Hormone Replacement Therapy and the Risk of Invasive Epithelial Ovarian Cancer in Swedish Women

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Background: **Estrogen replacement therapy (ERT), which is mainly used to relieve climacteric symptoms, increases a woman's risk for uterine endometrial cancer and epithelial ovarian cancer (EOC). Estrogens are often combined with progestins in hormone replacement therapy (HRT) to reduce the risk of uterine endometrial cancer. Data on the association between HRT including progestins and EOC risk are limited. This nationwide case–control study examined EOC risk in relation to HRT regimens with sequentially added progestins (HRTsp) and continuously added progestins (HRTcp).** ***Methods:*** **Between 1993 and 1995, we enrolled 655 histologically verified incident case patients with EOC and 3899 randomly selected population controls, all 50–74 years of age. Data on HRT use were collected through mailed questionnaires. Multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by the use of unconditional logistic regression.** ***Results:*** **Risks of EOC were elevated among ever users as compared with never users of both ERT (OR = 1.43, 95% CI = 1.02 to 2.00) and HRTsp (OR = 1.54, 95% CI = 1.15 to 2.05); risks were elevated for serous, mucinous, and endometrioid subtypes. For all EOC types combined, the greatest risk increases were seen with hormone use exceeding 10 years. Ever use of HRTcp was not associated with increased EOC risk relative to HRTcp never use (OR = 1.02, 95% CI = 0.73 to 1.43). The risk of EOC was elevated among HRTsp ever users as compared with HRTcp ever users (OR = 1.78, 95% CI = 1.05 to 3.01). ORs for EOC after ever use of low-potency estrogens were 1.18 (95% CI = 0.89 to 1.55) for oral and 1.33 (95% CI = 1.03 to 1.72) for vaginal applications, but no relationship was seen between EOC risk and duration of use.** ***Conclusion:*** **Ever users of ERT and HRTsp but not HRTcp may be at increased risk of EOC. [J Natl Cancer Inst 2002;94:497–504]**

Hormone replacement therapy (HRT) containing estrogens is used to relieve climacteric symptoms and to prevent osteoporosis and coronary heart disease *(1).* In women with an intact uterus, estrogen replacement therapy (ERT) increases the risk of uterine endometrial cancer *(2),* an effect that is averted by combining estrogens with sequential or continuous progestins *(3,4).* Low-potency estrogens (oral and vaginal estriol, dienestrol, and low-dose estradiol) are effective only for alleviating vaginal atrophy and urogenital symptoms and are mostly used without progestins *(4).*

Epidemiologic findings on HRT and the risk of epithelial ovarian cancer (EOC) are conflicting. In three studies, HRT use was associated with a reduced risk of EOC *(5–7),* whereas other studies showed no association *(8–14)* or moderately increased risks of EOC *(15–29).* Most studies investigated ERT *(6,13,15,16,19–23,28,29)* or HRT without specifying whether estrogens were taken unopposed or supplemented by progestins *(14,17,18,26,27).* Studies evaluating EOC risk according to progestins in HRT *(7,12,23,25)* were hampered by the inclusion of relatively few exposed subjects, and it remains unknown whether sequential or continuous progestin supplements, or both, alter the risk of EOC.

We conducted a nationwide case–control study to investigate the association of HRT and other factors with the risk of epithelial ovarian malignancies of different histologic subtypes in perimenopausal and postmenopausal women. In Sweden, both the prevalence of HRT use and the annual incidence of EOC are high *(30).* We report here on associations between various HRT regimens that differ in progestin content and the risk of EOC.

Subjects and Methods

Subjects

Women in this case–control study were aged 50–74, born in and residents of Sweden, and recruited from October 1, 1993, to December 31, 1995. Eligible case patients presented with newly diagnosed EOC and were identified through six regional cancer registries that together provide an almost complete nationwide cancer registration *(31).* After being approached by their physicians, case patients signed an informed consent form before study enrollment. Data were collected through mailed self-administered questionnaires. The study was approved by the Ethics Committees of the University of Uppsala and the Karolinska Institute (Stockholm).

In total, 1205 women with incident ovarian tumors of any histologic type were reported to the regional cancer registries, and 914 (76%) without any previous ovarian malignancy or bilateral oophorectomy agreed to participate. Nonparticipation was due to patient refusal (181 [15%]) and physicians' refusal to contact the patients (110 [9%]), mostly because of patient death or poor health. To verify the epithelial origin of the ovarian tumors, the study pathologist (H. Nordlinder), who was blinded to the original pathology reports and to participants' exposure data, reviewed tumor specimens. Tumor specimens were retrievable for 878 of the 914 participants, and 803 tumors were re-

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See "Notes" following "References."

viewed as epithelial. The agreement on epithelial and nonepithelial subtype between the reviewed series and the original pathology report was 94%. Of the 36 patients whose specimens were not retrievable, 25 patients whose tumors were classified as epithelial in the original pathology reports were also included in the case series. In total, 828 cases of epithelial ovarian tumors were included in the final data set. We used the original pathology reports to classify the epithelial tumors by histologic subtype. Of the 828 cases, 655 (79%) classified as EOC are considered here, while borderline tumors are reported elsewhere *(32)*.

Control women were randomly selected from a population registry covering all residents in Sweden and sampled simultaneously with the case patients. Among 4996 control women initially invited, 4148 (83%) agreed to participate, 811 (16%) refused to participate, and 37 (1%) did not participate because of poor health. Of the 4148 control women, 3596 (87%) completed questionnaires and the other 552 (13%) did not respond initially but agreed to answer parts of the questionnaire in a telephone interview. (Case patients were not interviewed by telephone because 94% of those who had given consent to be approached completed the mailed questionnaire). After the exclusion of 249 control women who were not at risk of EOC because of previous bilateral oophorectomy, 3899 control women remained in the data set. So that we could use resources efficiently, most of the control women also participated in parallel case–control studies on breast *(33)* and endometrial *(3)* cancers, using identical study designs. Until March 31, 1995, the control subjects were frequency matched to the expected age distribution of breast cancer cases; after that date, they were frequency matched to the expected age distributions of ovarian and endometrial cancer cases.

The questionnaire covered social, medical, gynecologic, reproductive, and lifestyle characteristics. To facilitate recall of oral contraceptive and HRT use, subjects were shown charts picturing all the brands commercially available in Sweden beginning in 1950. For each episode of exogenous hormone use, the brand, dose, and starting and stopping dates were recorded. For case patients, the mean interval from diagnosis to arrival of the questionnaire was 4.5 months (standard deviation 2.0 months). Telephone interviewers who were blinded to the study hypotheses contacted approximately 50% of both case patients and control subjects to clarify inconsistencies or to fill in missing details from the questionnaires.

Based on questionnaire responses, we categorized HRT use as follows: 1) ERT (estradiol, conjugated estrogens, and synthetic estrogens); 2) estrogens combined sequentially with progestins (HRTsp) (<16 days/cycle, most commonly 10 days/cycle); 3) estrogens combined continuously with progestins (HRTcp) (≥19 days/cycle, most commonly 28 days/cycle); 4) low-potency estrogens (oral or vaginal estriol, dienestrol, or low-dose estradiol [25 μg/day]). The ERT category was further subdivided according to dose of estrogen (conjugated estrogens: low dose <0.625 mg/day, high dose ≥0.625 mg/day; estradiol: low dose <2 mg/day, high dose ≥2 mg/day). Combinations of estrogens with progestins were further categorized by progestin type (19-nortestosterone derivatives: norethisterone, levonorgestrel, lynestrenol; 17-hydroxyprogesterone derivative: medroxyprogesterone acetate). All exposures were censored after an index date, which for case patients was 3.0 months before the date of diagnosis and for control subjects was 7.5 months before the date of questionnaire arrival (i.e., the mean time of 4.5 months from diagnosis to questionnaire arrival in case patients plus 3.0 months).

Statistical Methods

Statistical analyses were performed with the SAS statistical package (SAS Institute, Cary, NC) *(34)*. Relative risk estimates for EOC in relation to HRT were computed as odds ratios (OR) with corresponding 95% confidence intervals (CI), with the use of unconditional logistic regression models fit by the maximum likelihood method. All *P* values and CIs are 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. All models included age (5-year categories), parity (0, 1, 2, 3, 4, or 5–13 full-term pregnancies), body mass index (<22, ≥22 to <25, ≥25 to <27, ≥27 to <30, or ≥30 kg/m^2), age at menopause (premenopausal, <49, 49–52, or ≥53 years), duration of oral contraceptive use (never, <1, or ≥1 years), and hysterectomy (no or yes). Women may have used various types of HRT in different time periods. When analyzing EOC risk in women who used a particular type of HRT, we compared users with never users of this HRT type, further adjusting for other regimens of HRT (ever use of ERT, HRTsp, and HRTcp). To validate these models we also compared the subset of users of only one regimen of HRT with never users of any HRT. In recency analyses the models also included duration of the various HRT regimens (ERT, HRTsp, or HRTcp in <3 and ≥3 years categories) and interaction terms for duration and recency. Tests of interaction were conducted using the likelihood ratio test, comparing models with and without interaction terms. To consider the potential effect of other confounders, we also added to the models data on incomplete pregnancies, extrauterine pregnancies, age at menarche, infertility evaluation, irregular menstrual cycles, tubal ligation, unilateral oophorectomy, menopausal symptoms, family history of reproductive cancers, level of physical activity, smoking, alcohol consumption, and dietary habits. None of these variables materially altered the risk estimates or improved the goodness of fit.

Results

According to the original pathology reports, the 655 EOC cases were classified as follows: serous, 337 (51%); mucinous, 60 (9%); endometrioid, 180 (27%); clear-cell, 43 (7%); and undifferentiated or others, 35 (5%). This distribution was different from the EOC histologies classified by the study pathologist (of the 803 cases classified after review as epithelial, 617 were classified as EOC and 186 as borderline tumors); the 617 EOC cases were classified as follows: serous, 227 (37%); mucinous, 36 (6%); endometrioid, 302 (49%); clear-cell, 42 (7%); and undifferentiated or others, 10 (2%). The main difference between the original and reviewed EOC series was caused by a reclassification of serous to endometrioid EOC, but there were also smaller reclassifications among invasive, borderline, and the other histologic subgroups. All results presented here are based on the original pathology reports.

Comparison of the characteristics of the 655 case patients with invasive EOC and the 3899 control subjects (Table 1) shows that case patients were slightly younger, were less likely

Table 1. Descriptive characteristics of epithelial ovarian cancer case patients and control women, Sweden 1993–1995

	Case patients											
	Serous No. = 337		Mucinous No. = 60		Endometrioid No. = 180		Clear-cell No. = 43		All invasive No. = 655		Control women No. = 3899	
Characteristic	Mean	SD*	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age at diagnosis/questionnaire, y	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, y	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, y†	50.6	3.6	49.7	4.2	50.3	3.5	50.8	3.6	50.4	3.6	50.1	3.8
Parity	1.9	1.3	2.0	1.3	1.7	1.2	1.3	1.3	1.8	1.3	2.1	1.4
Body mass index, kg/m^2‡	25.2	4.4	26.2	4.0	26.0	5.7	27.0	5.5	25.7	4.9	25.4	4.2
	n	%	n	%	n	%	n	%	n	%	n	%
Nulliparous	62	18.4	9	15.0	33	18.3	16	37.2	126	19.2	435	11.2
Ever use of oral contraceptives	91	27.0	28	46.7	60	33.3	12	27.9	206	31.5	1351	34.7
Ever use of HRT	89	26.4	15	25.0	44	24.7	8	18.6	169	25.9	796	20.6
Estrogens only (ERT)	29	8.7	8	13.3	18	10.2	1	2.4	59	9.2	259	6.8
With sequential progestins (HRTsp)	49	14.8	7	11.9	23	13.1	5	11.9	87	13.7	348	9.2
With continuous progestins (HRTcp)	28	8.5	4	6.8	18	10.2	1	2.4	55	8.6	280	7.4
Ever use of low potency estrogens	77	22.8	12	20.3	38	21.3	9	20.9	147	22.5	782	20.2
Oral administration	42	12.5	6	10.2	17	9.6	5	11.6	77	11.8	425	11.0
Vaginal administration	48	14.2	7	11.9	26	14.6	4	9.3	91	14.0	447	11.6
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
Ever smoking regularly	113	33.7	26	43.3	77	42.8	11	26.2	239	36.7	1649	42.6

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

to have given birth, and were less likely to have used oral contraceptives. Overall, more case patients (26%) than control subjects (21%) used HRT.

Risk estimates of EOC after use of unopposed ERT, which was used by 9.2% of case patients and 6.8% of control subjects, are shown in Table 2. Elevated risks with ever use were observed for serous, mucinous, and endometrioid cancers and for all types combined (OR = 1.43, 95% CI = 1.02 to 2.00), although the CI included 1.0 for serous and endometrioid cancers and was wide for mucinous cancers. For endometrioid cancers and for all EOC, women who had used ERT for more than 10 years had the highest risk. Too few case patients with mucinous cancers had used ERT to enable us to draw conclusions regarding duration of use and risk of this cancer type. Only one case patient with clear-cell cancer reported ERT use. The ORs of all EOC according to dose of estrogens were 1.41 (95% CI = 0.91 to 2.19) among users of high-dose ERT preparations relative to never users and 1.24 (95% CI = 0.69 to 2.21) for users of low-dose ERT preparations relative to never users. An elevated risk of EOC was observed in ever users as compared with never users of both conjugated estrogens (OR = 1.53, 95% CI = 0.85 to 2.74) and estradiol (OR = 1.59, 95% CI = 1.09 to 2.30), although the risk increase was statistically significant only for estradiol users. The ORs of EOC among ever users of ERT, as compared with never users, were 1.06 (95% CI = 0.40 to 2.85) in hysterectomized women and 1.50 (95% CI = 1.04 to

Table 2. Odds ratios and 95% confidence intervals for epithelial ovarian cancer (EOC) according to use of unopposed estrogens*, Sweden 1993–1995

		No. case patients				No. control women	OR† of EOC by histologic subgroup							
							Serous		Mucinous		Endometrioid		All	
Category		Serous	Mucinous	Endometrioid	All		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Ever use of ERT‡	No§	304	52	159	583	3531	1.0		1.0		1.0		1.0	
	Yes	29	8	18	59	259	1.33	0.85 to 2.09	2.40	1.02 to 5.65	1.57	0.88 to 2.78	1.43	1.02 to 2.00
	P value‖						.23		.07		.14		.04	
Duration of ERT use, y‡	Never§	304	52	159	583	3531	1.0		1.0		1.0		1.0	
	<1	8	3	4	17	74	1.34	0.62 to 2.89	3.41	0.99 to 11.72	1.26	0.44 to 3.63	1.40	0.79 to 2.49
	⩾1 to <2	2	—	2	5	34	0.83	0.19 to 3.61	—		1.51	0.34 to 6.69	1.07	0.40 to 2.88
	⩾2 to <5	3	3	2	8	58	0.67	0.20 to 2.24	4.96	1.40 to 17.64	0.88	0.21 to 3.74	0.99	0.45 to 2.15
	⩾5 to <10	7	1	3	11	38	2.01	0.81 to 5.01	2.14	0.27 to 16.86	1.96	0.57 to 6.77	1.80	0.86 to 3.75
	⩾10	6	—	5	12	36	1.87	0.70 to 4.95	—		3.41	1.15 to 10.14	2.14	1.03 to 4.46
	P value‖						.50		.11		.42		.25	

*Estrogen replacement therapy (ERT) excluding low-potency estrogens.
†OR = odds ratio; CI = confidence interval; — = missing value due to unexposed subjects or missing data on covariates in the statistical models.
‡Adjusted for age, parity, body mass index (kg/m^2), age at menopause, hysterectomy, duration of oral contraceptive use, and ever use of sequential (HRTsp) and continuous (HRTcp) estrogen–progestin combinations as categorized variables.
§Reference category.
‖*P* value for the likelihood ratio test of general heterogeneity.

2.16) in women with an intact uterus; too few subjects reported tubal ligation to allow an examination of an interaction between this procedure and ERT with regard to EOC risk.

Risk estimates of EOC according to HRTsp and HRTcp use are shown in Table 3. The OR for EOC among ever users of HRTsp, compared with never users, was 1.54 (95% CI = 1.15 to 2.05). Women who had used HRTsp for 10 or more years were at highest risk of EOC overall, compared with never users (OR = 2.10, 95% CI = 0.99 to 4.48), and the increased risk was highest for serous cancers. By contrast, HRTcp use had no impact on EOC risk, with ORs close to unity both overall (OR = 1.02, 95% CI = 0.73 to 1.43) and for serous, mucinous, and endometrioid histologic subtypes considered individually. ORs for clear-cell cancers were 1.69 (95% CI = 0.61 to 4.68) for HRTsp and 0.27 (95% CI = 0.04 to 2.05) for HRTcp ever use compared with never use, but duration exposure data were too sparse for analysis (data not shown).

We also attempted to evaluate whether the type of progestin in HRTsp and HRTcp is related to the risk of EOC. The progestins in HRTsp and HRTcp were more commonly derivatives of 19-nortestosterone (used by 115 case patients and 476 control subjects) than of 17-hydroxyprogesterone (used by 28 case patients and 138 control subjects). In the stratified analyses of EOC risks among HRTsp and HRTcp users by type of progestin derivation, risks associated with 19-nortestosterone-derived progestins (data not shown) were similar to those associated with all progestins combined. The small number of case patients who had been exposed to HRT regimens that included 17-hydroxyprogesterone precluded further analyses of this group.

The recency of intake of the different HRT regimens showed no clear association with EOC risk, either overall (Table 4) or by histologic subtype (data not shown).

Over time, women may use various types of HRT. Several strategies can be used to analyze the independent associations of different HRT regimens with EOC risk. In the analyses presented so far, we compared users of a particular type of HRT with never users and adjusted for other types of HRT used. Alternatively, women who had used one type of HRT exclusively can be compared with a common referent group of never users of any HRT. In this analysis, the ORs of EOC were 1.58 (95% CI = 1.03 to 2.42) for ERT ever users, 1.98 (95% CI = 1.40 to 2.78) for HRTsp ever users, and 1.11 (95% CI = 0.71 to 1.74) for HRTcp ever users, as compared with never users of any HRT. A direct comparison of HRTsp ever users with HRTcp ever users also indicated an elevated risk of EOC in HRTsp users (OR = 1.78, 95% CI = 1.05 to 3.01). We could not analyze EOC risk by duration of HRT use among women who had used one type of HRT exclusively because the sample size was too small.

Ever use of low-potency estrogens was reported by 23% of case patients and 20% of control subjects. ORs of EOC among ever users as compared with never users of low-potency estro-

Table 3. Odds ratios and 95% confidence intervals for epithelial ovarian cancer (EOC) according to hormone replacement therapy (HRT) that includes progestins, Sweden 1993–1995

							OR* of EOC by histologic subgroup							
		No. case patients				No. control women	Serous		Mucinous		Endometrioid		All	
HRT category		Serous	Mucinous	Endometrioid	All		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Ever use of estrogens and sequential progestins (HRTsp)†	No‡	282	52	152	550	3434	1.0		1.0		1.0		1.0	
	Yes	49	7	23	87	348	1.75	1.21 to 2.53	1.06	0.44 to 2.54	1.45	0.87 to 2.42	1.54	1.15 to 2.05
	P value§						.004		.91		.16		.004	
Duration of use of HRTsp, y†	Never‡	282	52	152	550	3434	1.0		1.0		1.0		1.0	
	<1	11	3	8	23	66	1.75	0.86 to 3.57	1.96	0.55 to 7.04	2.32	1.04 to 5.16	1.88	1.11 to 3.17
	⩾1 to <2	9	1	3	17	69	1.54	0.74 to 3.21	0.67	0.09 to 5.27	0.93	0.28 to 3.06	1.47	0.84 to 2.59
	⩾2 to <5	12	—	6	21	97	1.66	0.87 to 3.18	—		1.29	0.53 to 3.13	1.30	0.77 to 2.19
	⩾5 to <10	7	1	1	9	51	1.77	0.77 to 4.11	0.95	0.12 to 7.45	0.45	0.06 to 3.39	1.07	0.51 to 2.27
	⩾10	6	1	3	10	30	2.51	1.00 to 6.34	1.59	0.19 to 13.33	2.24	0.64 to 7.89	2.10	0.99 to 4.48
	P value§						.12		.46		.30		.08	
Ever use of estrogens and continuous progestins (HRTcp)‖	No‡	303	55	158	583	3494	1.0		1.0		1.0		1.0	
	Yes	28	4	18	55	280	1.00	0.64 to 1.58	0.80	0.23 to 2.39	1.20	0.68 to 2.12	1.02	0.73 to 1.43
	P value§						.99		.68		.54		.91	
Duration of use of HRTcp, y‖	Never‡	303	55	158	583	3494	1.0		1.0		1.0		1.0	
	<1	11	2	6	21	79	1.37	0.70 to 2.69	1.17	0.26 to 5.20	1.37	0.57 to 3.31	1.28	0.77 to 2.15
	⩾1 to <2	4	—	3	7	46	0.92	0.32 to 2.63	—		1.31	0.39 to 4.43	0.84	0.37 to 1.92
	⩾2 to <5	6	2	1	11	67	0.97	0.41 to 2.31	1.74	0.39 to 7.87	0.30	0.04 to 2.18	0.91	0.47 to 1.76
	⩾5 to <10	1	—	6	8	51	0.20	0.03 to 1.50	—		2.78	1.12 to 6.91	0.91	0.42 to 1.97
	⩾10	2	—	—	2	9	3.22	0.64 to 16.25	—		—		1.80	0.37 to 8.82
	P value§						.24		—		.19		.89	

*OR = odds ratio; CI = confidence interval; — = missing value due to unexposed subjects or missing data on covariates in the statistical models.

†Adjusted for age, parity, body mass index (kg/m^2), age at menopause, hysterectomy, duration of oral contraceptive use, and ever use of estrogen only (estrogen replacement therapy [ERT]) and continuous estrogen–progestin combinations (HRTcp) as categorized variables.

‡Reference category.

§*P* value for the likelihood ratio test of general heterogeneity.

‖Adjusted for age, parity, body mass index (kg/m^2), age at menopause, hysterectomy, duration of oral contraceptive use, and ever use of estrogen only (ERT) and sequential estrogen–progestin combinations (HRTsp) as categorized variables.

Table 4. Odds ratios and 95% confidence intervals for epithelial ovarian cancer (EOC) according to recency of different hormone replacement therapy (HRT) regimens*, Sweden 1993–1995

	Estrogens only (ERT)†				Estrogens and sequential progestins (HRTsp)				Estrogens and continuous progestins (HRTcp)			
	<3		⩾3		<3		⩾3		<3		⩾3	
Duration, y	OR‡§	95% CI	OR‡§	95% CI	OR‡‖	95% CI	OR‡‖	95% CI	OR‡¶	95% CI	OR‡¶	95% CI
Recency of HRT use, y												
Current#	1.0		1.0		1.0		1.0		1.0		1.0	
<5	0.78	0.23 to 2.68	1.29	0.33 to 5.02	1.29	0.57 to 2.95	0.66	0.24 to 1.81	1.17	0.46 to 3.02	2.86	0.83 to 9.90
⩾5	1.01	0.34 to 2.97	1.16	0.45 to 3.00	1.29	0.58 to 2.90	0.29	0.08 to 1.08	2.80	0.98 to 8.01	—	
P value**	.89		.92		.76		.12		.17		.06	

*Low-potency estrogens are excluded.

†ERT = estrogen replacement therapy; OR = odds ratio; CI = confidence interval; — = missing value due to unexposed subjects or missing data on covariates in the statistical models.

‡Adjusted for age, parity, body mass index (kg/m^2), age at menopause, hysterectomy, duration of oral contraceptive use as categorized variables.

§Adjusted for duration of ERT use (never, <3, ⩾3 years) as a categorized variable and for an interaction term of ERT duration and recency.

‖Adjusted for ever use of ERT, ever use of continuous estrogen–progestin HRT (HRTcp), and duration of sequential estrogen–progestin HRT (HRTsp) use (never, <3, ⩾3 years) as categorized variables, and for an interaction term of HRTsp duration and recency.

¶Adjusted for ever use of ERT, ever use of HRTsp, and duration of HRTcp use (never, <3, ⩾3 years) as categorized variables, and for an interaction term of HRTcp duration and recency.

#Reference category.

**P* value for the likelihood ratio test of general heterogeneity.

gens were 1.18 (95% CI = 0.89 to 1.55) with oral ever use, and 1.33 (95% CI = 1.03 to 1.72) following vaginal administration. No trend between duration of use and EOC risk was seen.

Discussion

To our knowledge, this is the first epidemiologic study to evaluate EOC risk in relation to use of HRT containing estrogens alone or with sequentially or continuously added progestins. Our main finding was an elevated risk of EOC in women who had used estrogen, either unopposed (ERT) or combined with sequential progestins (HRTsp). By contrast, no change in risk was observed in women who had used estrogens continuously supplemented by progestins (HRTcp).

The strengths of our study include its nationwide, population-based design; reliable ascertainment of cases; and detailed classification of HRT use. Our study also has several limitations. It is large but still limited by few cases in some histologic subgroups and exposure categories. There is a possibility of selection bias; in particular, case patients with advanced disease were more likely to be excluded, although the fairly high participation rates reduce the concern of selection bias overall. We lacked information on nonresponders and, therefore, do not know if they differed in exposures as compared with responders. Another possible limitation of the study is that use of HRT was not validated against clinical records; however, good correlation between self-reported use and clinical records has been reported *(35).* Recall bias is unlikely to explain the different associations between HRT and EOC risk by type of regimen because differential recall of alternative HRT regimens is improbable. In addition, we cannot exclude an impact of unidentified confounding factors. However, when we introduced additional covariates to the statistical models the risk estimates were undistorted, suggesting a lack of substantial confounding from available covariates.

Another potential concern of our study is the divergence between the histologies of the EOC tumors as given in the original pathology reports and the histologic classifications they were given after review by our study pathologist. Endometrioid cancers constituted 49% of the EOC histologies after review by our pathologist, exceeding the 4%–32% found in other studies *(6,9,12,16,18,22,36–38)* and the 27% reported by local pathologists for the case patients in our study. Indeed, the histology classifications according to the local pathologists are compatible with those reported in most previous epidemiologic investigations. To avoid the possibility of systematically misclassifying serous tumors as endometrioid, we decided to present our results based on the histologies in the original pathology reports, and we used the pathology review only to verify the epithelial origin of the tumors. The validity of this approach is supported by the suggestion that the histology examinations of local pathologists are more reliable than histologic reviews *(39).* Previously, it has been shown that distinguishing borderline from invasive lesions may be difficult *(40),* although the difficulty is less for serous than for mucinous tumors *(22,41,42)*; in addition, separating mucinous from serous cancers may be easier than distinguishing serous from endometrioid cancers *(22,43).*

There are several possible explanations for the divergent histologic classifications in our study. In contrast to local field pathologists, our pathologist was blinded to clinical data, had access to only a limited number of specimen slides for some cases, and classified mixed EOC according to the dominant histologic component. Also, our pathologist's interpretation of the World Health Organization criteria *(44),* in which endometrioid cancers of the ovarian epithelium are defined as tumors resembling endometrial cancer of the uterus, might have been different from that of pathologists in other studies. To address the possible impact of the inconsistent classifications, we also conducted analyses based on the reviewed histology classification (data not shown). If the reviewed histology distribution is correct, then the positive associations that we observed for endometrioid EOC after long-term ERT use would have been overestimated, and the associations for serous cancers would have been underestimated. However, the overall risk estimates were not materially altered

when the reviewed and original histology classifications were compared.

Over time, women may use various types of HRT and, when analyzing the association between HRT and EOC risk, several strategies can be used to account for the variation in HRT regimen. Our main strategy was to compare users of a particular type of HRT with never users, adjusting for use of other types of HRT, but we also compared users of only one type of HRT with never users of any HRT. Both strategies yielded similar risks of EOC after ever use of ERT, HRTsp, and HRTcp, validating our main strategy. Also, in the direct comparison of HRTsp to HRTcp ever use, our data indicate an increased risk of EOC among HRTsp users.

An excess risk of EOC after ERT has emerged in other studies *(15,16,19–23,25,27,28),* whereas only a few studies examined the association between progestin-combined HRT and EOC risk *(7,12,23,25).* In a hospital-based case–control study, the OR of EOC in ever users of estrogens combined with either progestins or testosterone as compared with never users was 0.7 (95% CI = 0.2 to 1.8), but the conclusions were limited by the small numbers of patients exposed to progestins or testosterone *(12).* The studies by Risch *(23)* and Hempling et al. *(7)* also yielded limited information about EOC risk in ever users of progestin-combined HRT, because there were few exposed subjects. A recent study *(25)* reported that the OR of EOC among ever users as compared with never users of estrogens opposed by progestins was 1.34 (95% CI = 0.83 to 2.17), but it was not specified whether the progestins were given sequentially or continuously. In the same study, the OR of EOC among ever users of progestins only (without estrogens) was 2.18 (95% CI = 0.91 to 5.20). However, because continuous progestins are frequently administered to treat ovarian cysts, the possible risk increase (the result was not statistically significant) of EOC after progestin-only use could be caused by confounding by indication, because some cysts may have been malignant at the time of treatment. In another study *(45),* which examined the effect of different types of HRT on the mortality from EOC after surgery for ovarian cancer, the risk of dying was not related to HRT use after diagnosis (OR = 0.73, 95% CI = 0.44 to 1.20), and the findings were similar for both progestin-opposed and progestin-unopposed estrogens.

The elevated risks of endometrioid cancers among users of ERT in this study are in line with most *(15,16,22,23,25,29)* but not all *(6,7,12,13,18)* previous research. Our finding of elevated risks of serous EOC is also in accord with some *(15,22,23)* but not other *(6,7,12,25)* investigations. Most studies indicate that HRT use is not associated with mucinous EOC *(6,15,22,23,25),* but statistically nonsignificant associations between HRT use and mucinous cancers have been reported *(12).*

We also tried to determine whether the various types of progestins were differently associated with the risk of EOC, but because the progestins in HRTsp and HRTcp were predominantly derivatives of 19-nortestosterone rather than 17-hydroxyprogesterone, we were unable to resolve this issue.

ORs for EOC were elevated after ever use compared with never use of vaginal low-potency estrogens, but no risk increase was seen with prolonged use, making an association between these preparations and EOC unlikely. Oral low-potency estrogen exposure was not associated with an increased risk of EOC.

Several hypotheses have been put forward to explain EOC etiology. The incessant ovulation hypothesis suggests that an increased number of ovulations may be carcinogenic, through the recurrent epithelial proliferation at the ovulatory sites *(46).* The gonadotropin hypothesis holds that elevated levels of gonadotropins increase the risk of EOC by stimulating growth of ovarian epithelium *(47).* Another hypothesis suggests a role for retrograde transportation of carcinogens *(48),* possibly mediated by retrograde bleeding through the Fallopian tubes *(49),* in the etiology of EOC. This hypothesis is compatible with our findings of increased EOC risk after both ERT (which is associated with frequent breakthrough and withdrawal bleeding) and HRTsp (which is associated with regular withdrawal bleeding) and the absence of increased risk after HRTcp (which is associated with an atrophic endometrium and only occasional bleeding). The retrograde transportation hypothesis is further supported by our finding of the lack of an association between ERT and EOC in hysterectomized women and by the finding *(25)* that women using ERT who had an intact genital tract had a considerably higher risk of EOC than did women with prior hysterectomy or tubal ligation. Closely linked to the retrograde transportation hypothesis are inflammatory processes in the ovarian environment, which have been the focus of several recent publications *(48,50–52).* Cytokines *(53),* growth factors, or some other endometrial factor contained in menstrual discharge *(48)* could explain the increased risk of EOC that we observed among users of HRT types in which endometrial bleeding is likely.

Whatever the etiology of EOC, it is possible that progestins exert a direct protective effect to reduce EOC risk *(54).* Pregnancy and oral contraceptive use are associated with a reduced risk of EOC, although it is not clear whether this protective association is mediated by the suppression of ovulation only or by a direct antiproliferative effect of a high-progestin environment at the ovarian epithelium. In an experimental study on cynomolgus macaque monkeys, progestin induced apoptosis of epithelial ovarian cells *(55),* possibly through direct action on steroid receptors *(56).* Some of our findings support this hypothesis, because the progestins in HRTcp seem to counteract the increase in EOC risk associated with ERT use. However, HRTcp did not reduce the risk of EOC; moreover, the magnitudes of the risk increase of EOC were similar for ERT and HRTsp.

Although our data indicate an elevated risk of EOC associated with the use of ERT and HRTsp, we are not yet able to confirm a causal association. Circumstantial data from studies such as those on the Hiroshima cohort *(57)* and reports on the age distribution of borderline ovarian tumors compared with invasive EOC *(58,59)* point to a latency period from tumor induction to EOC carcinogenesis of 10–25 years. If this latency period is correct, then, assuming a causal association between ERT or HRTsp and EOC, and given that HRT is used mainly by women in their late 40s and 50s, we would have predicted more elderly case patients than were seen in this study. An alternative possibility is that the increased EOC risk among ERT and HRTsp users is mediated through growth promotion of a preexisting tumor *(60–62).* Such a role would still be clinically relevant because of the high morbidity and mortality of EOC.

We advocate cautious interpretation of our results and do not recommend changes to current HRT prescribing practices. For women to make an informed decision on whether or not to use HRT, all beneficial and adverse hormonal aspects concerning osteoporosis, coronary heart disease, venous thrombosis, and other health effects must be addressed. In particular, attention needs to be paid to the association between HRTcp and a pos-

sibly increased risk of breast cancer *(33)*. Still, if our findings are replicated it would be valuable to consider the EOC risk increase associated with the use of certain HRT regimens, especially given the prevalence of HRT use and the poor prognosis of EOC.

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NOTES

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