§§ Assuming that later age at menarche leads to prolonged progesterone synthesis.

pause and EOC risk appeared (5, 6, 11, 16–18). We observed no major differences between mucinous and nonmucinous cancers with regard to reproductive events, except for an increased risk of mucinous EOC in women who had experienced menopausal symptoms compared with those who had not.

There is strong evidence of the reduced risk of EOC after oral contraceptive use in the majority of studies examining this association, and our odds ratio of 0.73 (95 percent CI: 0.59, 0.90) for ever users of oral contraceptives compared with never users corresponds to the risk estimates reported by others (4, 6, 8–12, 16, 28–30, 45, 46). In agreement with other studies, we also found decreased EOC risks with longer duration of use, an effect seen for serous, endometrioid, and all EOCs combined. Previous studies have shown the protection of oral contraceptives on EOC risk to persist for many years after cessation of use, with a 50 percent lower risk after 15 years off the pill (4, 10, 12, 29, 45). In our study, protection still prevails 20–24 years after last use. We observed no protection from oral contraceptive use on the risk of mucinous EOC, which supports the lack of protection of oral contraceptive use on mucinous tumors seen in some (23, 28, 29), but not all (30, 31, 45), studies.

The moderately increased EOC risk after ever use of HRT in this study is in agreement with the elevated risks observed in some (12, 17, 23, 24), but not other, studies in which either no association (6, 9, 16, 22) or a weak protection (14, 25, 26) appeared. We found the highest risks among women with endometrioid and serous cancers who had used HRT for longer than 10 years, as was observed in other reports (23, 24). No association was seen between HRT use and mucinous EOC, which supports the findings of Risch et al. (23). In our analyses, HRT use was categorized as medium-potency estrogens taken either unopposed or with progestin supplements, which has been the standard definition in several other studies. Our data on HRT and EOC risk, considering the separate effects of estrogens and progestins, are reported elsewhere (47).

Tubal ligation, hysterectomy, and unilateral oophorectomy were rather infrequent procedures among our subjects. The nonsignificantly reduced risks of EOC after both tubal ligation (6, 8, 9, 10, 12, 14, 20–22) and hysterectomy (6, 8, 9, 10, 14, 21) are in agreement with the risk reductions observed by others in populations in which both procedures are more common. In our study, unilateral oophorectomy also protected against EOC, in contrast to the report of Kreiger et al. (21).

We found elevated risks of serous, endometrioid, and all EOCs combined in women who reported ovarian cancer in a mother or a sister, while mucinous EOC was only weakly and statistically nonsignificantly related to such family history. This is consistent with other studies supporting hereditary factors for endometrioid and serous, but not mucinous, EOC (23, 27).

The etiology of ovarian cancer is unknown, although several hypotheses have been suggested to explain ovarian carcinogenesis. The incessant ovulation hypothesis holds that the risk of ovarian cancer increases with an increased number of ovulations in which the ovarian epithelium is recurrently repaired and exposed to estrogen-rich follicular fluid (32). The gonadotropin hypothesis indicates higher risk of EOC after elevated levels of gonadotropins, which may stimulate the ovarian epithelium (33). Other hypotheses explore the retrograde transportation of contaminants (35) or conditions with progesterone deficiency (37). The incessant ovulation and gonadotropin hypotheses have been exten-

sively evaluated in previous studies on EOC epidemiology, whereas the retrograde transportation hypothesis is less frequently discussed in relation to other EOC risk factors than are tubal ligation, hysterectomy, talc use, and endometriosis. In table 7, the expected effects on EOC risk according to etiologic hypotheses by epidemiologic factors known to influence EOC risk are compared with epidemiologic findings observed in both this and previous studies. The retrograde transportation hypothesis, which may operate through retrograde bleeding through the fallopian tubes, seems consistent with all of the epidemiologic associations (35, 48). The primary support of this suggestion is the cessation of retrograde bleeding after tubal ligation and hysterectomy, but other reproductive data are also supportive. Some studies indicate an increase in menstrual volume (49, 50) and alleviation of dysmenorrhea (51) after childbirth, which may reflect less retrograde menstruation, possibly mediated by less outflow resistance in the parous uterine cervical canal. Further, one of the benefits of oral contraceptive use is a 50 percent reduction in menstrual blood loss, which also most likely decreases retrograde menstruation as well as dysmenorrhea (42, 51); dysmenorrhea has been associated with an increased risk of EOC in one study (9). The modest increase in risk after HRT seen in several studies (4, 12, 17, 24) can also be explained through extended periods of bleeding induced by many HRT regimens. Additional support for the retrograde transportation hypothesis comes from observed associations between EOC and talc (9, 12, 52, 53), the increase in risk after pelvic inflammatory disease (54), the protection of antiinflammatory drugs (55), and the coexistence of EOC and endometriosis (56, 57). It is likely that growth factors (35, 58), cytokines (58), and inflammatory mediators (59, 60) may gain access to the ovarian epithelium through retrograde bleeding, although it is unknown whether these factors are related to EOC risk. In table 7, the expected risk alterations according to the other hypotheses are inconsistent with a number of epidemiologic findings on EOC risk.

In conclusion, we found protection from EOC with increasing parity, late age at first birth, incomplete pregnancies, and an early age at menopause. The risk of EOC increased with a family history of ovarian cancer and was not associated with early age at menarche, irregular menses, lactation, or menopausal symptoms. Oral contraceptive use reduced the risk of nonmucinous EOC, and the protection increased with longer duration of use and persisted up to 25 years off the pill. Ever users compared with never users of oral contraceptives had an increased risk of mucinous cancers, but no clear associations appeared with duration or recency. The risk of EOC was elevated among ever users compared with never users of HRT, and the increase in risk was highest in those who had used HRT for longer than 10 years. We also discussed etiologic hypotheses of EOC in relation to EOC risk factors and suggest that the retrograde transportation hypothesis seems compatible with most established epidemiologic associations.

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