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Hormone Therapy and Ovarian Cancer

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Context Studies have suggested an increased risk of ovarian cancer among women taking postmenopausal hormone therapy. Data are sparse on the differential effects of formulations, regimens, and routes of administration.

Objective To assess risk of ovarian cancer in perimenopausal and postmenopausal women receiving different hormone therapies.

Design and Setting Nationwide prospective cohort study including all Danish women aged 50 through 79 years from 1995 through 2005 through individual linkage to Danish national registers. Redeemed prescription data from the National Register of Medicinal Product Statistics provided individually updated exposure information. The National Cancer Register and Pathology Register provided ovarian cancer incidence data. Information on confounding factors and effect modifiers was from other national registers. Poisson regression analyses with 5-year age bands included hormone exposures as time-dependent covariates.

Participants A total of 909 946 women without hormone-sensitive cancer or bilateral oophorectomy.

Main Outcome Measure Ovarian cancer.

Results In an average of 8.0 years of follow-up (7.3 million women-years), 3068 incident ovarian cancers, of which 2681 were epithelial cancers, were detected. Compared with women who never took hormone therapy, current users of hormones had incidence rate ratios for all ovarian cancers of 1.38 (95% confidence interval [CI], 1.26-1.51) and 1.44 (95% CI, 1.30-1.58) for epithelial ovarian cancer. The risk declined with years since last use: 0 to 2 years, 1.22 (95% CI, 1.02-1.46); more than 2 to 4 years, 0.98 (95% CI, 0.75-1.28); more than 4 to 6 years, 0.72 (95% CI, 0.50-1.05), and more than 6 years, 0.63 (95% CI, 0.41-0.96). For current users the risk of ovarian cancer did not differ significantly with different hormone therapies or duration of use. The incidence rates in current and never users of hormones were 0.52 and 0.40 per 1000 years, respectively, ie, an absolute risk increase of 0.12 (95% CI, 0.01-0.17) per 1000 years. This approximates 1 extra ovarian cancer for roughly 8300 women taking hormone therapy each year.

Conclusion Regardless of the duration of use, the formulation, estrogen dose, regimen, progestin type, and route of administration, hormone therapy was associated with an increased risk of ovarian cancer.

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PRIMARY PREVENTION OF OVARIAN cancer is challenging because little is known about its etiology. A review and meta-analysis of data published between 1966 and 2006 concluded that current use of postmenopausal hormone therapy (HT) increased the risk of ovarian cancer by 30% compared with the absence of HT and suggested that ovarian cancer risk with estrogen therapy (ET) alone was higher than the risk associated with estrogen plus progestin therapy (EPT).[1,2] However, the Million Women Study[3] with 948 576 women and 2273 incident cases of ovarian cancer found an increased risk of ovarian cancer, but no significant differential effect of ET vs EPT.

Furthermore, cyclic treatment has been found to increase the risk of ovarian cancer more than continuous combined treatment.[4,5] This finding, however, was not supported by the Million Women Study.[3] Little is known about a potentially differential effect of routes of administration on ovarian cancer risk. To our knowledge no evidence exists on the risks associated with vaginal ET or transdermal vs oral EPT.[3] Therefore, more data are needed to clarify the risk of ovarian cancer associated with different HT formulations, regimens, and routes of administration.

We examined the risk of ovarian cancer associated with different HT types.

METHODS

The Danish Sex Hormone Register Study (DaHoRS) initiated in 1995 follows a national cohort of Danish women aged 15 through 79 years to explore the influence of sex hormones on the risk of cardiovascular diseases and different female cancers.[6]

Since 1960, all citizens in Denmark have a personal identification number, registered in the Civil Registration System that also records the date of birth, immigration and emigration status, deaths, and actual residence. The personal identification number allows reliable linkage between various national registers for scientific purposes.

To explore the influence of sex hormones on the risk of cardiovascular diseases and various female cancers, including ovarian cancer, the DaHoRS cohort has been linked to 7 national registers: (1) the Civil Registration System: (2) the

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National Register of Medicinal Product Statistics, which includes information on all redeemed prescriptions at Danish pharmacies since January 1994; (3) the Danish Cancer Register, which includes all cancer cases since 1943; (4) the Pathology Register, which includes information on all histological examinations performed at Danish pathology departments since 1978, however, complete since 1997; (5) the National Register of Patients, which comprises information on discharge diagnoses and surgical codes on all somatic hospitalizations since 1976 and information on births since 1960; (6) the Cause of Death Register, which comprises information on causes of death from death certificates; and (7) Statistics Denmark, which provides a yearly update on the education and employment status on all Danish citizens based on the integrated database for labor market research.

Because the National Register of Medicinal Product Statistics is considered complete as of January 1, 1995, this was the date of study start.

Study Population

The present study includes women from the DaHoRS restricted to all Danish women who were at least 50 years by January 1, 1995, through December 31, 2005 (n=960 887; FIGURE 1).

The study was approved by the Danish Data Protection Agency and the Danish Medicinal Agency (Lægemiddelstyrelsen). The Danish Ethical Committee takes no interest in Danish Register studies and informed consent is not required.

Exclusion Criteria and Censoring

From the initial 960 887 women, we excluded women registered in the Danish Cancer Register with a diagnosis of ovarian cancer prior to entry (1943-1995 or after January 1, 1995, but prior to their 50th birthday). This was to ensure that all the women in the analysis had not ever had ovarian cancer.

Because the National Register of Patients was updated until December 31, 2005, we used this register for censoring during follow-up of other cancers that potentially would have caused a change in ordination of HT in Denmark. The same register was used for exclusion of these cancers prior to entry (1980-1995 or after January 1, 1995, but prior to their 50th birthday). The cancers were specified by the World Health Organization *International Classification of Diseases* (*ICD*) codes version *ICD-8* for the years 1980-1993 and *ICD-10* from 1994 to present (*ICD-8*/*ICD-10*). For breast cancer, the codes were 174/DC50; cervical cancer, 180/DC53; endometrial cancer, 182/DC54; tubal cancer, 183.19/DC57; colon cancer, 153/DC180-89; rectal cancer, 154/DC190-211; and malignant hematological diseases, 201-207/DC81-96. A total of 34 827 women were excluded for cancer diagnoses other than ovarian cancer.

Women who, according to the National Register of Patients, prior to entry (1980-1995 or after January 1, 1995, but prior to their 50th birthday) had bilateral oophorectomy (surgical code, 60120 or KLAE20/21) or bilateral salpingo-oophorectomy (60320 or KLAF10/11) were excluded (n=16 006).

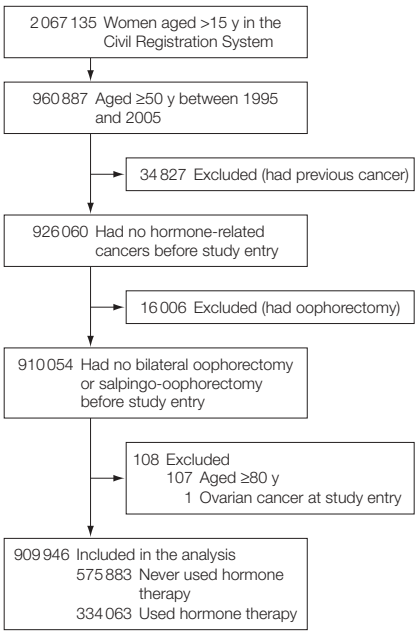
Women who were 80 years or older (n=107) or had a diagnosis of ovarian cancer on the day of study entry (n=1) were excluded. This left a total of 909 946 women at study entry.

Censoring was made at time of death, emigration, event of other cancers known to influence hormone use, at time of bilateral oophorectomy or salpingo-oophorectomy, at 80 years, or at the end of the study period.

Identification of Exposure (Postmenopausal Hormone Use)

The study cohort was linked to the National Register of Medicinal Product Statistics using the personal identification number as the key identifier. The register includes information on the date of the redeemed prescription, the specific Anatomical Therapeutical Chemical code, dose, number of packages, defined daily doses, and route of administration (tablet, patch, gel, etc). The included codes have been previously described.[6] Briefly, prior to data retrieval, detailed rules were used to allocate the different subgroups of hormone use and for shift between different groups. The prescribed defined daily doses determined the length of use, and combination therapy trumped single-preparation therapy in the case of contemporary prescriptions even though the estrogen dose was upgraded.

Figure 1. Flow Diagram of Study Participants



The information on initiation of hormone use (ie, redeemed prescriptions) was updated daily for each individual during the study period. All the records of hormone exposure were prolonged by 4 months at the expiration of the prescription to account for delay in the recorded diagnoses in Danish registers, prolonged HT for those taking less than the defined daily dose prescribed, and a minor latency time. Thus, gaps between prescriptions were filled prospectively if not longer than 4 months.[7]

Because HT probably acts as a promoter of the ovarian cancer carcinogenesis with a minor latency time, women currently taking hormones were allocated to the hormone type taken for the longest period during the study period. However, these variables were time dependent, ie, a change in HT type would recategorize a woman

into a new category of HT, if at the time she was taking a new HT longer than the former HT.

Exposure to hormones before age 50 years, but within the 11-year study period, was added to the hormone status and duration of use. This allowed for sensitivity analyses on the effect of less complete exposure history among women entering the cohort at older ages.

To account for women redeeming only 1 prescription (nonadherence), a category of less than a year of use was included in the duration variable. Hormone therapy was categorized according to HT status, which includes never, past, current nonvaginal HT, current vaginal estrogen (0.25 mg/d typically taken over 2-3 days) or hormone intrauterine device (IUD); hormone formulation, which includes never, past, estrogen only, estrogen/progestin, progestin only, tibolone and raloxifene, hormone IUD, or vaginal estrogen; hormone regimen, which includes never, past, cyclic combined EPT, long-cycle combined EPT (ie, simultaneous redemption 7-14 times more than the defined daily dose of estrogen than the defined daily dose of progestin), continuous combined EPT, progestin only therapy, estrogen only therapy, tibolone, raloxifene, hormone IUD, or vaginal estrogen; route of administration, which includes never, past, oral estrogen, dermal estrogen, oral combined estrogen plus progestin, dermal combined estrogen plus progestin, hormone IUD, or vaginal estrogen; progestin type, which includes never, past, noresthisterone acetate, medroxyprogesteron, levonorgestrel, cyproterone acetate, estrogen only, tibolone, raloxifene, hormone IUD, or vaginal estrogen; estrogen dose, which includes never, past, high (>2 mg/d of estradiol), middle (1-2 mg/d), low (<1 mg/d), tibolone, raloxifene, hormone IUD, or vaginal estrogen; duration of HT, which includes never, past, current, <1, 1 to 4, >4 to 7, and >7 years, hormone IUD, or vaginal estrogen; and time since last use in years among former users, which includes current, 0 to 2, >2 to 4, >4 to 6, and >6 years, never, hormone IUD, or vaginal estrogen).

Identification of Ovarian Cancer Cases

The Danish Cancer Register was used until December 31, 2002, for identification of primary invasive ovarian cancer using the *ICD* for oncology topography code 183.0 and morphology codes ending with a 3. At the time of this study, information from January 2003 was not updated in the Danish Cancer Register. Thus, from 2003 the Pathology Register was used for case finding until December 31, 2005. The Systemized Nomenclature of Medicine topography codes were between 87 000-87 800 and the morphology codes ending with a 3.

Information on the histology of tumors was obtained from the Danish Cancer Register until 2003 and from the Pathology Register from 2003. The tumors were classified as either epithelial tumors (ie, clear cell, endometroid, mucinous, serous, adenocarcinoma not otherwise specified, and epithelial or nonepithelial tumors (ie, sex cord stromal, germinal cell, and tumors not otherwise specified or other morphology codes ending with a 3). Borderline tumors were not included. No histology information was available for 8 women with ovarian cancer. These women were excluded from the analyses of the associations between HT and epithelial ovarian cancer but were included in the overall ovarian cancer analyses.

Analysis

The data were analyzed with Poisson regression analysis using SAS statistical software version 9.1 (SAS Institute Inc, Cary, North Carolina). Incidence rate ratios (RRs) and 95% confidence intervals (CIs) were calculated for each model. Age was calculated from birth dates, which were extracted from personal identification numbers. Age was used as the timescale in the Poisson regression analyses, and data were divided into 5-year age bands (50-54, etc), assuming a constant risk of ovarian cancer within each band. Each model was checked for significance of interaction between age and exposure. All tests were 2 sided with a 5% significance level.

Furthermore, hysterectomy, period of use, and duration of HT were evaluated as possible effect modifiers; no effect modification was found, however. Potential confounders were number of births (0, 1, 2, >2) (*ICD8/ICD10*: 650-666/DO 60-84), hysterectomy (surgical code, 610/KLCD00-97), sterilization (608-640/KLGA), unilateraloophorectomy (60100/KLAE10-11), and unilateral salpingo-oophorectomy (60300/LAE00/01), endometriosis (625.29-39/DN80), infertility (628/DN97), and educational status in 1995 (no education after elementary or high school; occupational basic education; short-term, middle-term, or long-term education; or educational status unknown). In addition, adjustments were made for period of use (1995-2002 or 2003-2005) to account for possible differences in ovarian cancer diagnosis in the Danish Cancer Register and Pathology Register. The following variables were time dependent: HT variables, hysterectomy, sterilization, unilateral oophorectomy or salpingo-oophorectomy, and number of births. Women who had been diagnosed with endometriosis or infertility were considered being in this condition during the study period.

The crude models included hormone exposure, age, and period of use.

Analyses were performed for all ovarian cancers as well as for all epithelial cancers. The number of women exposed to progestin-only therapy, raloxifene, tibolone, hormone IUD combinations, and conjugated estrogens were too few to determine risk estimates.

The reference group were those who had never used any HT.

Differences between HT types were tested; ET vs EPT, long cyclic and cyclic vs continuous EPT, and transdermal or vaginal vs oral HT. We took consistency of findings into consideration when the interpretation was made.

The least detectable difference between never and current users with a power of 80% and significance level of 5% was an RR of 1.14. For comparisons between ET vs EPT and cyclic vs continuous EPT, the least detectable difference was an RR of 1.3.

Two sensitivity analyses were performed. In the first analysis, we carried forward the first recorded HT that each woman used to the remaining exposed time. Thus, events of ovarian cancer were linked to the first-used HT. In the second analysis, we censored women who had changed to another HT type during follow-up but were included in the analysis if they had started and stopped the same HT.

Incidence rates (cases/person-years) were calculated among never and current users per 1000 years using crude data. The absolute risk difference (incidence rates^{exposed} –incidence rates^{unexposed}) and the number needed to harm (1/(incidence rates^{exposed} –incidence rates^{unexposed}) were also calculated.

RESULTS

From 1995 to 2005, 909 946 perimenopausal and postmenopausal women with no previous hormone-sensitive cancer or bilateral oophorectomy or salpingo-oophorectomy accumulated 7.3 million women-years corresponding to an average follow-up of 8.0 years. The number of incident malignant ovarian cancers during the study period was 3068. Of these, 2681 were epithelial tumors, including 1336 serous tumors, 377 endometroid, 293 mucinous, 159 clear cell, and 115 nonspecified epithelial tumors, and 401 adenocarcinoma not otherwise specified. Only 55 were nonepithelial tumors, and 324 were unspecified. Eight cases had no information on histology. The focus of this study was on the epithelial cancers.

At the end of follow-up, 63% of the women had not been taking HT, 22% were previous users of hormones, and 9% current users of hormones. Among the current users, 46% had used hormones for more than 7 years (TABLE 1). Compared with never users, more hormone users had hysterectomy or unilateral salpingo-oophorectomy (Table 1). Among the never users, fewer women were sterilized and fewer were parous (Table 1). Compared with never users, more women taking ET and transdermal HT had surgical procedures (hysterectomy, unilateral salpingo-oophorectomy, or oophorectomy) and endometriosis. More women taking ET were

Table 1. Characteristics of the Study Population According to Hormone Use

Characteristic at End of Follow-up	Hormone Status			Formulation		Type of Combined Regimen		Route of Administration[a]	
	Never	Previous	Current[b]	Estrogen[c]	Combined	Continuous	Cyclic[d]	Transdermal	Vaginal ET
Women, No.	575 883	198 184	83 810	28 590	60 310	23 839	33 880	9588	36 652
Women-years, No.	4 987 264	841 491	1 183 980	355 420	802 083	242 637	512 566	121 885	218 382
Incidence of ovarian cancer, No.	2011	320	620	195	405	123	252	55	104
Age, y, No. (%)									
50-54	22.7	15.4	19.1	14.0	20.3	12.5	26.3	22.8	10.1
55-59	19.0	25.3	26.4	22.2	29.4	26.5	31.4	34.3	20.0
60-64	16.8	24.4	22.3	21.9	23.8	26.2	21.7	25.1	20.8
65-69	14.8	15.9	15.2	17.0	14.8	18.9	11.7	11.3	18.4
70-74	13.7	10.4	10.1	13.2	7.9	10.3	6.3	4.1	15.4
75-79	13.2	8.7	7.0	11.8	3.8	5.6	2.7	2.4	15.2
Age, mean (SD), y	62.5 (8.8)	62.4 (7.5)	61.5 (7.5)	63.5 (7.9)	60.6 (6.8)	62.2 (6.8)	59.4 (6.5)	59.3 (6.0)	64 (8.0)
Duration of HT, y, No. (%)[e]									
<1[f]		18.6	5.1	4.7	5.4	5.1	5.8	5.3	
1-4		31.4	15.2	12.8	16.1	14.8	17.1	14.8	
>4-7		20.7	18.1	15.0	19.6	20.5	19.1	19.6	
>7		29.2	45.8	56.2	44.0	46.1	24.4	42.3	
Higher education, No. (%)[g]	17.8	19.4	20.6	16.3	23.3	20.7	25.3	27.3	22.1
Parous women, No. (%)	75.2	83.5	80.8	76.1	84.6	82.9	85.5	86.8	77.6
No. of children, mean (SD)	1.7 (1.3)	1.9 (1.2)	1.6 (1.2)	1.8 (1.1)	1.8 (1.2)	1.8 (1.1)	1.8 (1.1)	1.8 (1.0)	1.7 (1.2)
Medical history, No. (%)									
Hysterectomy	6.2	12.2	18.0	50.9	3.4	3.5	3.3	27.7	8.4
Unilateral salpingo-oophorectomy	1.9	3.7	5.7	12.3	2.8	2.7	2.8	6.5	2.4
Unilateral oophorectomy	0.6	1.2	1.8	3.8	0.9	0.9	1.0	2.2	0.9
Sterilized	5.4	7.9	8.4	8.4	8.6	7.7	9.1	9.9	5.5
Infertility	1.6	2.0	2.2	2.1	2.4	1.9	2.8	2.8	1.6
Endometriosis	1.1	2.1	3.4	7.3	1.7	1.5	1.7	4.6	1.5

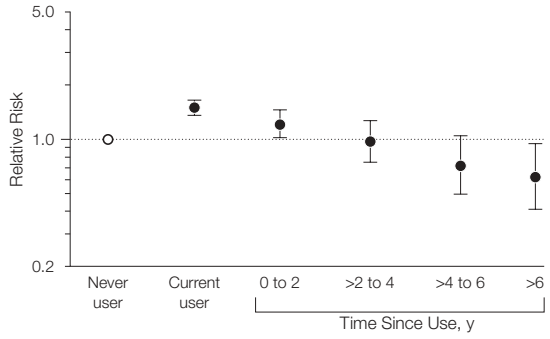
[a] Hormone interuterine device (IUD) not shown. Oral hormone therapy (HT) not shown, because current use mainly comprises oral administration.
[b] Exclusive vaginal estrogen therapy (ET), hormone IUD, and injections (2 cases).
[c] Exclusive vaginal ET.
[d] Exclusive long cyclic estrogen plus progestin therapy.
[e] Exclusive vaginal ET and hormone IUD, thus percentages do not sum to 100%.
[f] To account for women redeeming only 1 prescription (nonadherence).
[g] Educational status in 1995; higher education includes short term (1-2 y) (3.2%), middle term (3-4 y) (13.1%), and long (5-6 y) (2.1%) education.

Table 2. Risk of Ovarian Cancer by Hormone Therapy Status and Duration of Use

	All Malignant Ovarian Cancers			Epithelial Ovarian Cancers[a]		
	No. of Cases	Person-Years	RR (95% CI)[b]	No. of Cases	Person-Years	RR (95% CI)[b]
HT status						
Never	2011	4 987 264	1 [Referent]	1725	4 987 230	1 [Referent]
Previous	320	841 491	1.00 (0.88-1.12)	280	841 491	1.15 (1.01-1.30)
Current	620	1 183 980	1.38 (1.26-1.51)	572	1 183 961	1.44 (1.30-1.58)
Other[c]	117	258 209		104	258 206	
Duration of HT, y						
0-4	338	643 375	1.33 (1.18-1.49)	308	643 363	1.41 (1.24-1.59)
>4-7	185	332 137	1.32 (1.13-1.53)	175	332 131	1.45 (1.24-1.69)
>7	97	208 468	1.48 (1.20-1.83)	89	208 467	1.57 (1.26-1.95)
Other[c]	117	258 209		104	258 206	

Abbreviation: CI, confidence interval; HT, hormone therapy, RR, relative risk.
[a] Due to missing information on histology, 8 cases were excluded
[b] Adjusted for age, period of use, number of births, hysterectomy, sterilization, unilateral oophorectomy or salpingo-oophorectomy, endometriosis, infertility, and educational status.
[c] Comprises vaginal estrogen therapy, hormone interuterine device, and injections (2 cases).

Figure 2. Risk of Epithelial Ovarian Cancer Among Former Hormone Users by Time Since Use



Error bars indicate 95% confidence intervals.

long-term users (>7 years) and fewer were parous than were women taking EPT (Table 1). Current users of HT had an overall increased risk of ovarian cancer (RR, 1.38; 95% CI, 1.26-1.51). When restricting the analyses to epithelial ovarian cancer, the RR among current users was 1.44 (95% CI, 1.30-1.58; TABLE 2). Previous users had an RR of 1.15 (95% CI, 1.01-1.30) compared with women who had never used HT. The RR values for ovarian cancer and epithelial ovarian cancer did not increase significantly with increasing durations of HT (Table 2). The duration categories of less than a year and between 1 to 4 years were combined because the risk values were similar.

We subcategorized previous users according to time since last use and found an increased risk for epithelial ovarian cancer for a period of up to 2 years after cessation of HT. Thereafter, the risk approached that observed in never users (FIGURE 2). The RRs for time since use in years were 1.22 (95% CI, 1.02-1.46) from 0 to 2 years, 0.98 (95% CI, 0.75-1.28) from more than 2 to 4 years, 0.72 (95% CI, 0.50-1.05) from more than 4 to 6 years, and 0.63 (95% CI, 0.41-0.96) for more than 6 years. The RR values for time since last use were similar after additional adjustment for previous hormone duration. Crude and adjusted RR values were nearly identical (data not shown).

Estrogen Therapy vs Combined Therapy

Compared with women who had never taken HT, those who had were at increased risk of epithelial ovarian cancer (RR, 1.31; 95% CI, 1.11-1.54) (TABLE 3). Similarly, women currently taking EPT also had an increased risk of epithelial ovarian cancer compared with never users (RR, 1.50; 95% CI, 1.34-1.68; Table 3). The difference between ET and EPT was not statistically significant ($P=.16$).

Compared with women who never took HT, increasing the daily dose of estrogen was not consistently associated with the risk of epithelial ovarian cancer, and adjustment for the duration of HT did not change the estimates (Table 3). Increasing the duration of ET was weakly associated with the risk of epithelial ovarian cancer, while no consistent associations between duration of EPT use and risks of epithelial ovarian cancer were found (FIGURE 3).

Continuous vs Cyclic Therapies

Compared with women who had never taken HT, women taking cyclic EPT or EPT for long cycles were at higher risk of epithelial ovarian cancer (RR, 1.50; 95% CI, 1.31-1.72 and RR, 2.05; 95% CI, 1.44-2.93, respectively). For women taking EPT continuously, the risk of epithelial ovarian cancer was also increased (RR, 1.40;95% CI, 1.16-1.69), a risk not statistically significantly different from the cyclic combined regimens ($P=.55$ and $P=.06$, respectively; Table 3).

Combined therapy with norethisterone was associated with an increased risk of epithelial ovarian cancer (RR, 1.55; 95% CI, 1.36-1.76), which was not significantly different from the RRs associated with medroxyprogesterone, levo-

norgestrel, or cyproterone acetate (Table 3).

Route of Administration

Compared with never users, the group treated with transdermal administration of ET had a risk of ovarian cancer of 1.13 (95% CI, 0.74-1.71) vs an increased risk for those taking oral ET (RR, 1.34; 95% CI, 1.12-1.60); however, the difference was not statistically significant ($P = .44$; Table 3). Also, vaginal administration of ET was associated with a slightly increased risk of epithelial ovarian cancer (RR, 1.23; 95% CI, 1.00-1.52), not different from oral estrogen ($P = .53$).

Women taking oral EPT had an increased risk of epithelial ovarian cancer (RR, 1.48; 95% CI, 1.32-1.65) compared with women who never took HT (Table 3). There was no significant difference in the risk of epithelial ovarian cancer between the use of oral and transdermal EPT ($P = .54$).

Crude Absolute Risks

Crude incidence rates for ovarian cancer per 1000 years was 0.40 in never users and 0.52 in current users, which translates to an absolute risk difference of 0.12 per 1000 years. If the difference in risk between never users and current users is due to HT, these results imply that use of HT resulted in about 1 extra case of ovarian cancer for roughly every 8300 women taking HT each year. Applying the absolute risk difference to the hormone use in Denmark from 1995 to 2005 (number of person years: 1 183 980), hormone use is estimated to have resulted in about 140 additional cases of ovarian cancer over the mean follow-up of 8 years.

Sensitivity Analyses

The results did not change when women were allocated to the HT type used first. Nor did the results change when women were censored during follow-up at time of change to another HT type.

COMMENT

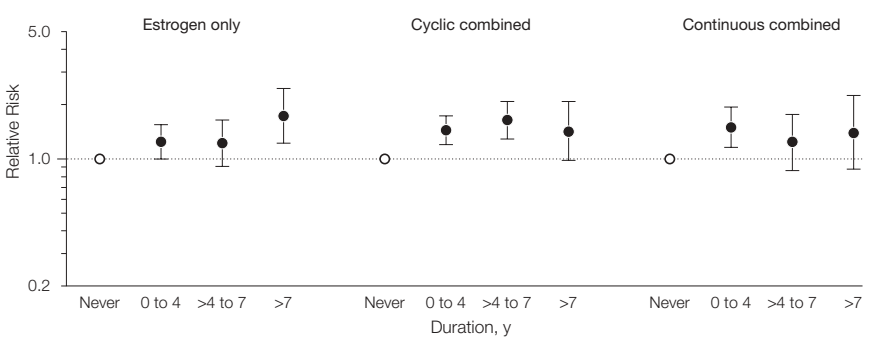
This cohort study confirms that women who have taken HT are at higher risk

Table 3. Risk of Epithelial Ovarian Cancer by Current Use of Different Types of Hormone Therapy[a]

Hormone Use	No of Cases	Person-Years	RR (95% CI)[b]
Never	1725	4 987 230	1 [Referent]
Previous	280	841 491	1.15 (1.01-1.30)
Formulation			
Estrogen only[c]	170	355 420	1.31 (1.11-1.54)
Estrogen + progestin	384	802 082	1.50 (1.34-1.68)
Other[d]	122	282 841	
Estrogen dose[e]			
Low	77	168 277	1.39 (1.10-1.74)
Middle	235	459 219	1.51 (1.32-1.74)
High	224	479 099	1.41 (1.22-1.62)
Other[d]	140	335 573	
Type of combined regimen[f]			
Long-cycle estrogen + progestin	31	46 891	2.05 (1.44-2.93)
Cyclic estrogen + progestin	238	512 562	1.50 (1.31-1.72)
Continuous estrogen + progestin	115	242 630	1.40 (1.16-1.69)
Other[d]	292	355 542	
Progestin type			
Noresthisterone acetate	269	534 312	1.55 (1.36-1.76)
Medroxyprogesterone	38	91 860	1.37 (0.99-1.89)
Levonorgestrel	32	78 880	1.30 (0.92-1.85)
Cyproterone acetate	6	23 508	0.87 (0.39-1.93)
Other[d]	331	713 607	
Route of administration			
Oral estrogen	145	286 926	1.34 (1.12-1.60)
Transdermal estrogen	23	64 155	1.13 (0.74-1.71)
Oral estrogen + progestin	376	789 960	1.48 (1.32-1.65)
Transdermal estrogen + progestin	28	57 717	1.67 (1.15-2.42)
Vaginal estrogen alone	94	218 379	1.23 (1.00-1.52)
Other[d]	10	25 030	

Abbreviation: CI, confidence interval, RR, relative risk.
[a] The table is based on 5 separate regression models for formulation, regimen, route, estrogen dose, and progestin type.
[b] Adjusted for age, time period, number of births, hysterectomy, sterilization, unilateral oophorectomy and salpingo-oophorectomy, endometriosis, infertility, and educational status.
[c] Exclusive vaginal estrogen. A total of 2 cases were receiving estrogen injections.
[d] Comprises the other hormone therapy types not relevant for the specific hormone of interest.
[e] Additionally adjusted for duration of use.
[f] Long-cycle estrogen plus progestin therapy: 7-14 times more defined daily dose of estrogen than the defined daily dose of progestin; cyclic estrogen plus progestin therapy: up to 7 times more estrogen than progestin; continuous estrogen plus progestin therapy: daily estrogen and progestin administration.

Figure 3. Risk of Epithelial Ovarian Cancer According to Duration of Different Hormone Therapies



Error bars indicate 95% confidence intervals.

of epithelial ovarian cancer than women who have not (range, 30%-58%). In agreement with findings from the Million Women Study, the risk of ovarian cancer did not differ significantly by formulation, regimen, type of progestin, or route of administration.[3]

Duration and Dosage

Our data show increased risk of ovarian cancer even with short durations of hormone use (0-4 years). This finding contrasts some prior studies that were not able to detect increased risk with HT of less than 5 years.[2-4]

In regard to ET, we found an increasing risk of cancer with increasing length of use, which is in accordance with findings from the Nurses' Health Study.[2] One Danish study found that the cumulative ET dose was more important than the duration of use.[8] In our study, however, no consistent association was found between increasing dose of ET and the risk of ovarian cancer.

In accordance with the Million Women Study and the Nurses' Health Study, past HT users had only a slightly increased risk of ovarian cancer, and the excess risk was not apparent 2 years after cessation.[2,3]

Estrogen vs Combined Therapy

In agreement with 2 recent studies, we found that ET and EPT were associated with an approximately similar and increased risk of ovarian cancer.[3,5] A review and meta-analysis of data published between 1966 and 2006 also supports our finding of an increased risk of ovarian cancer associated with both ET and EPT.[1] Another recent study was only able to detect increased risks of ovarian cancer with use of combined therapies for 5 or more years.[5]

Cyclic vs Continuous Hormone Regimen

A higher risk of ovarian cancer has been suggested for women taking EPT cyclically than women taking EPT continuously.[4,5] The Women's Health Initiative (WHI) reported an increased risk of ovarian cancer associated with continuous EPT compared with placebo.[9] We found that both cyclic and continuous EPT increased the risk of ovarian cancer, but the risks did not differ significantly in magnitude. Typically, women taking EPT continuously have taken cyclic EPT previously. However, the results were similar after restricting the analyses to women not changing HT type during follow-up.

Administration and Hormone Types

In accordance with the Million Women Study, we found no significant difference in risk according to route of administration.[3] The slightly increased risk with vaginal administration of ET is not documented in other studies. Therefore, caution should be taken with conclusions assuming causality. In the present study, norethisterone demonstrated the same risk as the other types of progestins, which is in line with a previous study.[3] Few women, however, were exposed to the other progestins; therefore, we were unable to detect minor differences in risk.

Implications

The absolute risk increase was 0.12 per 1000 years. If this association is causal, use of hormones has resulted in roughly 140 extra cases of ovarian cancer in Denmark over the mean follow-up of 8 years, ie, 5% of the ovarian cancers in this study. Even though this share seems low, ovarian cancer remains highly fatal, so accordingly this risk warrants consideration when deciding whether to use HT.

Strengths

Our nationwide study is a large-scale (historical) prospective cohort study with 909 946 Danish women followed up for 11 years. We had complete follow-up until diagnosis of cancer, bilateral oophorectomy, emigration, death, or end of study. Our large number of outcomes permitted us to perform detailed subanalyses of separate hormone formulations, regimens, routes of administration, progestin types, different estrogen dosages, as well as different durations of HT. We consider the validity of our outcome to be high, because the Cancer Register has both a high level of completeness and correctness of diagnosis.[10-12] We used the Pathology Register for case finding from 2002 until 2005. The agreement of histological ovarian cancer diagnoses between the Pathology Register and the Cancer Register is high, and our estimates did not depend on the source of diagnoses.[13]

The validity of our exposure is presumed to be high because recall bias was eliminated. The information on the prescribed HT was transferred automatically from the pharmacies by bar codes. Our information on both exposures and confounders was updated daily. The exposure information comprised at what time the women were exposed during our follow-up, for how long, and to which type of HT. Information on HT and ovarian cancer was registered in the Danish registers without the aim of exploring the association between HT and clinical outcomes, making differential ascertainment of exposure and cancer incidence unlikely.

We excluded women with previous hormone-sensitive cancer because this might affect both HT and the subsequent risk of ovarian cancer. Our results were adjusted for age, period of use, educational status, number of births, hysterectomy, sterilization, unilateral oophorectomy and salpingo-oophorectomy, endometriosis, and infertility. There was no significant confounding by any of the included variables. We attempted to account for delay in the diagnosis of ovarian cancer by prolonging exposure data by 4 months. Finally, our sensitivity analyses showed that our results remained the same after addressing HT first used and women exposed only to 1 type of HT during follow-up.

Limitations

We were not able to adjust for age at menopause and use of oral contraceptives. Women with early natural menopause are more likely to use hormones compared with women with late natural menopause. Because natural early menopause tends to decrease the

risk of ovarian cancer, more women taking HT could have an a priori decreased risk of ovarian cancer. Similarly, more previous users of oral contraceptives become hormone users in later life.[14,15] Because oral contraceptives decrease the risk of ovarian cancer, our results may be slightly underestimated. The Million Women Study adjusted for age at menopause, oral contraceptive use, body mass index, alcohol consumption, smoking, and physical activity, but these adjustments did not show substantial changes in their findings, indicating only minor confounding by these factors.[3] In addition, the Nurses' Health Study reported only minimal changes in the association between HT and ovarian cancer after adjustment for relevant potential confounders, including duration of oral contraceptive use, natural menopause, and age at menarche.[2]

Women with a family history of cancer are less likely to use HT. The lack of this potential confounder might have underestimated our results. For high body mass index and smoking, a recent Danish study found no associations with ovarian cancer risk as a combined outcome.[16] The effect of physical activity on ovarian cancer risk is controversial.

Information on women who underwent surgical procedures was not available in the registers among the oldest women. Hysterectomy and oophorectomy reduce the risk of ovarian cancer and often lead to HT, probably causing an underestimation of our results among the older women. However, despite our uneven adjustment for confounders, the risk of ovarian cancer was nearly identical across age groups and was similar for the different HT types across age.

The missing potential confounders in this study are therefore not a major concern and will most likely not overestimate the effect.

Another limitation is the lack of information on hormone exposure prior to study entry. Thus, older women who were not prescribed HT during follow-up might have been taking hormones before the study entry. However, the association between HT use, duration of use, and risk of ovarian cancer was similar among young women for whom complete information on HT exposure history was available, compared with older women. This finding reduces the probability of bias caused by exposure misclassification. Finally, it is worth stating that whether the prescribed medicine was actually taken is unknown. Repeated prescriptions, however, reduce this potential bias. It is possible that some women take fewer pills than the prescribed defined daily doses, thereby prolonging the HT. This would tend to underestimate our results.

CONCLUSION

In conclusion, our study suggests an increased risk of ovarian cancer with both estrogen therapy and combined HT, with little influence of different regimens, progestin types, routes of administration, length of use, and different doses. Thus, the risk of ovarian cancer is one of several factors to take into account when assessing the risks and benefits of hormone use.

Author Contributions: Ms Mørch had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analyses.
Study concept and design: Mørch, Lidegaard, Løkkegaard, Andreasen.
Acquisition of data: Mørch, Lidegaard, Løkkegaard.
Analysis and interpretation of data: Mørch, Lidegaard, Løkkegaard, Andreasen, Krüger-Kjær.
Drafting of the manuscript: Mørch.
Critical reversion of the manuscript for important intellectual content: Mørch, Lidegaard, Løkkegaard, Andreasen, Krüger-Kjær.
Statistical expertise: Mørch, Andreasen.
Obtaining funding: Lidegaard.
Study supervision: Mørch, Lidegaard, Løkkegaard, Andreasen, Krüger-Kjær.
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REFERENCES

1. Greiser CM, Greiser EM, Dören M. Menopausal hormone therapy and risk of ovarian cancer: systematic review and meta-analysis. *Hum Reprod Update*. 2007; 13(5):453-463.
2. Danforth KN, Tworoger SS, Hecht JL, Rosner BA, Colditz GA, Hankinson SE. A prospective study of postmenopausal hormone use and ovarian cancer risk. *Br J Cancer*. 2007;96(1):151-156.
3. Beral V, Bull D, Green J, Reeves G; Million Women Study Collaborators. Million Women Study Collaborators, Bull D, Green J, Reeves G. Ovarian cancer and hormone replacement therapy in the Million Women Study. *Lancet*. 2007;369(9574):1703-1710.
4. Riman T, Dickman PW, Nilsson S, et al. Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. *J Natl Cancer Inst*. 2002;94(7):497-504.
5. Lacey JV Jr, Brinton LA, Leitzmann MF, et al. Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study Cohort. *J Natl Cancer Inst*. 2006;98(19): 1397-1405.
6. Løkkegaard E, Lidegaard O, Møller LN, Agger C, Andreasen AH, Jørgensen T. Hormone replacement therapy in Denmark, 1995-2004. *Acta Obstet Gynecol Scand*. 2007;86(11):1342-1351.
7. Nielsen LH, Løkkegaard E, Andreasen AH, Keiding N. Using prescription registries to define continuous drug use: how to fill gaps between prescriptions. *Pharmacoepidemiol Drug Saf*. 2008;17(4):384-388.
8. Glud E, Kjaer SK, Thomsen BL, et al. Hormone therapy and the impact of estrogen intake on the risk of ovarian cancer. *Arch Intern Med*. 2004;164 (20):2253-2259.
9. Anderson GL, Judd HL, Kaunitz AM, et al; Women's Health Initiative Investigators. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA*. 2003;290(13): 1739-1748.
10. Storm HH. Completeness of cancer registration in Denmark 1943-1966 and efficacy of record linkage procedures. *Int J Epidemiol*. 1988;17(1):44-49.
11. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Register—history, content, quality and use. *Dan Med Bull*. 1997;44(5):535-539.
12. Jensen AR, Overgaard J, Storm HH. Validity of breast cancer in the Danish Cancer Registry. A study based on clinical records from one county in Denmark. *Eur J Cancer Prev*. 2002;11(4):359-364.
13. Kjaerbye-Thygesen A, Huusom LD, Frederiksen K, Kjaer SK. Danish Cancer Register and the Pathology Data Bank. Primary ovarian cancer: a comparison of registrations in the Danish Cancer Register and the Pathology Data Bank [in Danish]. *Ugeskr Laeger*. 2007;169(1):50-54.
14. Hammar M, Brynhildsen J, Dabrosin L, et al. Hormone replacement therapy and previous use of oral contraceptives among Swedish women. *Maturitas*. 1996;25(3):193-199.
15. Hundrup YA, Obel EB, Rasmussen NK, Philip J. Use of hormone replacement therapy among Danish nurses in 1993. *Acta Obstet Gynecol Scand*. 2000; 79(3):194-201.
16. Soegaard M, Jensen A, Høgdall E, et al. Different risk factor profiles for mucinous and nonmucinous ovarian cancer: Results from the Danish MALOVA Study. *Cancer Epidemiol Biomarkers Prev*. 2007; 16(6):1160-1166.