



## Original Contribution

# Hormone Therapy and Different Ovarian Cancers: A National Cohort Study

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Postmenopausal hormone therapy use increases the risk of ovarian cancer. In the present study, the authors examined the risks of different histologic types of ovarian cancer associated with hormone therapy. Using Danish national registers, the authors identified 909,946 women who were followed from 1995–2005. The women were 50–79 years of age and had no prior hormone-sensitive cancers or bilateral oophorectomy. Hormone therapy prescription data were obtained from the National Register of Medicinal Product Statistics. The National Cancer and Pathology Register provided data on ovarian cancers, including information about tumor histology. The authors performed Poisson regression analyses that included hormone exposures and confounders as time-dependent covariates. In an average of 8.0 years of follow up, 2,681 cases of epithelial ovarian cancer were detected. Compared with never users, women taking unopposed oral estrogen therapy had increased risks of both serous tumors (incidence rate ratio (IRR) = 1.7, 95% confidence interval: 1.4, 2.2) and endometrioid tumors (IRR = 1.5, 95% confidence interval: 1.0, 2.4) but decreased risk of mucinous tumors (IRR = 0.3, 95% confidence interval: 0.1, 0.8). Similar increased risks of serous and endometrioid tumors were found with estrogen/progestin therapy, whereas no association was found with mucinous tumors. Consistent with results from recent cohort studies, the authors found that ovarian cancer risk varied according to tumor histology. The types of ovarian tumors should be given attention in future studies.

histologic type; ovarian cancer; postmenopausal hormone therapy

Abbreviations: CI, confidence interval; EPT, estrogen/progestin therapy; ET, estrogen-only therapy; HT, hormone therapy; IRR, incidence rate ratio; NHS, Nurses' Health Study.

Ovarian cancer is the most lethal of gynecologic cancers. Unfortunately, little is known about its etiology. In recent meta-analyses, investigators have concluded that women taking postmenopausal hormone therapy (HT) have an increased risk of ovarian cancer compared with never users (1, 2). Two large prospective studies, the Million Women Study and Danish Sex Hormone Register Study, found an overall increased risk of 30%–40% (3, 4).

Less is known about the association between hormone use and the risk of different histologic subtypes of epithelial ovarian cancer. Other risk factors for ovarian cancer have been found to differ between mucinous and nonmucinous ovarian tumors, supporting the hypothesis of different etiologies (5, 6). However, previous studies on HT and different types of ovarian tumors were mainly case-control studies, and the numbers of

cases were small, especially for mucinous tumors (1, 7–10). Most prospective cohort studies either did not examine tumor type (1, 4) or had incomplete information on histology (11).

Recently, Danforth et al. (12) found that estrogen-only therapy (ET) was more strongly associated with the risk of endometrioid tumors than with the risk of other types of epithelial tumors in the Nurses' Health Study (NHS). The Million Women Study found that with HT use, the highest risk was for serous tumors, whereas there was a lower risk of mucinous tumors (3). Knowledge about the associations between HTs and subtypes of ovarian cancer will add to the understanding of how HT acts as a promoter of ovarian cancer carcinogenesis. Moreover, if different types of ovarian tumors are to be viewed as separate diseases, that fact should be considered when creating the study designs for future research. Therefore, the aim of the

present study was to explore the risks of HT associated with different histologic types of ovarian cancer.

## MATERIALS AND METHODS

The Danish Sex Hormone Register Study is an ongoing study of a national cohort of Danish women who were 15–79 years of age in 1995. The study was developed to explore the influence of sex hormones on the risk of cardiovascular diseases and different cancers in women; a detailed description of the cohort is available elsewhere (4, 13). Briefly, since 1968, all citizens in Denmark have had personal identification numbers recorded in the Civil Registration System, which also records the dates of birth, immigration, emigration, and death, as well as actual residence. The personal identification number allows reliable linkage between different national registers for scientific purposes. The Danish Sex Hormone Register Study cohort has been linked to several national registers, including: 1) the National Register of Medicinal Product Statistics, which includes information on all prescription-based medications (including HT) through registration of all redeemed prescriptions in Denmark since January 1994; 2) the Danish Cancer Register, which includes data on cancer cases since 1943; 3) the Pathology Register, which includes information on histologic examinations since 1978; 4) the National Register of Patients, which comprises information on discharge diagnoses and surgical codes on somatic hospitalizations since 1976; and 5) Statistics Denmark, which provides information on educational levels and employment of Danish citizens. Because the data in the National Register of Medicinal Product Statistics are considered complete from January 1, 1995, onward, this was the start date of the study. The study was approved by the Danish Data Protection Agency (casework no. 2003-41-2872) and the Danish Medicinal Agency (Lægemiddelstyrelsen) (casework no. 5121-59).

### Study population

The current study population includes women from the Danish Sex Hormone Register Study who were at least 50 years of age sometime in the period between January 1, 1995, and December 31, 2005 ( $n = 960,887$ ). We excluded women with a diagnosis of ovarian cancer before study entry (before 1995 or after January 1, 1995, but before their 50th birthdays), as well as women who had a diagnosis of another type of cancer before study entry that potentially could have influenced the prescription of HT. Those cancers were breast cancer, cervical cancer, endometrial cancer, tubal cancer, colon cancer, rectal cancer, and malignant hematologic diseases. This led to the exclusion of 34,827 women.

Women who had bilateral oophorectomy or bilateral salpingo-oophorectomy before entry into the study were excluded ( $n = 16,006$ ). Women who were 80 years of age or older ( $n = 107$ ) or had a diagnosis of ovarian cancer on the day of study entry ( $n = 1$ ) were also excluded. This left a total of 909,946 women at study entry. Participants were censored at the time of death, emigration, development of other cancers, bilateral oophorectomy or salpingo-oophorectomy, 80 years of age, or the end of the study period.

### Exposure assessment (postmenopausal hormone use)

The study cohort was linked to the National Register of Medicinal Product Statistics using participants' personal identification numbers as the key identifiers. The National Register of Medicinal Product Statistics includes information on the date of the redeemed prescriptions and the specific Anatomical Therapeutic Chemical code, dose, number of packages, defined daily doses, and route of administration (tablet, patch, gel, etc.) The specific Anatomical Therapeutic Chemical codes included in the present study have been described previously (13).

The information on initiation of HT use (i.e., redeemed prescriptions) was updated daily for each individual during follow-up. The prescribed defined daily doses were used to determine the length of use. We included 4 months after the expiration of the prescription in all records of hormone exposure to account for any delay in recorded diagnoses in Danish registers, prolonged HT use for those taking less than the defined daily dose prescribed, and minor latency time. Thus, gaps between prescriptions of less than 4 month were filled prospectively; that is, a woman was classified as user of the drug at a given point in time if the dispensed supply from the last redemption had not run out or if it had run out within the last  $m$  days (where  $m$  is the allowed gap length) (14).

Because HT is likely to act as a promoter of ovarian cancer carcinogenesis with a yet unknown latency time, women currently taking hormones were categorized by the regimen that they took for the longest period during the study period. These variables were time varying; that is, if a woman began a new HT regimen, she would be recategorized if and when the time taking that regimen exceeded the amount of time she took the prior categorization HT regimen. The length of use was calculated as the time spent taking all systemic treatments during the study period. Whether a woman had taken hormones before 50 years of age but within the 11-year study period was accounted for in the hormone status categories, and the amount of time for which she took the hormones was accounted for in the duration of use category. The HT categories were HT use (never, past, current nonvaginal HT use, or other current use (i.e., current use of vaginal ET or a hormone intrauterine device)); hormone formulation (ET, estrogen/progestin therapy (EPT), or other (i.e., tibolone, raloxifene, progestin only, or vaginal estrogen)); hormone regimen (cyclic EPT, continuous EPT, or other); route of administration (oral ET, oral EPT or tibolone, dermal ET, dermal EPT, or other); duration of HT in years (never, current, 0.01–4 years, 4.01–7 years, or >7 years or use of vaginal ET or a hormone intrauterine device); and time since last use among former users (never, current, 0.01–2 years, 2.01–4 years, 4.01–6 years, or >6 years or use of vaginal ET or a hormone intrauterine device).

### Ovarian cancer cases

Until December 31, 2002, we used the Danish Cancer Register to identify cases of primary invasive ovarian cancers and their histologies, using the *International Classification of Diseases for Oncology* topography code 183.0 and morphology codes ending with a 3. At time of the present study, information from January 2003 had not been updated in the

Danish Cancer Register. Thus, from 2003 onward, the Pathology Register was used for case findings and information on histology. The invasive epithelial tumors were classified as serous (codes M84413, M84603, M84613, and M90143), endometrioid (codes M83803 and M83813), mucinous (codes M84703, M84803, and M90153), clear-cell (codes M83103 and M83133), adenocarcinoma not otherwise specified (code M81403), or epithelial not otherwise specified (codes M80203, M80703, M81303, M85603, M89333, M89803, and M90003). Nonepithelial invasive tumors and borderline tumors were not included. Eight women for whom we did not have histologic information were excluded. Information on the stages of disease was available from the Danish Cancer Register until December 31, 2002.

### 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 and 95% confidence intervals were calculated for each model. Age was calculated using birth dates, which were extracted from personal identification numbers. Age was used as a timescale in the Poisson regression analyses with 5-year age bands (50–54 years of age, etc), assuming a constant risk of ovarian cancer within each band. As a model control, we tested the significance of the interaction between age and HT and between age and risk of ovarian cancer. All tests were 2-sided with a 5% significance level. Furthermore, hysterectomy and time period (1995–2002 or 2003–2005) were evaluated as possible effect modifiers; however, no effect modification was found. The incidence rate ratios were similar across the possible effect modifiers.

The National Register of Patients and Statistics Denmark provided information on potential confounders. Potential confounders were number of births (0, 1, 2, or >2), hysterectomy, sterilization, unilateral oophorectomy or salpingo-oophorectomy, endometriosis, infertility, and educational status in 1995 (<2 years of education after high school, 3–4 years of education after high school (including bachelor degrees), university degrees (≥5 years of education after high school), or unknown). Furthermore, we adjusted for the year in which the diagnosis was made to account for possible differences in ovarian cancer diagnosis in the Cancer and Pathology Register. The following variables were time-dependent, and data were updated daily: HT variables, hysterectomy, sterilization, unilateral oophorectomy or salpingo-oophorectomy, and number of births. Women who had been diagnosed with endometriosis or infertility were considered to have that condition throughout the study period. The crude models included exposure, age, and time period.

For a subgroup of the cohort (women followed from 1995–2002), we conducted analyses by the stage of disease. Women for whom we did not have information on the stage of disease were excluded ( $n = 112$ ). Separate analyses were conducted to assess the risk of each of the different subtypes of epithelial ovarian cancer associated with hormone use. There were too few women exposed to other hormones (i.e., progestin-only therapy, raloxifene, tibolone, hormone

intrauterine device combinations, and conjugated estrogens) to allow determination of reliable risk estimates. The reference group was women who had never used any hormones.

### RESULTS

From 1995 to 2005, a total of 909,946 perimenopausal and postmenopausal women with no previous cancer or removal of ovaries accumulated 7.3 million person-years of observation, corresponding to an average follow-up period of 8.0 years. The number of incident malignant epithelial ovarian cancers during the study period was 2,681. Of these, 1,336 were serous tumors, 377 were endometrioid tumors, 293 were mucinous tumors, 159 were clear-cell tumors, 115 were nonspecified epithelial tumors, and 401 were adenocarcinomas not otherwise specified. At the end of follow up, 63% of the women remained never users of HT, 22% were previous users, and 9% were current users. Compared with never users, hormone users were more likely to have undergone a hysterectomy (18.0% versus 6.2%) or unilateral salpingo-oophorectomy (5.7% versus 1.9%), to have been sterilized (8.4% versus 5.4%), and to be parous (80.8% versus 75.2%). The characteristics of the study population have been published previously (4).

#### Hormone use

Compared with never users, current users of hormones had an increased risk of serous tumors (incidence rate ratio (IRR) = 1.7, 95% confidence interval (CI): 1.5, 1.9) and of endometrioid tumors (IRR = 1.7, 95% CI: 1.3, 2.2). Current use of hormones was not associated with the risk of mucinous or clear-cell tumors (Figure 1). The incidence rate ratios for serous ovarian cancer increased with duration of hormone use (0.01–4 years, IRR = 1.5, 95% CI: 1.3, 1.8; 4.01–7 years, IRR = 1.7, 95% CI: 1.4, 2.1; and >7 years, IRR = 2.1, 95% CI: 1.6, 2.8). The incidence rate ratios for other types of epithelial ovarian cancer were not consistently associated with duration of use (Figure 2).

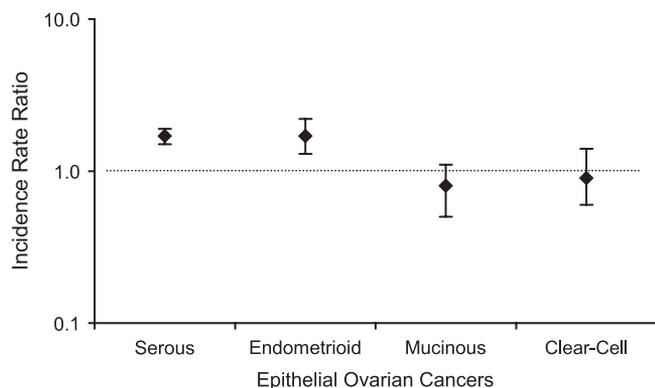
#### Time since hormone use

We found increased incidence rate ratios for serous ovarian cancers for a period of up to 2 years after cessation of HT. Thereafter, the risk approached that observed in never users. For endometrioid tumors, the risk was not significantly increased after cessation of HT (Figure 3).

#### Estrogen therapy

Compared with never users, women on unopposed ET had an increased risk of serous tumors (IRR = 1.7, 95% CI: 1.4, 2.1) and a tendency toward an increased risk of endometrioid tumors (IRR = 1.4, 95% CI: 0.9, 2.1). In contrast, the risk of mucinous tumors was decreased (IRR = 0.3, 95% CI: 0.1, 0.8). No association was found between ET and the risk of clear-cell tumors (IRR = 0.6, 95% CI: 0.2, 1.5) (Figure 4).

Women on oral ET had a statistically significantly increased risk of endometrioid tumors (IRR = 1.5, 95% CI: 1.0, 2.4), and the risks for serous, mucinous, and clear-cell tumors were similar to the risks found for all ET. Because the risk



**Figure 1.** Incidence rate ratios of epithelial ovarian cancers associated with current use of hormone therapy, Danish Sex Hormone Register Study, 1995–2005. Values were adjusted for age, period of use, number of births, hysterectomy, sterilization, unilateral oophorectomy or salpingo-oophorectomy, endometriosis, infertility, and educational level. The reference group was never users of hormone therapy (dashed line). Bars, 95% confidence interval.

associations between transdermal ET and ovarian cancers were based on a few cases, the data are not shown. Vaginal estrogen alone was associated with an increased risk of serous tumors (IRR = 1.4, 95% CI: 1.1, 1.9), whereas no associations were found with endometrioid, mucinous, or clear-cell tumors (data not shown).

### Combined therapy

Women on combined EPT had increased incidence rate ratios for serous tumors (IRR = 1.6, 95% CI: 1.4, 1.9) and endometrioid tumors (IRR = 2.0, 95% CI: 1.5, 2.6), whereas no associations were found with mucinous or clear-cell tumors (Figure 4). Similar risk associations were found among women on oral EPT. Because there were few cases, data for transdermal EPT are not shown.

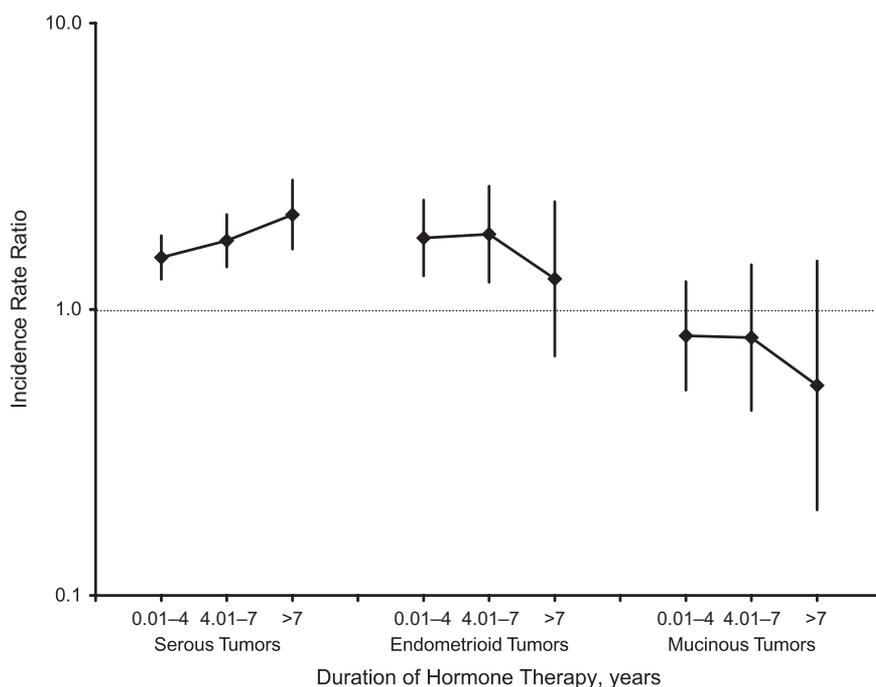
### Duration of HT

The incidence rate ratios for serous ovarian cancer increased with increased duration of ET and after 7 years reached an incidence rate ratio of 2.9 (95% CI: 1.9, 4.3). The risks for endometrioid ovarian cancer were similar for all durations of ET (Table 1).

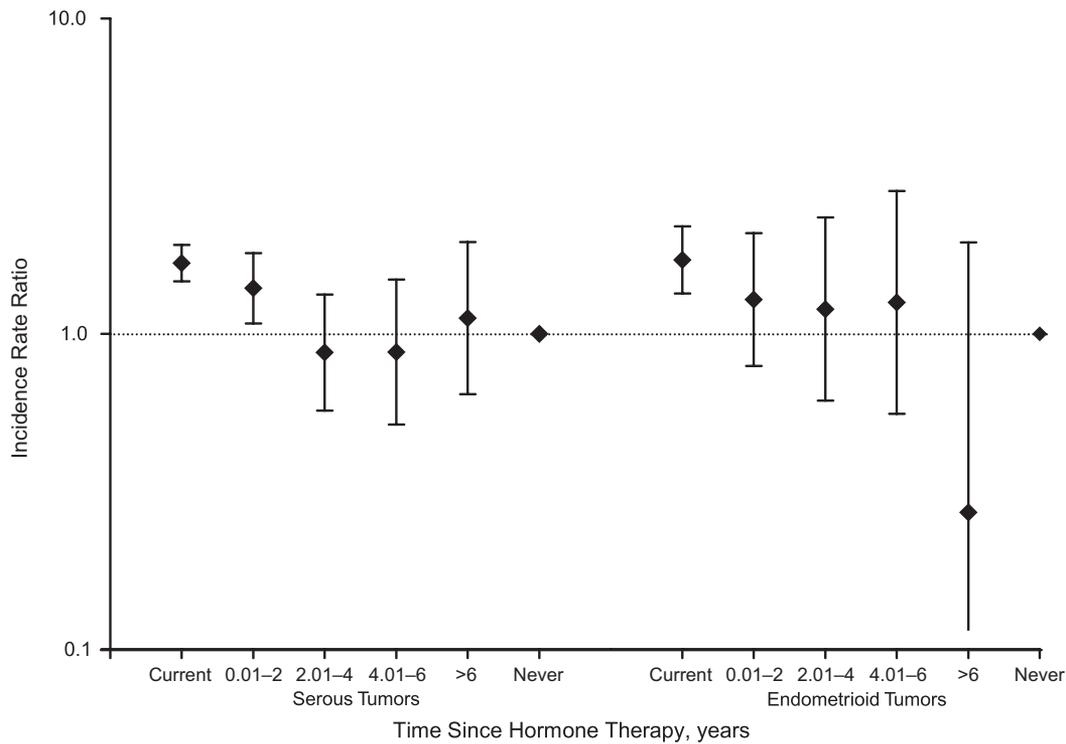
Among women on cyclic EPT, the risk of endometrioid ovarian cancer was increased by 70%–140%, whereas the risk was not increased among women on continuous EPT. The risks for serous ovarian cancer were similar regardless of the duration of cyclic or continuous EPT (Table 1). Results from crude and adjusted analyses were almost identical (data not shown).

### Stage of disease

Overall, the associations between HT and risks of different ovarian tumors did not change after adjustment for the stage of disease (Table 2). Although the analyses were



**Figure 2.** Incidence rate ratios of epithelial ovarian cancers associated with durations of hormone therapy in years, Danish Sex Hormone Register Study, 1995–2005. Values were adjusted for age, period of use, number of births, hysterectomy, sterilization, unilateral oophorectomy or salpingo-oophorectomy, endometriosis, infertility, and educational level. The reference group was never users of hormone therapy (dashed line). Risk estimates for clear-cell cancer are not shown because there were few cases. Bars, 95% confidence interval.



**Figure 3.** Incidence rate ratios of serous and endometrioid ovarian cancers associated with time since last hormone therapy use in years, Danish Sex Hormone Register Study, 1995–2005. Values were adjusted for age, period of use, number of births, hysterectomy, sterilization, unilateral oophorectomy or salpingo-oophorectomy, endometriosis, infertility, and educational level. The reference group was never users of hormone therapy (dashed line). Bars, 95% confidence interval.

slightly weakened by a lower number of cases, the results roughly showed similar incidence rate ratios across the stages of disease (Table 2).

## DISCUSSION

The present large cohort study suggests that there is a differential influence of HT on different subtypes of ovarian cancer. Hormone users had an excess risk of serous and endometrioid tumors but not of mucinous and clear-cell cancers of the ovaries. Both combined EPT and unopposed ET were associated with increased risks of serous ovarian cancer. Furthermore, cyclic EPT and oral ET were associated with increased risks of endometrioid ovarian cancer. In contrast, no HT was associated with risk of clear-cell ovarian cancer, and women who had used ET had a decreased risk of mucinous ovarian cancer.

### Serous ovarian cancer

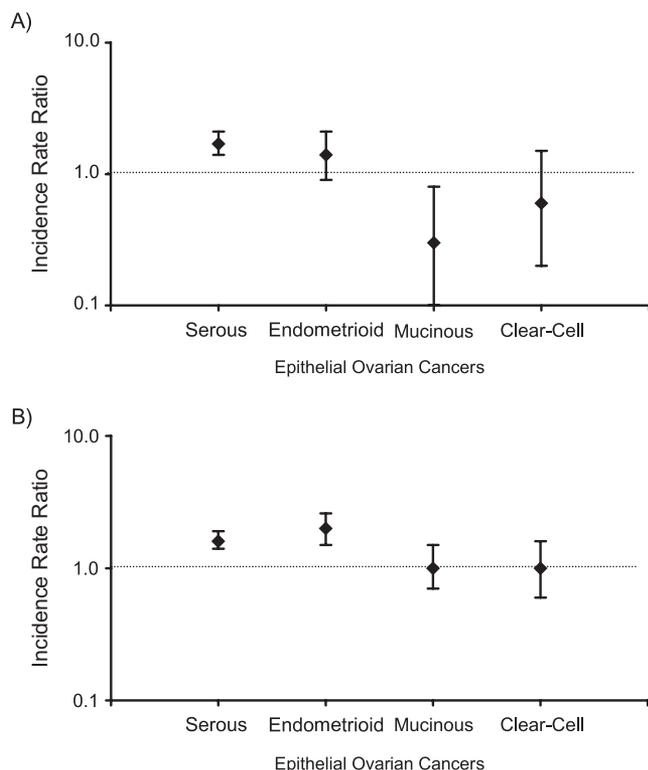
Two large prospective cohort studies, the NHS and the Million Women Study, also found an increased risk of serous ovarian cancer among hormone users (3, 12). In accordance with our finding, the Million Women Study reported an approximately 50% increased risk with HT (3).

The NHS supports our finding that increasing duration of ET is associated with increasing rate ratios for serous ovarian cancer (12).

### Endometrioid ovarian cancer

Although the Million Women Study found no association between any HT and the risk of endometrioid ovarian cancer, we found a 70% increased risk (3). The NHS found a 50% increased risk of endometrioid tumors after 5 years of ET (12). In our study, women on oral ET had an up to 2-fold increased risk of endometrioid tumors. Because ET increases the risk of endometrial cancer (15) and endometrioid ovarian tumors are histologically similar to endometrial tissue (16), it seems likely that ET acts through similar biologic mechanisms in the development of endometrioid ovarian cancer, a hypothesis suggested by Danforth et al. (12).

Furthermore, the present study suggests that women on cyclic EPT have an increased risk of endometrioid ovarian cancer, whereas the risk is not increased in women on continuous EPT. Only one study addressed the risk of endometrioid ovarian tumors among women on cyclic versus continuous EPT, and those investigators were not able to demonstrate an increased risk with cyclic or continuous EPT (7). With regard to the development of endometrial cancer, the increased risk



**Figure 4.** Incidence rate ratios of epithelial ovarian cancers associated with hormone therapy, Danish Sex Hormone Register Study, 1995–2005. A) Estrogen-only therapy; B) estrogen/progestin therapy. Values were adjusted for age, period of use, number of births, hysterectomy, sterilization, unilateral oophorectomy or salpingo-oophorectomy, endometriosis, infertility, and educational level. The reference group was never users of hormone therapy (dashed line). Bars, 95% confidence interval.

has been found to be confined to women on cyclic EPT (15). Thus, it is possible that cyclic EPT acts through similar biologic mechanisms in the development of endometrioid ovarian cancer.

### Mucinous ovarian cancer

Compared with women who were never prescribed HT, women on ET had a 70% decreased risk of mucinous ovarian cancer. The Million Women Study also found a decreased risk of approximately 30% with the use of HT (3). A few other studies have also suggested that HT is associated with a decreased risk of mucinous ovarian cancer (12, 17, 18). One group of mucinous tumors is similar to endocervical epithelium and another is similar to colonic epithelium (16). Both HT in general and ET specifically have been found to decrease the risk of colon cancer (19, 20). It therefore seems plausible that ET could also decrease the risk of mucinous ovarian cancer. Risch et al. (5) were the first to suggest different etiologies for mucinous and nonmucinous ovarian cancers, and a recent Danish study supported this hypothesis by suggesting significant differences in the risk between mucinous and nonmucinous tumors (6).

### Implications

Using the same data as in current study, Mørch et al. (4) found a 40% increase in the overall risk of ovarian cancer in current users of hormones, regardless of the duration and type of HT. However, in the present study, the risk of serous ovarian tumors increased with increasing durations of hormone use. This association was more pronounced among women using ET. After 7 years, the risk of serous ovarian cancer had increased 3-fold among women using ET compared with never users. On the other hand, restricting the analysis to mucinous tumors showed a decreased risk among women using ET. Thus, important information about a differential impact of HT, HT types, and associations with duration of hormone use are not described when different ovarian tumors are examined as a combined outcome.

Moreover, the clarification of the different associations between HT and subtypes of ovarian cancer adds to the understanding of how HT acts as a promoter of ovarian cancer carcinogenesis, as the results are in line with the current knowledge about HT-associated risks of cancers with similar epithelial origins. Because of this, it seems plausible that there is a causal association between HT and ovarian cancer. Other risk factors for ovarian cancer differ based on the type of tumor (mucinous vs. nonmucinous), supporting the hypothesis of different etiologies (5, 6). The differences should be considered in research study design and suggest that different types of ovarian tumors should be viewed as separate diseases.

### Strengths of study

To our knowledge, our nationwide cohort study is the largest conducted thus far to explore the influence of HT on the risk of histologic subtypes of epithelial ovarian cancer. The validity of our outcome is considered to be high, as data from the Cancer Register validated the diagnoses (21–23). The agreement of histologic ovarian cancer diagnoses between the Pathology Register and the Cancer Register is high, and our estimates did not depend on the source of diagnoses (24). The information on prescribed HT is transferred electronically from all Danish pharmacies by using bar codes, eliminating recall bias. Our information on both exposures and confounders was updated daily through the national registers, making it possible for us to account for changes in exposures. We excluded women with previous cancer because it might affect both the use of hormones and the subsequent risk of ovarian cancer. Our results were adjusted for age, time period, educational level, number of births, and history of hysterectomy, sterilization, unilateral oophorectomy, salpingo-oophorectomy, endometriosis, or infertility. There was, however, no significant confounding by any of the included variables. We found no evidence of earlier detection (surveillance bias) of ovarian tumors among women on HT. Finally, the stage of disease did not bias the differential association between HT and different tumor types.

### Limitations of study

Data from the National Register of Medicinal Product Statistics is not complete for the time period before January 1995. Thus, information about prescriptions for oral

**Table 1.** Relative Risks<sup>a</sup> of Serous and Endometrioid Ovarian Cancers, by Duration of Hormone Therapy, Denmark, 1995–2005

| Hormone Therapy Duration, years       | Type of Tumor <sup>b</sup> |     |          |              |     |          |
|---------------------------------------|----------------------------|-----|----------|--------------|-----|----------|
|                                       | Serous                     |     |          | Endometrioid |     |          |
|                                       | No. of Cases               | IRR | 95% CI   | No. of Cases | IRR | 95% CI   |
| Estrogen-only therapy                 |                            |     |          |              |     |          |
| 0.01–4                                | 43                         | 1.4 | 1.0, 1.9 | 14           | 1.4 | 0.8, 2.4 |
| 4.01–7                                | 30                         | 1.7 | 1.2, 2.4 | 9            | 1.5 | 0.8, 3.1 |
| >7                                    | 25                         | 2.9 | 1.9, 4.3 | 4            | 1.2 | 0.4, 3.3 |
| Cyclic estrogen/progestin therapy     |                            |     |          |              |     |          |
| 0.01–4                                | 64                         | 1.5 | 1.2, 2.0 | 25           | 2.1 | 1.4, 3.2 |
| 4.01–7                                | 42                         | 1.9 | 1.4, 2.6 | 15           | 2.4 | 1.4, 4.1 |
| >7                                    | 14                         | 1.5 | 0.9, 2.6 | 5            | 1.7 | 0.7, 4.2 |
| Continuous estrogen/progestin therapy |                            |     |          |              |     |          |
| 0.01–4                                | 31                         | 1.6 | 1.1, 2.0 | 10           | 1.8 | 0.9, 3.4 |
| 4.01–7                                | 15                         | 1.3 | 0.8, 2.6 | 5            | 1.5 | 0.6, 3.8 |
| >7                                    | 12                         | 1.9 | 1.1, 2.6 | 1            | 0.5 | 0.1, 3.9 |

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

<sup>a</sup> Adjusted for age, time period, number of births, educational level, and history of hysterectomy, sterilization, unilateral oophorectomy or salpingo-oophorectomy, endometriosis, and infertility. The reference group was never users of hormone therapy.

<sup>b</sup> Because there were few cases, the incidence rate ratios for mucinous and clear-cell tumors are not presented. For the same reason, data for the group on long-cycle estrogen/progestin therapy are not presented for any of the tumor types.

contraceptive use was not available for the women in current study who were 50 years of age or older from 1995–2005. Our incidence rate ratios may be underestimated because of confounding by use of oral contraceptives, as oral contraceptive use decreases the risk of ovarian cancer and often leads to HT (25, 26). We were not able to restrict our analyses to nonobese women. The ovarian cancer risk associated with HT use is probably clearer in nonobese women (i.e., in women with a body mass index, measured as weight in kilograms divided by height in meters squared, <30) (27). Consequently, our results might be underestimated among nonobese. However, the Million Women Study adjusted data for oral contraceptive use, body mass index, age at menopause, alcohol consumption, smoking, and physical activity,

and the adjustments did not result in material changes in their estimates (3). Also, the NHS reported only minimal changes in the association between HT and the risk of ovarian cancer after adjustment for relevant potential confounders, including duration of oral contraceptive use, occurrence of natural menopause, and age at menarche (12). The lack of information on family history of cancer might have caused an underestimation of risk in our results, as women with a family history of cancer are probably less likely to use hormones. Information on women who underwent surgical procedures was not available in the registers for the oldest women. Hysterectomy and oophorectomy reduce the risk of ovarian cancer and often lead to HT use, probably causing an underestimation of risk in older women in our results.

**Table 2.** Relative Risks<sup>a</sup> of Ovarian Cancers With Hormone Therapy by Stage of Disease, Denmark, 1995–2002

|                                  | Type of Tumor |            |              |            |          |            |            |             |
|----------------------------------|---------------|------------|--------------|------------|----------|------------|------------|-------------|
|                                  | Serous        |            | Endometrioid |            | Mucinous |            | Clear Cell |             |
|                                  | IRR           | 95% CI     | IRR          | 95% CI     | IRR      | 95% CI     | IRR        | 95% CI      |
| Current hormone use              | 1.64          | 1.41, 1.89 | 1.81         | 1.39, 2.36 | 0.74     | 0.51, 1.08 | 0.81       | 0.50, 1.32  |
| Current hormone use <sup>b</sup> | 1.50          | 1.29, 1.75 | 1.82         | 1.39, 2.39 | 0.86     | 0.59, 1.27 | 0.87       | 0.53, 1.43  |
| Stage I                          | 1.85          | 1.09, 3.13 | 2.59         | 1.43, 4.72 | 0.74     | 0.33, 1.64 | 0.59       | 0.20, 1.75  |
| Stage II                         | 2.12          | 0.89, 5.00 | 0.52         | 0.15, 1.84 | 0.39     | 0.05, 3.25 | 1.02       | 0.09, 11.66 |
| Stage III                        | 1.50          | 1.16, 1.92 | 1.34         | 0.73, 2.48 | 0.96     | 0.44, 2.10 | 0.56       | 0.13, 2.51  |
| Stage IV                         | 1.44          | 1.03, 2.02 | 2.22         | 1.08, 4.57 | 0.65     | 0.19, 2.24 | 0.28       | 0.04, 2.19  |

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

<sup>a</sup> Adjusted for age, time period, number of births, educational level, and history of hysterectomy, sterilization, unilateral oophorectomy or salpingo-oophorectomy, endometriosis, and infertility. The reference group was never users of hormone therapy.

<sup>b</sup> Additionally adjusted for the stage of disease.

However, despite our uneven adjustment for confounders, the risks for ovarian tumors were nearly identical across age groups.

Smoking has been found to increase the risk of mucinous ovarian cancer but not of nonmucinous tumors (6, 28). One Danish study suggested that smoking was unrelated to HT use, whereas 2 other Danish studies found slightly more smokers among hormone users (29–31). Thus, the decreased risk of mucinous ovarian cancer with ET found in our study may be underestimated. In a pooled analysis of 10 case-control studies, the most important confounders (parity and oral contraceptive use) were equally associated with different histologies (28). Thus, the potential bias by, for example, oral contraceptives, would equally underestimate the risk associations between HT and ovarian tumors, not affecting the differential influence of HT on the different subtypes of ovarian cancer. In conclusion, the missing potential confounders in the present study were not likely to cause overestimation of the associations between HT and ovarian cancer.

We did not have an independent pathologist review the histologic classifications of cases. A prior Danish study did this in approximately 30% of women diagnosed with ovarian cancer between 1995 and 1999 and found a discrepancy between the original histologic classification (serous, endometrioid, mucinous, or other) and their classification in 17.8% of cases (6). There was a 3% discrepancy in tumors categorized as mucinous/nonmucinous (6). Assuming this applies to our study, it may have biased the results towards lower observed differences between mucinous and nonmucinous tumors.

Older women who entered our study in 1995 might have been taking hormones before the study entry and could potentially have been misclassified either as never users or short-term users. This potential misclassification would tend to weaken the true risk associations with both HT use and duration of HT use among the older women. However, the associations among HT, duration of use, and risks of ovarian tumors were similar among young women for whom complete information on HT exposure history was available and older women. These findings reduce the probability of bias caused by exposure misclassification. In addition, our results indicate that increasing durations of HT use increased the risk of serous ovarian tumors, an association that was more pronounced among women taking ET. Thus, a potential misclassification of durations of hormone use should then be restricted to women diagnosed with specific ovarian tumors and to women using specific HT, which seems unlikely. Finally, dispensed medicine is not necessarily taken. Repeated prescriptions, however, reduce this potential bias, as it seems unlikely that women continue to redeem prescription for medication they do not take.

## Conclusion

Hormone users had an excess risk of serous and endometrioid but not mucinous or clear-cell cancers of the ovary. In contrast, ET was associated with decreased risk of mucinous ovarian cancer. The results are consistent with recent cohort studies. Thus, the HT associated risk of ovarian cancer should be examined according to tumor histology and viewed as separate diseases.

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