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Use of hormone replacement therapy before and after ovarian cancer diagnosis and ovarian cancer survival

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Use of hormone replacement therapy (HRT) has been hypothesized to affect survival of epithelial ovarian cancer (EOC). We studied 5-year survival in patients with invasive EOC and borderline ovarian tumors (BOT) according to HRT use before and after diagnosis in a prospective nation-wide cohort study of 799 women diagnosed with EOC (n = 649) and BOT (n = 150) aged 50–74 years in 1993–1995 in Sweden. Cox regression was used to obtain multivariate age-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Multivariate models included indicator variables for age, tumor stage, grade and histological subtype. After 5 years of follow-up, 45% of the patients with EOC and 93% of the patients with BOT were alive. For women with BOT there were no associations between HRT-use pre- or postdiagnosis and survival. There was no overall difference in 5-year EOC survival according to use HRT before diagnosis (multivariate HR = 0.83, 95% CI = 0.65–1.08), except for serous EOC (HR = 0.69, 95% CI = 0.48–0.98). Analyses of different HRT preparations, duration and recency of use did not reveal any variations in pattern of survival. We observed a better survival for EOC-patients who used HRT after diagnosis (multivariate HR = 0.57, 95% CI = 0.42–0.78). We conclude that HRT-use prior to diagnosis of EOC does not affect 5-year survival, except for a possible survival advantage in serous EOC. Women using HRT after diagnosis had a better survival than women with no use, but we cannot rule out that this latter finding may reflect a subtle selection process.
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Hormonal factors are believed to be of fundamental importance in the etiology of ovarian cancer, the 6th most frequent type of female cancer in the world.[1] Ovarian cancer is usually associated with a rather poor prognosis, with overall 5-year survival rates commonly less than 40%.[2]

In recent decades in Sweden, HRT has been widely used for relief of climacteric symptoms and to prevent osteoporosis. Progestins without estrogens are mainly used for the treatment of climacteric bleeding irregularities, and for the alleviation of symptoms related to benign appearing ovarian cysts. Estriol can be bought over the counter, and is mostly used for symptomatic treatment of vaginal or urethral atrophy among elderly women.[3,4]

While effectively relieving women of climacteric symptoms, use of menopausal hormones has been shown to increase risks of different types of cancer. For breast cancer, there is growing evidence that cyclically combined estrogen–progestin therapy increase risk even more than estrogens alone.[5–8] For endometrial cancer estrogens alone increase risk substantially, as do use of cyclically combined estrogen–progestins.[8–10] For epithelial ovarian cancer (EOC) estrogen without progestins, or cyclically combined estrogen–progestins therapy increases risk.[8,11,12] There are few studies on the effects of regimens of estrogens continuously combined to progestins: this type of regimen seems to increase risk of breast cancer,[5,13] has not affect[11] or increase risk[14] of EOC and to decrease[9] or have no effect[14] on risk of endometrial cancer. Most importantly, use of HRT may increase risk of coronary heart disease, venous thrombosis and stroke.[7,15–17]

To date only a few studies[18–23] have investigated the possible association between use of hormone replacement therapy (HRT) and ovarian cancer mortality or survival. On the basis of limited sample sizes, the results of these studies have been inconsistent. In the only large prospective study[19,22] postmenopausal estrogen use for 10 or more years before cohort enrolment (and cancer diagnosis) was associated with and increased risk of ovarian cancer mortality that persisted up to 29 years after cessation of use. All studies investigating HRT use following diagnosis of ovarian cancer found it to be unrelated to survival.[18,20,21,23]

Our aim in the present study was to examine whether use of HRT *before or after* diagnosis of ovarian cancer affects 5-year survival. To our knowledge, this is the first study to investigate in detail ovarian cancer survival patterns according to HRT use both *before and after* diagnosis. Since use of HRT most likely affects the risk of developing ovarian cancer,[12] it is plausible that use would also influence survival, although the underlying biological mechanisms remain unclear.

Our study was based on a follow-up of patients who previously participated in a nation wide population-based case–control study in Sweden. Our study demonstrated an increased risk of EOC among ever-users compared with never users of HRT containing estrogens opposed by sequential progestins (OR = 1.53; 95% CI = 1.15–2.05), and the highest risks were observed among those who had used this type of HRT for more than 10 years. Ever-use of estrogens continuously combined with progestins was unrelated to EOC risk (OR = 1.02; 95% CI = 0.73–1.43). Estriol, a hormone sold over the counter in Sweden and considered by many as a ''weak'' estrogen, was not associated with ovarian cancer risk.[11]

Subjects and methods

Founding case–control study

In short, women were 50–74 years of age at study enrolment, born in and residents of Sweden, and had at least one intact ovary

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(women with bilateral oophorectomy were excluded). The recruitment period extended from October 1, 1993, to December 31, 1995. Eligible case patients were previously free of ovarian malignancies and presented with a newly diagnosed, histologically confirmed, invasive or borderline epithelial ovarian tumor. Patients were identified through reports to 6 regional cancer registries that together provide a complete nationwide cancer registration.[24]

After being informed about the study by their physicians, case patients agreeing to participate signed an informed consent form before study enrolment. A total of 1,205 women with incident ovarian tumors of any histological type were reported to the regional cancer registries, and 914 patients (76%) initially agreed to participate. Of these, 8 women declined participation in the present follow-up survival study, and 1 was excluded due to the physicians' denial of access to patient records. Of the 905 remaining cases, 68 had non-EOC; 13 other gynecologic malignant tumors; 1 record revealed relapse of a previous ovarian cancer diagnosed in 1991; 5 were intestinal cancers; 2 were benign tumors and 17 were described as cancers of the abdomen and peritoneum, according to pathological reevaluation during the patient's treatment in the clinics. The final study population consisted of 799 women with ovarian cancer, of which 150 had borderline epithelial ovarian tumors (BOT) and 649 invasive EOC. The histological classification was based on pathology reports alone.

Exposure data were collected through mailed self-administered questionnaires that covered demographic, medical, gynecological, reproductive and lifestyle factors including questions on height, weight, diet, physical activity, heredity, previous disease, gynecological surgery, pregnancies, births, menstruations and number of visits to gynecologists (prior to diagnosis). In 50% of the cases, the requested information was supplemented with a telephone interview to further enhance the accuracy of information attained. Detailed information pertaining to HRT and oral contraceptives was obtained. To facilitate the recall of oral contraceptives and HRT use, the questionnaire showed pictures of all the HRT brands commercially available in Sweden beginning in the 1950s.

Present cohort study and follow-up

All information on HRT use before cancer diagnosis was obtained through the initial questionnaire pertaining to exposure data, answered at enrolment in the founding case–control study.[11] The HRT exposure variables were classified as estrogen only (ERT—medium potency estrogens, *i.e.* conjugates estrogens, estradiol and other synthetic estrogens without added progestins); estrogens with progestins combined cyclically ($<$16 days/cycle, most commonly 10 days/cycle) or continuously ($\geq$19 days/cycle, most commonly 28 days/cycle). Information was also obtained on low potency estrogens (oral or vaginal estriol, dienestriol or low dose estradiol [25 μg/day]). In addition, information was available on progestin only therapy used in the treatment of perimenopausal bleeding irregularities and for the alleviation of symptoms related to benign appearing ovarian cysts. For HRT treatment, women were categorized as never users, exclusive users of only one HRT regimen and nonexclusive users who over time had taken more than one type of HRT. We calculated duration and recency of HRT use separately for each type of regimen (*i.e.* estrogens only, estrogens combined with progestins cyclically, estrogens combined with progestins in a continuous way and overall estrogens combined with progestins) and overall duration and recency of use for any type(s) of HRT taken. We categorized duration of use as never users; less than or equal to 3 years of use and greater than 3 years. All exposures were censored after an index date, which was defined as 3.0 months before the date of diagnosis for each patient. Women who used any type of HRT at the index date were defined as current users. Former users were all other users that were not current users.

Finally, we looked at the combined effects of duration and recency of any HRT treatment received by patients. This combined variable was classified as never users at baseline; current users and former users of shorter or longer duration ($\leq$3, $>$3 years). We could only consider these combined overall effects for women who had complete information for both, duration and recency of HRT use. Missing information was encountered when some women recalled HRT use, but not the specific duration or recency of use.

Other relevant data obtained from the initial questionnaires included socioeconomic status, duration of use of oral contraceptives, body mass index (BMI—defined as weight in kilograms divided by height in meters squared), smoking status 1 year prior to diagnosis, parity, age at menarche and menopause, history of tubal ligation and a family history of ovarian cancer in the mother or sister of the patient.

Additional patient data required for the present follow-up survival study included information on use and duration of HRT *after* diagnosis, and detailed clinical information on tumor characteristics, treatment modalities, recurrence and progression of the disease. Such data was abstracted from medical records by visits to 7 regional departments of gynecologic oncology, where all cases of ovarian cancer, with very few exceptions, are referred for treatment. For completion of the records, the referring local departments of gynecology and obstetrics in all 52 departments in hospitals throughout Sweden were visited in years 2000 and 2001. For this purpose, 2 oncology nurses were specifically trained for data abstraction. The information in the medical records was compiled into a comprehensive abstracting form with a manual for standardization of the data retrieval. Furthermore, an administrative database was constructed to facilitate the tracking of data sources and flow of information from the various hospitals.

Exposure information pertaining to HRT use *after* diagnosis was recorded on ever/never use, start and stop dates of treatment and if HRT treatment was ongoing at the time of data abstraction. If nothing was specifically stated in the patients' medical records about prescriptions of any type of HRT, it was recorded in the abstracting form as ''not stated.'' After consultation with local gynecological oncologists, we reclassified ''not stated'' as ''not users,'' since HRT are only sold or used under medical prescription in Sweden (except for low potency estrogens), and the absence of a prescription in the medical record of a cancer patient means with great certainty that HRT was not used. Information was *not* available for all patients about specific types of HRT prescribed *after* diagnosis, or if patients changed types of HRT. We categorized duration of use of HRT *after* diagnosis as never users; less than 1 year; 1–2 years and greater than 2 years. Information on prognostic factors included FIGO (International Federation of Gynecology and Obstetrics) stage (I, II, III, IV), WHO grade of differentiation (well differentiated, moderately differentiated and poorly differentiated), tumor size at diagnosis, residual tumor size, the presence of multiple simultaneous primary tumors, histological subtype (serous, mucinous, endometrioid, clear cell, undifferentiated, others), reasons for primary diagnosis (gynecological routine examination, the presence of symptoms, and other reasons) and treatment.

Abstraction of medical record data was successful for 770 women in the cohort (96% of all cases in the original study) that included the retrieval of 1,095 medical records (since each patient could have more than one medical record) in different clinics or hospitals. Information was successfully retrieved in 99.9% of these cases concerning FIGO stage, 75% for tumor grade, 100% for treatment and in 99% concerning follow-up of the events indicating recurrence in the 5-year follow up period. A gynecological oncologist double-checked the abstracted information for inconsistencies, incompleteness or doubtful information, which was then verified against the original records or with the treating physicians.

We considered as outcomes overall mortality (death from any cause) and cause specific mortality (death from ovarian cancer or related causes). We did not evaluate ovarian cancer recurrence in the present report.

Date and cause of death information was obtained through record linkage with a nationwide Cause of Death Register updated through December 31, 2002, using the individually unique national registration number. For consistency it was decided to use information on cause of death from the register and not the abstracted medical records data. The agreement between these 2 sources was 99.1%. Causes of death were classified according to The International Statistical Classification of Diseases and Related Health Problems (ICD) versions 9 and 10.

Causes of ovarian cancer deaths were defined as women dying from ovarian cancer (ICD-9 codes 183.0-183.9) and C56 (ICD-10) or having ''malignant tumor in the ovary'' as the underlying cause of death. Related causes of death were considered as death from possibly metastatic tumors, such as unspecified location of malignant tumor in the peritoneum ($n = 1$), several malignant tumors with different points of origin ($n = 1$), tumor of uncertain nature in the ovary ($n = 1$) and malignant tumor in the uterus except isthmus uteri ($n = 2$).

The Ethics Committees of the Karolinska Institutet, Sweden, approved the study.

Statistical methods

Overall survival time was defined as the time interval from the date of ovarian cancer diagnosis to the date of death from any cause. Cause-specific survival was defined as the time interval from the date of diagnosis to the date of death from ovarian cancer or related causes. All patients were followed for 5 years or until death. The end of follow-up for the analyses presented here was set to December 31, 2002.

STATA® Version 8.2 was used for data analyzes. Contingency tables and univariate summary measures were produced to describe the patients at the beginning of follow-up, in term of the hormone exposure variables and prognostic factors. Kaplan–Meier estimates and graphs were produced to describe the overall and stratified survival distribution. The log rank test was used to assess whether there was any statistical difference and those variables with a p-value less than 0.25 were considered eligible to be included in the multivariate analysis.[25]

In an initial step prior to multivariate analyses, graphical assessments were performed for all covariates to assess the proportionality assumptions.

The Cox proportional hazard regression model was subsequently fit to estimate the effect of HRT and its derived variables, adjusted by variables found to be important in the first part of the analysis: age, FIGO stage, WHO grade of differentiation and histological subtype of tumor. We used the likelihood ratio test based on the partial likelihood to assess the independent effect of the explicative variables as well as the interaction terms. Appropriated goodness-of-fits and diagnostic measures, together with graphic methods, based on the Schoenfeld and Martingales residuals[26] were ultimately produced to assess the appropriateness of the models chosen, such as the proportionality assumption underlying the Cox model.

Tests of association used in the analyses to test significance between groups were the likelihood ratio test and Pearson's χ^2 tests.

Results

Among the 799 patients studied, 347 died from ovarian cancer or related causes and 22 died for other reasons after 5 years of follow-up. There were 649 cases of EOC and 150 cases with BOT, and they were analyzed separately.

Invasive EOC

After 5 years of follow-up, 290 (45%) of the 649 women with EOC were alive, and 359 dead: 344 deaths were due to ovarian cancer and 22 were due to other causes. In the following only results from the *cause-specific analyses* will be reported in detail, as they did not differ substantially from the overall mortality.

As expected, elderly women had a poorer survival, while use of oral contraceptives, BMI before diagnosis, smoking, age at menarche and menopause, parity, family history of ovarian cancer and tubal ligation were unrelated with survival, as shown in Table I.

A significantly better survival was evident in women who were diagnosed through their routine gynecological examination (hazard ratio, HR = 0.47, 95% CI = 0.29–0.76), compared to women that were diagnosed primarily through the presentation of symptoms. The highest probability of death was observed in women with a FIGO stage IV tumor (HR = 13.82, 95% CI = 8.99–21.26) relative to those presenting with a FIGO stage I tumor. Compared to women with well-differentiated tumors (according to the WHO grade of differentiation classification), women with moderately and poorly differentiated tumors had a worst survival (HR = 2.46, 95% CI = 1.49–4.06; and HR = 3.94, 95% CI = 2.46–6.31, respectively). For residual tumor size after primary surgery, women with tumors greater than 2 cm had 1.43 (95% CI = 0.99–2.08) times the probability of dying from ovarian cancer compared to women with a residual tumor size less than 2 cm. However, the greatest probability of death was observed in women whose tumors were nonmeasurable due to difficulties in quantifying the residual tumor mass at time of surgery (HR = 2.32, 95% CI = 1.57–3.44). The majority of the ovarian tumors was of serous subtype ($n = 326$), followed by endometrioid ($n = 168$), mucinous ($n = 62$) and other types ($n = 79$). Women with mucinous type of ovarian tumor had a slightly better survival than women with other histological types of EOC (Table I).

Use of HRT before EOC diagnosis

In total, HRT was used by 166 women (26%) before EOC diagnosis. Overall, there were no clear differences in EOC survival between women that had used any type of HRT compared to never users (multivariate adjusted HR = 0.83; 95% CI = 0.65–1.08) (Table II).

Use of different types of HRT before diagnosis (exclusive users of estrogen, estrogens with cyclically added progestins, estrogens with continuously added progestins and combined estrogens and progestins) was not associated with EOC survival. Duration or recency of use of HRT before diagnosis—considered separately or in combination—were not associated with survival (Table II). The majority of women (68%) who had ever used HRT had done so in the year preceding ovarian cancer diagnosis.

There was no clear difference in risk of death between exclusive and nonexclusive users of any type of HRT. However, the patterns observed for estrogen only (nonexclusive use), estrogen with continuously added progestins (both for exclusive and nonexclusive use) and combined estrogen–progestin (nonexclusive use) are suggestive of better survival in users, albeit nonsignificant (Table II).

Use of estriol (administrated orally or vaginally) before diagnosis was rare, and not associated with EOC survival (Table II). In the following we will present results on HRT use overall and according to different combinations disregarding use of estriol.

The proportion of HRT users and nonusers before diagnosis was similar among women being diagnosed with different tumor FIGO stages (Stage I = 29% users, 28% nonusers; Stage II = 13% users,11% nonusers; Stage III = 46% users, 46% nonusers; Stage IV = 12% users, 14% nonusers) WHO grade of differentiation (well differentiated = 13% users, 14% nonusers; moderately differentiated = 26% users, 26% nonusers; poorly differentiated = 54% users, 51% nonusers, not stated = 8% users, 9% nonusers) and histological ovarian tumor subtypes (Table II). Diagnosis through routine gynecological examination was more frequent among users of HRT compared to never users (13.9–7.1%, respectively), notably for diagnosis of highly differentiated FIGO stage I tumors.

TABLE I – INVASIVE EOC SURVIVAL 5 YEARS AFTER DIAGNOSIS ACCORDING TO DIFFERENT CHARACTERISTICS OF THE STUDY POPULATION (ONLY DEATHS DUE TO OVARIAN CANCER ARE PRESENTED)

	No. cases (total 649)	Ovarian cancer deaths (total 344) [*n* (%)]	Median survival (years)	Age adjusted 5 year survival (% alive after 5 years)	HR or risk or death 5 years after EOC diagnosis (95% CI) age adjusted
Age at diagnosis (years)					
50–54	141	70 (50)	>5	50	1.00 (reference)
55–59	134	57 (42)	>5	57	0.77 (0.55–1.10)
60–64	118	64 (54)	4.25	45	1.11 (0.79–1.55)
65–69	125	76 (61)	3.21	38	1.35 (0.97–1.86)
70–75	131	77 (59)	3.35	40	1.31 (0.95–1.81)
Reasons for diagnosis					
°Routine examination	58	18 (31)	>5	68	0.47 (0.29–0.76)
°Symptoms	572	317 (55)	3.96	44	1.00 (reference)
°Other reasons	15	7 (47)	4.61	47	0.83 (0.39–1.76)
°Not stated	4	2 (50)	1.90	50	1.00 (0.25–4.01)
FIGO stage					
I	185	29 (16)	>5	84	1.00 (reference)
II	74	27 (36)	>5	63	2.60 (1.54–4.40)
III	301	207 (69)	2.83	30	6.87 (4.64–10.17)
IV	89	81 (91)	1.96	9	13.82 (8.99–21.26)
WHO grade of differentiation					
Well differentiated	89	19 (21)	>5	78	1.00 (reference)
Moderately differentiated	170	78 (46)	>5	54	2.46 (1.49–4.06)
Poorly differentiated	333	216 (65)	3.17	34	3.94 (2.46–6.31)
Not stated	57	31 (54)	3.92	45	3.27 (1.84–5.80)
Residual tumor size at 1st surgery[1]					
<2 cm	86	54 (63)	3.62	37	1.00 (reference)
>2 cm	76	56 (74)	2.44	25	1.43 (0.99–2.08)
Nonmeasurable	53	47 (89)	1.68	11	2.32 (1.57–3.44)
Not stated	173	127 (73)	2.53	26	1.40 (1.02–1.94)
Histological subtype					
Serous	326	184 (56)	4.03	42	1.00 (reference)
Mucinous	62	22 (35)	>5	63	0.57 (0.37–0.89)
Endometrioid	168	80 (48)	>5	52	0.78 (0.60–1.01)
Others	79	49 (62)	3.24	38	1.20 (0.88–1.64)
Unclassified histology	14	9 (64)	2.76	36	–
Any HRT use before diagnosis[2]					
Never	467	251 (54)	4.03	46	1.00 (reference)
Ever	166	82 (49)	>5	50	0.92 (0.71–1.18)
No information	16	11 (69)	2.76	31	–
HRT use after diagnosis[1]					
Never	499	293 (59)	3.44	41	1.00 (reference)
Ever	150	51 (34)	>5	66	0.46 (0.34–0.63)
Use of oral contraceptives[3]					
Never	433	240	3.97	45	1.00 (reference)
Ever	174	83	>5	51	0.89 (0.67–1.17)
BMI before diagnosis[3]					
<20	8	5	2.46	39	1.34 (0.55–3.27)
20–24.99	298	157	4.43	46	1.00 (reference)
25–29.99	223	119	4.12	46	1.00 (0.79–1.27)
30+	81	41	4.92	50	0.93 (0.66–1.30)
Smoking[3]					
Never	400	224	3.88	44	1.00 (reference)
Current	111	51	>5	50	0.81 (0.60–1.11)
Former	120	58	>5	50	0.84 (0.63–1.12)
Age at Menarche					
≤13 years	341	184	4.37	46	1.00 (reference)
>13 years	308	160	4.25	47	0.97 (0.78–1.20)
Age at Menopause					
≤50	394	212	4.51	46	1.00 (reference)
>50	255	132	4.12	46	0.97 (0.78–1.20)
Parity[3]					
0	121	69	3.51	42	1.00 (reference)
1–2	356	174	>5	51	0.78 (0.59–1.03)
3–4	142	83	3.68	41	1.02 (0.74–1.41)
5+	16	9	4.47	34	0.73 (0.36–1.45)
Family history ovarian cancer (mother or sister)					
No	554	284	4.61	48	1.00 (reference)
Yes	37	26	3.58	29	1.39 (0.93–2.12)
Do not know	40	22	4.43	41	1.00 (0.64–1.54)
Tubal ligation[3]					
No	620	328	4.37	46	1.00 (reference)
Yes	15	7	>5	47	0.88 (0.42–1.87)

[1]Information available for 388 patients (284 deaths, or 73%) who underwent surgery.–[2]HRT, hormone replacement therapy (medium potency estrogens with or without progestins) before diagnosis of cancer, regardless of estriol use.–[3]Missing information for oral contraceptives 42 patients (21 deaths), for BMI before diagnosis: 39 patients (22 deaths), smoking 18 patients (11 deaths), parity 14 patients (9 deaths); tubal ligation: 14 patients (9 deaths).

TABLE II – USE OF HORMONE REPLACEMENT THERAPY (HRT) BEFORE THE DIAGNOSIS OF INVASIVE EPITHELIAL OVARIAN CANCER AND SURVIVAL

	Total no. of cases (n = 633)	Deaths [n (%)] total 333 (53%)	Age adjusted median survival (years)	Age adjusted 5 year survival (%)	Hazard ratio (95% CI) age adjusted	Hazard ratio (95% CI) (adjusted age, FIGO stage and WHO grade)
Any HRT[1] use						
Never	467	251 (54)	4.29	46	1.00 (reference)	1.00 (reference)
Ever	166	82 (49)	4.79	49	0.92 (0.71–1.18)	0.83 (0.65–1.08)[2,3]
Duration of use ≤3 years	86	44 (51)	4.03	42	1.00 (0.72–1.39)	0.87 (0.62–1.21)
Duration of use >3 years	72	35 (49)	>5	51	0.87 (0.61–1.24)	0.79 (0.56–1.13)
Current users	108	49 (45)	>5	53	0.87 (0.63–1.20)	0.75 (0.54–1.03)
Former users	52	31 (60)	4.12	43	1.05 (0.72–1.52)	1.01 (0.69–1.47)
Estrogen only treatment (ERT)[1,4]						
Exclusive users	33	18 (55)	3.89	48	0.93 (0.58–1.51)	–[5]
Nonexclusive users	27	10 (38)	>5	64	0.57 (0.30–1.08)	
Duration of use ≤3 years[6]	27	13 (48)	>5	52	0.84 (0.48–1.47)	
Duration of use >3 years[6]	28	13 (46)	>5	56	0.72 (0.41–1.27)	
Current users[6]	25	11 (44)	4.25	48	0.78 (0.42–1.46)	
Former users[6]	30	15 (50)	>5	78	0.70 (0.41–1.20)	
Estrogens and cyclically added progestins[1]						
Exclusive users	54	28 (52)	>5	52	1.12 (0.74–1.69)	–[5]
Nonexclusive users	29	11 (37)	>5	61	0.64 (0.35–1.17)	
Duration of use ≤3 years[6]	49	21 (43)	>5	57	0.83 (0.52–1.31)	
Duration of use >3 years[6]	28	15 (54)	4.44	48	1.10 (0.65–1.86)	
Current users[6]	50	23 (46)	>5	56	0.95 (0.61–1.48)	
Former users[6]	27	13 (48)	>5	52	0.89 (0.51–1.56)	
Estrogens and continuous combined progestins[1]						
Exclusive users	26	10 (38)	>5	57	0.68 (0.36–1.29)	–[5]
Nonexclusive users	27	11 (41)	>5	59	0.65 (0.36–1.20)	
Duration of use ≤3 years[6]	33	13 (39)	>5	58	0.72 (0.41–1.26)	
Duration of use >3 years[6]	16	5 (31)	>5	70	0.48 (0.20–1.16)	
Current users[6]	34	14 (41)	>5	57	0.74 (0.43–1.27)	
Former users[6]	15	4 (27)	>5	75	0.41 (0.15–1.11)	
Combined estrogens and progestins (cyclically or continuously)[1]						
Exclusive users	80	38 (48)	>5	53	0.95 (0.67–1.36)	–[5]
Nonexclusive users	39	16 (41)	>5	59	0.67 (0.40–1.11)	
Duration of use ≤3 years[6]	68	29 (43)	>5	52	0.80 (0.54–1.19)	
Duration of use >3 years[6]	43	20 (46)	>5	58	0.88 (0.56–1.39)	
Current users[6]	81	37 (46)	>5	54	0.90 (0.63–1.29)	
Former users[6]	30	12 (40)	>5	59	0.68 (0.38–1.03)	
Estriol						
Vaginally						
Never	546	290 (53)	4.36	46	1.00 (reference)	–[5]
Ever	86	43 (50)	4.92	50	0.86 (0.62–1.18)	
Orally						
Never	560	294 (53)	4.49	47	1.0 (reference)	–[5]
Ever	72	39 (54)	4.03	44	0.91 (0.65–1.29)	
Serous tumors[1]						
Never used HRT	239	142 (59)	3.56	40	1.00 (reference)	1.00 (reference)
Ever used HRT	87	42 (48)	5.0	50	0.74 (0.52–1.06)	0.69 (0.48–0.98)[7]
Current users (all)	58	29 (50)	3.80	42	0.83 (0.54–1.26)	0.72 (0.47–1.09)
Former users	26	12 (46)	>5	53	0.65 (0.36–1.17)	0.61 (0.34–1.11)
Mucinous tumors[1]						
Never used HRT	46	16 (35)	>5	64	1.00 (reference)	1.00 (reference)
Ever used HRT	16	6 (38)	>5	61	1.13 (0.43–2.97)	1.94 (0.52–7.21)[2]
Current users	10	1 (10)	>5	98	0.19 (0.02–1.51)	0.60 (0.06–5.92)
Former users	4	4 (100)	–[8]	–[8]	6.43 (1.72–23.99)	3.06 (0.39–23.70)
Endometrioid tumors[1]						
Never used HRT	124	58 (47)	>5	53	1.00 (reference)	1.00 (reference)
Ever used HRT	42	20 (48)	>5	52	1.05 (0.63–1.74)	1.10 (0.65–1.85)[2]
Current users	28	12 (43)	>5	56	1.00 (0.54–1.87)	0.92 (0.49–1.75)
Former users	13	8 (61)	3.3	33	1.24 (0.59–2.62)	2.05 (0.94–4.46)
Other tumors[1]						
Never used HRT	58	35 (60)	4.26	40	1.00 (reference)	1.00 (reference)
Ever used HRT	21	14 (67)	4.79	33	1.26 (0.66–2.39)	1.04 (0.54–2.02)[2]
Current users	12	7 (58)	>5	42	1.27 (0.52–3.12)	1.03 (0.39–2.72)
Former users	9	7 (62)	4.20	38	1.24 (0.55–2.80)	1.05 (0.45–2.42)

[1]HRT, hormone replacement therapy (medium potency estrogens with or without progestins), disregarding use of estriol.–[2]Inclusion of the variable ''HRT after diagnosis'' in this analysis did not change the risk estimates meaningfully).–[3]Addition in the model of an indicator variable for histological type entail an HR of 0.84 (95% CI = 0.65–1.08).–[4]ERT, estrogen replacement therapy.–[5]Adjustment for FIGO stage, and WHO grade was not possible due to small numbers.–[6]Exclusive and nonexclusive users combined.–[7]Inclusion of HRT after diagnosis in this model entail an HR = 0.74 (95% CI = 0.52–1.08).–[8]Lack of data due to few observations.

In Table II we also show the multivariate modeling for hazard estimates including indicator variables for stage and grade of tumor differentiation according to different aspects of HRT use. Except for an indication of better 5-year survival among users of HRT diagnosed with serous tumor (HR = 0.69, 95% CI = 0.48–0.98 after controlling for FIGO stage and WHO degree of differentiation at diagnosis) no evidence of better survival was observed. When we added an indicator variable for HRT use after

TABLE III – MULTIVARIATE SURVIVAL MODELING OF EOC ACCORDING TO USE OF HRT AFTER DIAGNOSIS, TEMPORAL RELATION OF HRT USE TO DIAGNOSIS AND HRT OVERALL DURATION OF USE AFTER DIAGNOSIS

HRT	No Cases	Deaths [*n* (%)]	HR (95% CI)[1]	HR (95% CI)[2]
Any HRT use after diagnosis[3]				
Never	499	293 (59)	1.00 (reference)	1.00 (reference)
Ever	150	51 (34)	0.46 (0.34–0.63)	0.57 (0.42–0.78)
Duration use <1 year	13	5 (38)	0.59 (0.24–1.44)	0.61 (0.25–1.47)
Duration use 1–2 years	8	6 (75)	1.16 (0.51–2.63)	1.18 (0.51–2.70)
Duration use >2 years	9	4 (44)	0.55 (0.20–1.48)	0.44 (0.16–1.19)
Current users at time of data abstraction	120	36 (30)	0.41 (0.29–0.58)	0.55 (0.38–0.79)
Former users at date of data abstraction	30	15(50)	0.64 (0.54 0.76)	0.75 (0.62–0.89)
Any HRT use in relation to diagnosis[4]				
Never users before or after diagnosis	395	230 (58)	1.00 (reference)	1.00 (reference)
Users before diagnosis, never users after diagnosis	92	54 (59)	1.02 (0.76–1.37)	0.92 (0.68–1.25)
Never users before diagnosis, users after diagnosis	72	21 (29)	0.39 (0.25–0.61)	0.55 (0.35–0.87)
Users before and after diagnosis	74	28 (38)	0.55 (0.37–0.82)	0.59 (0.39–0.87)
Serous tumors				
Never users after diagnosis	244	151 (62)	1.00 (reference)	1.00 (reference)
Ever users after diagnosis	82	33 (40)	0.52 (0.35–0.77)	0.65 (0.44–0.96)
Never users before or after diagnosis	197	126 (64)	1.00 (reference)	1.00 (reference)
Users before diagnosis, never users after diagnosis	47	25 (53)	0.76 (0.50–1.18)	0.69 (0.45–1.08)
Never users before diagnosis, users after diagnosis	42	16 (38)	0.47 (0.28–0.79)	0.63 (0.37–1.07)
Users before and after diagnosis	40	17 (42)	0.52 (0.31–0.88)	0.57 (0.34–0.96)
Mucinous tumors[5]				
Never users after diagnosis	45	18 (40)	1.00 (reference)	1.0 (reference)
Ever users after diagnosis	17	4 (23)	0.44 (0.13–1.46)	1.29 (0.28–6.14)
Users before and after diagnosis	9	2 (22)	0.48 (0.09–2.37)	2.71 (0.35–20.91)
Endometrioid tumors[5]				
Never users after diagnosis	129	70 (54)	1.00 (reference)	1.0 (reference)
Ever users after diagnosis	39	10 (26)	0.40 (0.21–0.79)	0.54 (0.28–1.06)
Users before and after diagnosis	20	8 (40)	0.73 (0.35–1.53)	0.90 (0.43–1.92)
Other tumors[5]				
Never users after diagnosis	70	46 (66)	1.00 (reference)	1.0 (reference)
Ever users after diagnosis	9	3 (33)	0.36 (0.11–1.19)	0.23 (0.06–0.91)
Users before and after diagnosis	5	1 (20)	0.25 (0.03–1.86)	0.12 (0.02–1.04)

[1]Hazard ratio estimates adjusted for age at diagnosis.–[2]Adjusted for age, FIGO stage and WHO grade. NB: additional adjustment for histological types in the analysis of all cancers combined did not entail meaningfully different results.–[3]Includes users and nonusers of any HRT before diagnosis.–[4]Only for women without missing data for use of any HRT before and after diagnosis.–[5]There was no effect of duration of use for the different histological subtypes.

diagnosis in this analysis, the confidence intervals (CIs) of the HR included unity (HR 0.74, 95% CI 0.52–1.08). The analysis of histological subtypes—including a detailed analysis of serous tumors—according to duration of use of HRT before diagnosis (never, <3 years, 3 or more years of HRT use) and recency of useanalyzed separately or in combination—did not reveal any clear patterns of association We also added an indicator variable for histological type in the models for all ovarian cancer together in relation to all types of HRT grouped, and the results were basically unchanged (Table II).

Use of HRT after diagnosis and EOC

Women who were prescribed HRT *after* tumor diagnosis (44%) were all below 60 years of age. Users of HRT *after* an EOC diagnosis were at a significantly lower risk of dying compared to never users after diagnosis (multivariate HR = 0.57, 95% CI = 0.42–0.78 when adjusting for age at diagnosis, tumor stage and grade of differentiation; Table III). Results did not change substantially when an indicator variable for the histological type was added in the models of all invasive ovarian cancers considered together (HR = 0.61; 95% CI = 0.45–0.84). The better survival was observed for women with serous tumors (multivariate HR = 0.65; 95% CI = 0.44–0.96) and other tumors (HR = 0.23, 95% CI = 0.06–0.91) but not clearly for women with mucinous or endometrioid tumors (Table III).

The finding of a significantly better survival was observed both amongst women who were current users and former users of HRT at time of data abstraction from medical records (Table III). Because of small numbers, this analysis was only possible when considering all tumors together.

Combined use of HRT before or after diagnosis

We also compared never users of HRT both before and after diagnosis with:

a. Users before diagnosis, never users after diagnosis,
b. Never users before diagnosis, users after diagnosis and
c. Users before and after diagnosis.

The Kaplan–Meier 5-year survival curves for the combination of use of HRT before and after EOC diagnosis are presented in Figure 1.

Women who were users of HRT after diagnosis had a lower risk of death, regardless of use of HRT before diagnosis (Table III). We repeated these analyses for the different histological subtypes of ovarian tumors. Women diagnosed with a serous tumor that had used HRT both before and after diagnosis had a lower risk of dying within 5 years of diagnosis. The use of HRT both before and after diagnosis did not entail survival advantage for women with mucinous, endometrioid and other ovarian tumors. However, the number of patients in each subgroup was relatively small, making estimates unstable in some subgroups (Table III).

The mean age of women who never used HRT (63.72 years; SD 7.02) was slightly higher than of users of HRT before diagnosis only (61.58 years; SD 7.24), after diagnosis only (58.81 years, SD 7.75), and both before and after diagnosis (58.11; SD 6.26). There was no difference in the proportion of women using chemotherapy among these groups of women. Use of HRT before EOC diagnosis was more common among white-collar workers (above 40%) than among blue-collar workers (about 25%), but use of HRT after diagnosis did not differ substantially after diagnosis according to social class (19% among blue-collar workers and 25% among

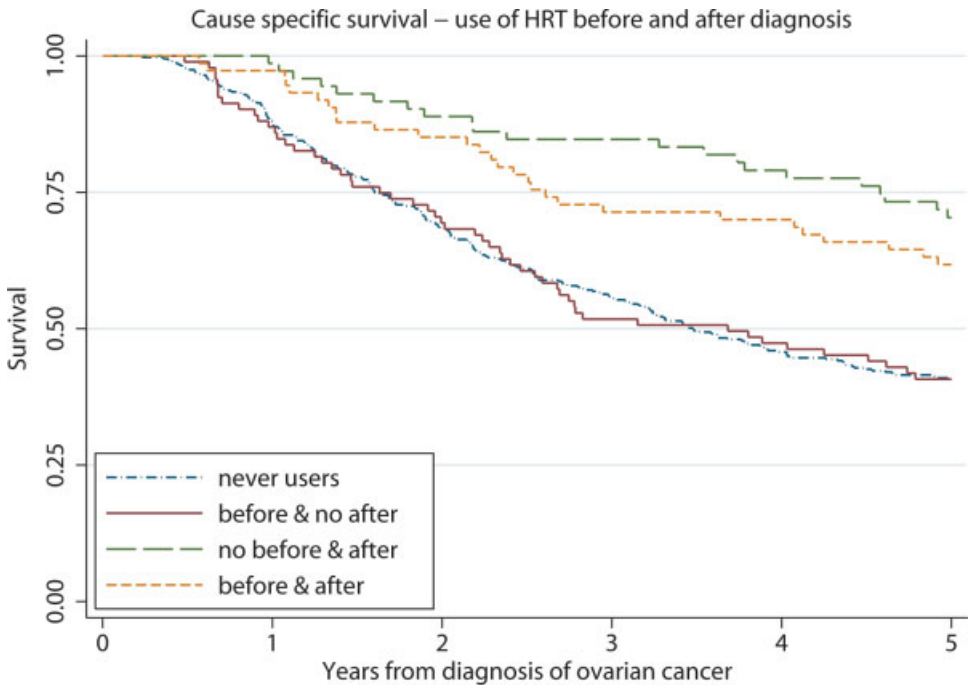

Figure 1 – Five-year EOC cause specific survival according to use of HRT before and after ovarian cancer diagnosis.

white-collar workers). However, the addition of indicator variables for socioeconomic status in the models already including age (as a continuous variable) and multivariate models with FIGO stage and WHO grade did not alter risk estimates for survival according to HRT use after diagnosis at all.

Borderline ovarian tumors and use of HRT before and after diagnosis

Among 150 women with BOT, 140 (93%) survived at least 5 years: 10 women died, 3 of them of ovarian cancer and 7 by other causes. Information on use of HRT before diagnosis was available for 141 women: 64 (45%) never used HRT before or after diagnosis; 29 (21%) used HRT before diagnosis, 72 (51%) used HRT after diagnosis. There were 24 (17%) women who used HRT both before and after diagnosis, 48 women (34%) used after diagnosis only and 5 women (4%) used HRT before diagnosis only. Of the 10 deaths for any cause occurring among women with BOT, only 1 had used HRT before diagnosis. The 3 deaths due to ovarian cancer among women diagnosed of BOT none had used HRT before or after diagnosis. The overall mean survival time for women with BOT was above 5 years.

Discussion

Invasive EOC

HRT before diagnosis. Overall, we found *no clear differences* in EOC survival among women who used *any type of HRT before* cancer diagnosis, and those who never used it. Similarly, use of estriol *before* cancer diagnosis was unrelated to EOC survival. There was some indication of a better survival for users of HRT before diagnosis of a *serous* EOC, although without a clear pattern according to duration or recency of use. For *endometrioid* EOC—for which results from a few studies have suggested a causal association with HRT[27]—we found no evidence of an association between HRT use before diagnosis and survival. Similarly, no indication of better survival was observed for mucinous or other histological subtypes of EOC and HRT use before diagnosis.

Women who use HRT are likely to visit their doctors more regularly than women who do not use these drugs, either to get prescriptions or to undergo routine examinations. Thus, they may have more opportunities to have malignancies—including ovarian tumors—detected at early stages by routine examinations. This was indeed what we observed in our study, where routine examination was the main mode of detection of tumors of high grade and early stages. Therefore, we adjusted our analysis for FIGO tumor stage and WHO grade. However, HR estimates for HRT use before cancer diagnosis remained virtually unaffected by these adjustments.

Our results do not corroborate findings from the Cancer Prevention Study II,[19,22] which suggested a worsened prognosis among women using estrogens (without added progestins) for over 10 years. We found no such effect, regardless of duration or recency of estrogen use before ovarian cancer diagnosis. However, the number of women in our study that had used estrogens for more than 3 years was rather small (28 cases/13 deaths), and we could not perform analysis for longer durations of use of estrogens only. It is plausible that longer duration of use could entail increased mortality risk. In the US the most common type of estrogens used before data collection of the Cancer Prevention Study II were conjugated equine estrogens, while in Sweden synthetic compounds such are estradiol 17-B and estradiol valerate were predominant. These compounds could, in theory, affect ovarian cancer survival differently. Moreover, the Cancer Prevention Study II had a larger number of ovarian cancer deaths (n = 944) than our study (n = 344), and had a very different study design: a large cohort answers a questionnaire including information on estrogen use in the early 1980s, and vital status was accessed in 1996. In our study the HRT information was collected a decade after, and most women in Scandinavian reported using combined estrogen/progestin regimens, and use of estrogens without progestins was rare. In the American study the history of hormone use was assessed at cohort enrolment, and therefore information on estrogen use in very recent years immediately preceding ovarian diagnosis were not reported. Our study population in Sweden were ovarian cancer cases identified in a nation-wide, population based case–control study, where information on lifelong use of different types of HRT was collected shortly after diagnosis, complemented by abstraction of medical records for use of HRT after diagnosis. Thus, the data retrieval methods were quite different between the 2 studies, making then differently predisposed to bias. Our find-

ings of *no association* between use of specific hormonal preparations before ovarian cancer diagnosis—*i.e.*, combined estrogen–progestin hormone replacement, use of estriol or progestins only—and survival are novel.

HRT after diagnosis. Among gynaecologic oncologists in Sweden and elsewhere, estrogens without progestins have been the most common type of hormone therapy prescribed among women diagnosed with ovarian cancer.[28] We found *an indication of better survival among women who used HRT after* diagnosis, particularly among patients with *serous and other* histological types, and a suggestion of better survival among endometrioid tumors too. We took into account that younger women were more likely to be prescribed HRT *after* diagnosis (mean age below 60 years for users, and above 60 years for nonusers), and conducted age adjusted multivariate analysis using 1 year age categories, besides including stage and grade in the models. We cannot, however, exclude that these findings may reflect a subtle selection process that could not be accounted for in our analysis. Patients with the best overall health status and prognosis as perceived by the treating physician, for example those with a radical and complete surgery including hysterectomy and bilateral salpingo-ophorectomy with omentectomy, were more likely to be prescribed HRT, although there was no difference in HRT prescription after diagnosis according to chemotherapy use. However, the adjustment for age at diagnosis, FIGO stage and WHO grade of the tumors, which are the most important known indicators of survival, did not affect HR estimates meaningfully. Use of HRT after diagnosis was rather similar in blue-collar and white-collar workers, and the inclusion of an even more detailed socioeconomic variable in the statistical models had no impact on the risk estimates. This indicates that socioeconomic status is note explaining the better survival among users of HRT after diagnosis.

The biological mechanisms through which HRT used after ovarian cancer diagnosis may act to influence tumor growth, and ultimately survival remains unclear.

Our findings on use of HRT *after* ovarian cancer diagnosis contradict a few previously published studies. In the observational study by Eeles *et al*.[18] investigating HRT use *after* ovarian cancer surgery in London, no statistically significant difference in disease free survival was found between HRT users (about half having used estrogens only and half estrogens combined with progestin) and nonusers. Our study differs from Eeles' on the age of the patients: below 50 years in Eeles *et al*., and between 50 and 74 years in our study. Moreover, the way the data was analyzed by Eeles *et al*. excluded deaths occurring in the first year of follow-up (the most severe cases which probably would not have had the chance to receive HRT after diagnosis), as we included those in our analysis.

In a observational study in Slovenia, Ursic Vrscaj *et al*.[23] selected 24 patients with a diagnosis of ovarian serous cystadenocarcinoma who were treated with HRT (16 receiving estrognes only and 8 receiving combined estrogens and progestins) *after* primary surgical treatment. Each such patient was compared with 2 control patients that did not receive HRT. The estimated risk of death between the 2 patient groups was not statistically different from each other. Limitations of our study include its design (a ''randomization'' backwards), and the very small number of patients.

Guidozzi and Daponte[20] randomized 130 patients younger than 59 years with invasive epithelial ovarian carcinoma to continuous oral conjugated equine estrogen or no supplementation, and followed up the patients for a minimum of 48 months. The differences in overall survival between the 2 groups were not statistically significant, although there was some indication of better survival in the estrogen users group.

Borderline ovarian tumors

Because of small numbers we were only able to perform a basic descriptive analysis of BOT. Almost all (94%) women with BOT were alive after 5 years follow-up, and there was no indication that use of HRT—*before or after* diagnosis—was associated with the few occurring deaths among women with BOT. We have been unable to identify other published studies with which to compare these findings.

In addition to its large size, our study has a number of strengths including a nationwide, population-based prospective design, reliable and detailed ascertainment of HRT use before diagnosis, complete follow-up of cases and successful retrieval of medical records with details on tumor characteristics and cancer treatment, including prescription of HRT after cancer diagnosis. Furthermore, to our knowledge, it is the only study to address both, pre- and postdiagnostic exposures to HRT in relation to ovarian cancer survival in the same study population. As a result, we were able to adjust for known and hypothesized prognostic factors such as stage and grade of the tumor, and mode of diagnosis.

One limitation of the present study was the possibility of selection bias in the parent study. The main reason for nonparticipation in the parent study was patient's refusal (24%), and it is conceivable that patients with advanced stages of disease may have been less willing to participate.[11] However, all the comparisons in our study were made between women who accepted to participate, and therefore can be considered as internally valid.

Of the women who accepted to participate in the parent study, only 8 declined participation in the follow-up study, and only 1 was excluded due to physician's denial to access the patient's records. We consider unlikely that these exclusions would affect meaningfully our results.

Our patients were younger than the national average age of ovarian cancer patients. The stage distribution was shifted towards earlier stages compared to national estimates where stages III and IV are slightly more prevalent and stage I and II less prevalent than in our cohort.[29] Also, we lack detailed information on nonparticipants, thus we do not know if they differed in HRT exposures or survival compared with study participants. Cause of death in some instances could have been incorrectly recorded as due to the cancer despite other severe comorbidity. Finally, we did not have information on type of HRT use after diagnosis, although the clinical practice in Sweden is to prescribe estrogens without progestin, particularly to women who undergo hysterectomy. We consider the abstracted information from medical records that was done after ovarian cancer diagnosis as reliable, since it was checked not only by the medical personnel in the treating hospitals, but also by our oncological nurse, and double checked by the study gynaecological oncologist. All drugs prescribed to cancer patients are systematically and carefully noted in the medical records. Also, the reliability of our ascertainment of HRT use before cancer diagnosis is evidenced by the clear associations we found in studies about use of different types of HRT and cancers of the breast,[5] endometrial,[9] and ovarian cancer,[11] as well as hip fractures.[30] All these studies were carried out in Sweden using the same self-administered questionnaire for data collection, and the same group of women as controls. The associations reported in these studies are now largely accepted and well established.

Given that ovarian cancer mortality rates overall are decreasing while incidence rates seem to be stable in recent years,[31] more women are surviving for many years after a diagnosis of ovarian cancer. Thus, assessing the risk-benefit and safety of use of HRT *after* ovarian tumor diagnosis is of relevance from the patients' perspectives. Our findings indicate that use of HRT *before* ovarian tumor diagnosis does not affect survival, while HRT use *after* diagnosis *may be* associated with better survival for EOC patients. Large randomized clinical trials on use of HRT after EOC diagnosis would be needed to confirm this possible association.

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