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ORIGINAL PAPER

Hormone therapy and ovarian borderline tumors: a national cohort study

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Abstract
Purpose Little is known about the influence of postmenopausal hormone therapy on the risk of ovarian borderline tumors. We aimed at assessing the influence of different hormone therapies on this risk.
Methods A total of 909,875 Danish women 50–79 years old without previous hormone-sensitive cancers or bilateral oophorectomy were followed in this nationwide cohort study 1995–2005. The National Register of Medicinal Product Statistics provided exposure information on all women who redeemed prescriptions on hormone therapy. The National Cancer and Pathology Register provided data on borderline ovarian tumors. Information on confounding factors was available from other national registers. Poisson regression analyses provided risk estimates with hormone exposures as time-dependent covariates.
Results In an average of 8.0 years of follow-up, 703 incident ovarian borderline tumors were detected. Compared with never users, hormone use for more than 4 years increased the risk of borderline tumors: relative risk (RR) 1.40; 95% confidence interval (CI), 1.09–1.81. Combined estrogen and progestin therapy for more than 4 years increased the risk: RR 1.49 (1.10–2.01), with no difference between cyclic and continuous combined therapy ($p = 0.83$); RR 1.56 (1.08–2.25) and 1.45 (0.87–2.43), respectively. The RR with estrogen therapy did not differ significantly from RR with combined therapy ($p = 0.58$): RR 1.27 (0.82–1.98). Disregarding the type of hormone therapy, hormone use for 4 years or less did not increase the risk of borderline tumors.
Conclusions Combined hormone therapy for more than 4 years increases the risk of ovarian borderline tumors.

Keywords Ovarian borderline tumors · Hormone therapy · Hormone regimens · And duration of hormone use

Abbreviations

RR	Relative risk
HT	Postmenopausal hormone therapy
ET	Estrogen-only therapy
EPT	Estrogen/progestin therapy
DaHoRS	Danish Sex Hormone Register Study
ATC	Anatomical therapeutical chemical code
DDD	Defined daily doses

Introduction

Ovarian borderline tumors are a low malignancy subgroup of ovarian tumors. It has long been held that borderline tumors can be precursors of invasive ovarian cancer. Many studies on the epidemiology of ovarian cancer have viewed borderline tumors and invasive carcinomas as one group. However, that view is increasingly questioned, as both

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epidemiological and biomedical studies have produced evidence of distinct differences between these two groups of tumors [1].

Postmenopausal hormone therapy (HT) is likely to increase the risk of ovarian cancer [2]. Recently, it has been suggested that the risk is increased irrespective of the type of HT [3, 4]. However, a differential risk between combined HT and estrogen-only therapy has also been suggested. [5] Only few studies have examined the association between HT and exclusively ovarian borderline tumor [6–8]. There is support for a weak-to-moderate association [6, 7]; however, also no association has been suggested [8]. One study finds the risk confined to estrogen therapy, whereas no risk was seen when progestins were added to the estrogen [7]. Thus, further data are needed to clarify the risk of ovarian borderline tumor with different HT formulations and regimens. Our aim was to provide such data.

Methods

The Danish Sex Hormone Register Study (DaHoRS) follows a National Cohort of Danish women 15–79 years old, from 1995 to explore the influence of sex hormones on the risk of cardiovascular diseases and different female cancers [4, 9, 10].

Since 1968, all citizens in Denmark have a personal identification number, which is registered in the Civil Registration System that also records the date of birth, immigration, emigration, deaths, and actual residence. The personal identification number allows reliable linkage between different national registers for scientific purposes.

In order to explore the influence of sex hormones on the risk of cardiovascular diseases and various female cancers, including ovarian tumor, the DaHoRS cohort has been linked to seven different national registers: (1) the Civil Registration System, (2) the 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, not complete until 1997, (5) the National Register of Patients, which comprises information on discharge diagnoses and surgical codes on all somatic hospitalizations since 1977 and information on births computerized since 1973, (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.

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

The study was approved by the Danish Data Protection Agency and the Danish Medicinal Agency (J. No 5121-59). The Danish Ethical Committee is not involved in register studies.

Study population

The present study includes women at least 50 years of age by 1 January 1995, through 31 December 2005 ($n = 960{,}887$).

From the initial 960,887 women, we excluded women with a diagnosis of invasive or ovarian borderline tumor prior to entry (1943–1995 or after 1 January 1995, but prior to their fiftieth birthday). The Danish Cancer Register (updated until 2002 at the time of data retrieval) was used for exclusion and was used for censoring of women with invasive ovarian cancer during follow-up until 2002. The Pathology Register was used from 2003 to 31 December 2005, for censoring of women with invasive ovarian cancer during follow-up. For identification of invasive ovarian cancer, we used the ICD for oncology topography code183.0 and morphology codes ending with 3 and the Systemized Nomenclature of Medicine topography codes (87,000–87,800) and the morphology codes ending with 3. The Danish Cancer Register was used until 31 December 2002, and the Pathology Register from 2003 for the identification of ovarian borderline tumors.

As the National Register of Patients was updated until 31 December 2005, we used this register for censoring during follow-up of other cancers that potentially could have caused a change in use of hormones. The same register was used for exclusion of these cancers prior to entry (1980–1995 or after 1 January 1995, but prior to their fiftieth birthday). The cancers were specified by the WHO's international classification of diseases (ICD) codes version ICD-8 (1980–1993)/ICD-10 (1994–) for breast cancer (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).

Women who, according to the National Register of Patients, prior to entry (1980–1995 or after 1 January 1995, but prior to their fiftieth birthday) had bilateral oophorectomy (surgical code 60120 or KLAE20/21) or bilateral salpingooophorectomy (60320 or KLAF10/11) were excluded.

Women who were 80 years of age or older or had a diagnosis of ovarian tumor on the day of study entry were excluded. This left a total of 909,875 women at study entry.

Censoring was made at the time of death, emigration, event of other cancers known to influence hormone use (including invasive ovarian cancer), at the time of bilateral oophorectomy or salpingooophorectomy, 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 (ATC), dose, number of packages, defined daily doses (DDD), and route of administration (tablet, patch, gel, etc.) The included ATC codes have been previously described [9]. Briefly, prior to data retrieval, detailed rules were used to allocate women to a specific subgroup of hormone use at a certain time and for shift between different groups. The prescribed defined daily doses determined the length of use, and combination therapy trumped estrogen-only therapy in case of contemporary prescription though the estrogen dose was upgraded.

The information on initiation of hormone use (i.e., redeemed prescriptions) was updated daily for each individual during the study period. All 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. Gaps between prescriptions were filled prospectively if not longer than 4 months [11].

Because HT is likely to act as a promoter of the ovarian cancer carcinogenesis with a yet unknown latency time, women currently taking hormones were allocated to the hormone type taken for the longest period during the study period. However, this allocation was time-dependent i.e., a change in HT type would re-categorize a woman into a new category of HT, if at that given time the new HT was taken for a longer period than the former HT. Length of use was calculated as the sum of all systemic treatments during the study period.

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

The HT categories are described in detail in a prior publication [4], briefly: *HT status* (never, past, current HT, others (i.e., current vaginal ET, hormone intrauterine device (IUD), and injections)), *hormone formulation* (never, past, estrogen only, estrogen/progestin, others (i.e., tibolone, raloxifene, progestin only, vaginal estrogen)), *estrogen dose* (never, past, high (>2 mg/day of oestradiol), middle (1–2 mg/day), low (<1 mg/day), others), *hormone regimen* (never, past, cyclic combined estrogen/progestin therapy, long-cycle combined estrogen/progestin therapy (defined as simultaneous redemption of 7–14 times more DDD estrogen than DDD progestin), continuous combined estrogen/progestin therapy, others), *duration of HT* in years (never, past, current: 0–4 and >4 years, others), and *time since last use* among former users (current, 0–2, >2–4, >4–6, >6 years, never).

Analysis

The data were analyzed with Poisson regression analysis using SAS statistical software version 9.1. Incidence rate ratios (RR) and 95% confidence intervals were calculated for each model. Age was calculated from birth dates, which were extracted from the personal identification numbers. Age was used as the timescale in the Poison regression analyses, and data were divided into 5-year age bands (50–54, etc.), assuming a constant risk of ovarian tumor within each band. As model control, each model was checked for interaction between age and exposure. All tests were two sided with 5% significance level. In initial analyses, finer age adjustments were conducted, however, with similar results. Therefore, 5-year age bands were used in the final analyses to improve the handling of data.

Potential confounders were hysterectomy (surgical code: 610/KLCD00-97), number of births (0, 1, 2, >2) (ICD8/ICD10: 650-666/DO 60-84), sterilization (surgical code: 608-640/KLGA), unilateral oophorectomy (60100/KLAE10-11), and unilateral salpingooophorectomy (60300/LAE00/01), endometriosis (ICD8/ICD10: 625.29-39/DN80), infertility (628/DN97), and educational status in 1995 (elementary school/high school, occupational basic education, short-term/middle-term/long-term education, or unknown). Furthermore, adjustments were made for time periods (1995–2002 and 2003–2005) to account for possible differences in ovarian tumor diagnosis by time in the Danish Cancer Register and Pathology Register.

The following variables were time-dependent: HT variables, hysterectomy, sterilization, unilateral oophorectomy or salpingooophorectomy, and number of births. Women who had been diagnosed with endometriosis or infertility were considered being in this condition during the study period.

A few cases had a surgical code of hysterectomy ($n = 23$), unilateral salpingooophorectomy ($n = 5$), or unilateral oophorectomy ($n = 2$) less than 1 month before the registration of ovarian borderline tumor. Due to a minor delay in registration of borderline tumors in the Cancer Register and Pathology Register, we considered these surgeries to be carried out concurrently with the removal of tumors. For the remaining cases with a surgical code of hysterectomy, salpingooophorectomy, or unilateral oophorectomy, the registration was 5 or more month before the diagnosis of ovarian borderline tumor (month before diagnosis: hysterectomy; ≥5 month, unilateral salpingooophocectomy; ≥12 month, unilateral oophorectomy; ≥15 month).

The number of women exposed to progestin-only therapy, raloxifene, tibolone, hormone-IUD, and long-cycle combined therapy was too few to determine risk estimates.

The reference group was those who had never used any HT (oral, transdermal, or vaginal).

Sensitivity analyses were conducted to explore the impact of a change between different HT types on the RR's. In these analyses, women were censored if they changed to another HT type during follow-up but were allowed to start and stop the same HT.

Role of the funding source

This study was supported by a grant from the Danish Cancer Society (J No DP05006). The Danish Cancer Society had no role in data collection, analysis, and interpretation of data; in writing of the report; and in decision to submit the article for publication.

Results

From 1995 to 2005, 909,875 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 of 8.0 years. The number of incident ovarian borderline tumors during the study period was 703. Censoring due to diagnosis of invasive ovarian cancer was made for 3,068 women during follow-up. At the end of follow-up, 63% of the women remained never users of hormones, 22% were previous, and 9% current users of hormones while 4% were on vaginal HT. Of current users, 63% had used hormones for more than 4 years. Compared to never users, more hormone users had hysterectomy (18.0% vs. 6.1%) and unilateral salpingooophorectomy (5.7% vs. 1.9%) were sterilized (8.3% vs. 5.4%) and were parous (80.8% vs. 75.2%). This corresponds to descriptive results presented in a prior publication [4].

Any hormone use and ovarian borderline tumors

Neither current nor past use of hormones was significantly associated with ovarian borderline tumors, compared with never use (Table 1).

Hysterectomy, age, and time period of hormone therapy were evaluated as possible effect modifiers. No effect modification was found by hysterectomy, age, or time period on the association between HT and risk of ovarian borderline tumor.

However, when current HT was stratified by duration of hormone use ($\leq$4 and >4 years), increased risk was observed among current users of 4 or more years, compared with never users (Table 1). Those who had taken hormones for more than 4 years were at an overall increased relative risk of ovarian borderline tumors of 1.40 (95% CI, 1.09–1.81).

Time since hormone use and ovarian borderline tumors

We subcategorized previous users according to time since last use and found an increased relative risk of borderline tumors for a period of up to 2 years after cessation of HT. Thereafter, the risk approached the risk observed among never users: 1.36 (95% CI, 1.00–1.84) from 0 to 2 years after cessation, 1.18 (95% CI, 0.76–1.83) from >2 to 4 years, 0.85 (95% CI, 0.45–1.59) from >4 to 6 years, and 1.41 (95% CI, 0.85–2.35) for >6 years.

Table 1 Risk of ovarian borderline tumors by hormone therapy status and duration of use

	Person-years	No. of cases	RR (95% CI)[a]	RR (95% CI)[b]
HT status				
Never	4986758	454	1 (Referent)	1 (Referent)
Previous	841363	95	1.13 (0.90–1.42)	1.12 (0.89–1.40)
Current	1183714	120	1.15 (0.94–1.41)	1.10 (0.90–1.35)
Other	258168	34		
Duration of current HT, years				
0–4	643262	47	0.85 (0.63–1.15)	0.83 (0.61–1.12)
>4	540451	73	1.47 (1.15–1.89)	1.40 (1.09–1.81)
Other	258168	34		

Cl confidence interval; *HT* hormone therapy; *RR* relative risk

[a] Adjusted for age and time period

[b] Adjusted for age, time period, number of births, sterilization, unilateral oophorectomy and salpingooophorectomy, endometriosis, infertility, and educational status

Different types of hormone therapies

We stratified current use of hormones by different types of hormone therapies; the RR values were approximately similar indicating no overall increased risk of ovarian borderline tumors with any specific type of hormone use (Table 2).

Duration of different types of hormone therapies

When analyses were restricted to women taking hormones for more than 4 years, combined estrogen and progestin therapy was associated with an overall increased relative risk of ovarian borderline tumors of 1.49 (95% CI, 1.10–2.01) (Table 3).

Use of estrogen therapy was associated with an increased relative risk of ovarian borderline tumors: RR: 1.27 (95% CI; 0.82–1.98), though not statistically significant. The risk was, however, not different from the risk with combined therapy ($p = 0.58$) (Table 3).

An increased relative risk of borderline tumors was found with cyclic estrogen/progestin therapy for more than 4 years: 1.56 (95% CI; 1.08–2.25). Continuous estrogen/progestin therapy was associated with a relative risk of 1.45 (95% CI; 0.87–2.43) of borderline tumors. However, the difference between cyclic and continuous estrogen/progestin therapy was not statistically significant ($p = 0.83$) (Table 3).

Use of any type of hormones for 4 years or less did not confer any increased risk of ovarian borderline tumors (Table 3).

Results from the simple adjusted and the multiple adjusted analyses were nearly identical indicating minimal confounding by other risk factors.

Sensitivity analyses

The results did not change when women were censored during follow-up at the time of change to another HT type.

Discussion

This large cohort study confirms that women who have taken hormones for more than 4 years are at an approximately 40% increased risk of ovarian borderline tumor, compared with those who have not taken hormones. Our data suggest that the hypothesized promoting effect of hormone use is not present for borderline tumors when hormones are taken for 4 years or less. The increased risk among current users decreased after cessation of HT and disappeared 2 years after cessation. The risk of borderline tumors did not vary markedly according to the type of HT used, and the results were similar after restricting the analyses to women not changing HT type during follow-up.

Previous studies

Hormone users in the current study population have an increased relative risk of invasive ovarian cancer that corresponds to the relative risk of borderline ovarian tumors found in the current study [4]. The risk of invasive tumors did not vary by type of HT, which is in line with the findings in the current study on hormone-associated risks of borderline tumors [4]. The association between time since last hormone use and relative risk of ovarian borderline tumors also corresponds to the association found for invasive tumors. The risk of ovarian tumors among

Table 2 Risk of ovarian borderline tumors by current use of different types of hormone therapies

Hormone use	Person-years	No. of cases	RR (95% CI)[a]
Never	4986758	454	1 (Referent)
Previous	841363	95	1.12 (0.89–1.40)
Formulation			
Estrogen only	355247	37	1.03 (0.72–1.48)
Estrogen + progestin[b]	802009	85	1.19 (0.94–1.50)
Other	284626	32	
Estrogen dose			
Low	168231	22	1.38 (0.90–2.12)
Middle	459093	47	1.09 (0.80–1.49)
High	479047	48	1.13 (0.84–1.53)
Other	335510	37	
Type of combined regimen[b,c]			
Cyclic estrogen + progestin	512519	51	1.11 (0.83–1.49)
Continuous estrogen + progestin	242600	30	1.39 (0.96–2.02)
Other	686763	73	

CI, confidence interval; *HT*, hormone therapy; *RR*, relative risk

[a] Adjusted for age, time period, number of births, sterilization, unilateral oophorectomy and salpingooophorectomy, endometriosis, infertility, and educational status

[b] Exclusive tibolone

[c] Due to few cases, RR value for EPT long-cycle therapy is not presented

Table 3 Risk of ovarian borderline tumors according to duration of different types of hormone therapies

Type of hormone use duration	Person-years	No. of cases	RR (95% CI)[a]
Never	4986758	454	1 (Referent)
Previous	841363	95	1.12 (0.89–1.40)
Formulation, years			
Estrogen only, 0–4	186847	14	0.78 (0.44–1.38)
Estrogen only, >4	168399	23	1.27 (0.82–1.98)
Estrogen + progestin, 0–4[b]	454523	37	0.89 (0.62–1.27)
Estrogen + progestin, >4[b]	347486	48	1.49 (1.10–2.01)
Other	284626	32	
Type of combined regimen, years[b,c]			
Cyclic estrogen + progestin, 0–4	298435	20	0.73 (0.45–1.17)
Cyclic estrogen + progestin, >4	214084	31	1.56 (1.08–2.25)
Continuous estrogen + progestin, 0–4	129214	15	1.26 (0.72–2.19)
Continuous estrogen + progestin, >4	113385	15	1.45 (0.87–2.43)
Other	686763	73	

[a] Adjusted for age, time period, number of births, sterilization, unilateral oophorectomy and salpingooophorectomy, endometriosis, infertility, and educational status

[b] Exclusive tibolone

[c] Due to few cases, RR value for EPT long-cycle therapy is not presented

previous users was similar to that among never users 2 years after cessation [4]. In contrast to the results in the current study, the relative risk of invasive tumors seemed to be increased disregarding the duration of hormone use [4].

An increased risk of ovarian borderline tumor with hormone use is supported by two case–control studies; however, the results were statistically insignificant when the analyses were not stratified by duration of HT or the histology of tumors, respectively [6, 7].

Our finding of no increased risk associated with hormones taken for 4 years or less does not concur with those by Mills et al. [6], who found a statistically significant increased odds ratio (OR) of 2.57 (95% CI; 1.05–6.32) after only 2–3 years of hormone use. However, the hormone use was self-reported and could therefore be subject to reporting bias, possibly causing misclassifications of the duration of use.

Our estimated risk of borderline tumors of 1.27 (95% CI; 0.82–1.98) with estrogen therapy taken for more than 4 years is in line with the finding by Riman et al. [7] showing an OR of 1.65 (95% CI; 0.95–2.79) with estrogen therapy. The finding by Riman et al. [7] was, however, independent of the duration of use, and the risk was restricted to serous tumors. Furthermore, Riman et al. found that the risk of ovarian borderline tumors was confined to estrogen therapy. This opposes our results as we found an increased risk of 1.54 (95% CI; 1.10–2.16) with combined therapy for more than 4 years, compared with never use.

Strengths of study

Our nationwide prospective cohort study followed 909,875 Danish women over 11 years with no loss to follow-up. The validity of our outcome is high as the Cancer Register has both a high level of completeness and validated diagnoses [12–14]. We used the Pathology Register for case findings from 2002 to 2005. The agreement of histological ovarian tumor diagnoses between the Pathology Register and the Cancer Register is high, and our estimates did not depend on the source of diagnoses [15]. The information on prescribed HT is transferred electronically from all Danish pharmacies by bar codes eliminating recall bias. Our information on both exposures and confounders was updated daily through the national registers making it possible to account for changes in exposures. We excluded women with previous cancer, since this might affect both the use of hormones and the subsequent risk of ovarian borderline tumor. Our results were adjusted for age, time period, education, number of births, hysterectomy, sterilization, unilateral oophorectomy and salpingooophorectomy, endometriosis and infertility. There was, however, no significant confounding by any of the included variables.

Limitations of study

Our relative risks may be underestimated due to confounding by body mass index (BMI) and family history of cancer. Obese women (BMI above 30) have been suggested to have an increased risk of borderline tumors and less frequently use hormones [7]. Thus, more women who never use hormones may have an increased risk of ovarian borderline tumor that potentially cause an underestimation of the true risk associated with hormone use. Similarly, the lack of information on family history of cancer may imply that our results tend to be underestimated, as women with family history of cancer are less likely to use hormones [6]. In contrast, smoking has been linked to the risk of

mucinous ovarian borderline tumors [7, 16]; one Danish study suggests smoking to be unrelated to HT, while two other Danish studies found slightly more smokers among hormone users [17–19]. Thus, the lack of adjustment for smoking in this study could have slightly overestimated our results. However, our finding of an increasing risk of ovarian borderline tumor with duration of hormone use seems less likely to be explained by a potential confounding effect of smoking.

We used a surrogate measure for age at menopause (50 years of age). To address potential confounding by age at menopause, a subanalysis was conducted among the older women whom all were postmenopausal. The RR values were similar, which indicate no confounding by age at menopause of the association between HT and risk of ovarian borderline tumors.

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 tumors and often lead to HT, probably causing an underestimation of our results among the older women. However, our RR values were similar across age. In conclusion, the overall effect of the missing potential confounders in this study is unlikely to overestimate the risk associated with hormone use.

The National Register of Medicinal Product Statistics is not complete before January 1995. Thus, information on prescriptions on oral contraceptive use is not available for the women in current study, who was 50 years or older in the years 1995–2005. Our relative risks might be slightly underestimated due to confounding by the use of oral contraceptives, because oral contraceptive use often leads to HT and has been suggested to decrease the risk of ovarian borderline tumors [20, 21].

Older women entering our study in 1995 might have been on HT before the study entry and have a chance of being misclassified either as never users or short-term users, while in reality they are users for some years before 1995. This potential misclassification would tend to weaken the true risk associations with HT use and duration of hormone use among the older women. However, the associations between hormone use, duration of hormone use, and risks of ovarian borderline tumors were similar among young women for whom complete information on HT exposure history was available, compared with older women. These findings reduce the probability of bias caused by exposure misclassification.

The praxis on coding borderline ovarian tumors in the Danish registers has changed over time, and it is likely that some borderline tumors have been coded as invasive tumors. Thus, the completeness of borderline tumors is not expected to be high in this study. On the other hand, the borderline tumors included in the registers are expected to be valid.

The aim of the current study was to nuance the current evidence of health risks associated with different types of HT. Future studies are needed about potentially differential risk associations between HT and risks for different histologic subtypes of ovarian borderline tumors.

Finally, redeemed 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 therapy for more than 4 years most likely increases the risk of ovarian borderline tumors. No difference in risk was found between estrogen-only therapy, cyclic combined therapy, and continuous combined therapy.

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Conflict of interest The authors Mørch, Løkkegaard, Andreasen, and Kjær have no conflicts of interest. Lidegaard has received grants from Schering AG, Berlin, for cover of research expenses and has received fees for speeches on pharmacoepidemiological issues from Schering Denmark and Novo Nordisk.

References

1. Crispens MA (2003) Borderline ovarian tumors: a review of the recent literature. Curr Opin Obstet Gynecol 15(1):39–43
2. Greiser CM, Greiser EM, Dören M (2007) Menopausal hormone therapy and risk of ovarian cancer: systematic review and meta-analysis. Hum Reprod Update 13(5):453–463
3. Beral V, Million Women Study Collaborators, Bull D, Green J, Reeves G (2007) Ovarian cancer and hormone replacement therapy in the Million Women Study. Lancet 369(9574): 1703–1710
4. Mørch LS, Løkkegaard E, Andreasen AH, Krüger-Kjaer S, Lidegaard O (2009) Hormone therapy and ovarian cancer. JAMA 302(3):298–305
5. Pearce CL, Chung K, Pike MC, Wu AH (2009) Increased ovarian cancer risk associated with menopausal estrogen therapy is reduced by adding a progestin. Cancer. 115(3):531–539
6. Mills PK, Riordan DG, Cress RD, Goldsmith DF (2005) Hormone replacement therapy and invasive and borderline epithelial ovarian cancer risk. Cancer Detect Prev 29(2):124–132
7. Riman T, Dickman PW, Nilsson S, Correia N, Nordlinder H, Magnusson CM et al (2001) Risk factors for epithelial borderline ovarian tumors: results of a Swedish case-control study. Gynecol Oncol 83(3):575–585
8. Risch HA, Marrett LD, Jain M, Howe GR (1996) Differences in risk factors for epithelial ovarian cancer by histologic type. Results of a case–control study. Am J Epidemiol 144(4):363–372
9. Løkkegaard E, Lidegaard O, Møller LN, Agger C, Andreasen AH, Jørgensen T (2007) Hormone replacement therapy in Denmark, 1995–2004. Acta Obstet Gynecol Scand 86(11):1342–1351
10. Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C (2009) Hormonal contraception and risk of venous thromboembolism:

national follow-up study. BMJ 339:b2890. doi:10.1136/bmj.b2890
11. Nielsen LH, Løkkegaard E, Andreasen AH, Keiding N (2008) Using prescription registries to define continuous drug use: how to fill gaps between prescriptions. Pharmacoepidemiol Drug Saf 17(4):384–388
12. Storm HH, Michelsen EV, Clemmensen IH, Pihl J (1997) The Danish Cancer Register–history, content, quality and use. Dan Med Bull 44(5):535–539
13. Storm HH (1988) Completeness of cancer registration in Denmark 1943–1966 and efficacy of record linkage procedures. Int J Epidemiol 17(1):44–49
14. Jensen AR, Overgaard J, Storm HH (2002) Validity of breast cancer in the Danish Cancer Registry. A study based on clinical records from one county in Denmark. Eur J Cancer Prevent 11:359–364
15. Kjaerbye-Thygesen A, Huusom LD, Frederiksen K, Kjaer SK (2007) 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]. Ugeskr Laeger 169(1):50–54
16. Huusom LD, Frederiksen K, Høgdall EV, Glud E, Christensen L, Høgdall CK et al (2006) Association of reproductive factors, oral contraceptive use and selected lifestyle factors with the risk of ovarian borderline tumors: a Danish case–control study. Cancer Causes Control 17(6):821–829
17. Lokkegaard E, Eplov LF, Koster A, Garde K (2005) Cardiovascular risk factors in a cohort of Danish women born in 1936 prior to use of hormone therapy. Maturitas 51:221–226
18. Lokkegaard E, Pedersen AT, Heitmann BL, Jovanovic Z, Keiding N, Hundrup YA et al (2003) Relation between hormone replacement therapy and ischaemic heart disease in women: prospective observational study. BMJ 326(7386):426–431
19. Tjonneland A, Christensen J, Thomsen BL, Olsen A, Overvad K, Ewertz M et al (2004) Hormone replacement therapy in relation to breast carcinoma incidence rate ratios: a prospective Danish cohort study. Cancer 100:2328–2337
20. Hammar M, Brynhildsen J, Dabrosin L, Frisk J, Lindgren R, Nedstrand E et al (1996) Hormone replacement therapy and previous use of oral contraceptives among Swedish women. Maturitas 25:193–199
21. Hundrup YA, Obel EB, Rasmussen NK, Philip J (2000) Use of hormone replacement therapy among Danish nurses in 1993. Acta Obstet Gynecol Scand 79:194–201