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Association of vaginal oestradiol and the rate of breast cancer in Denmark: registry based, case-control study, nested in a nationwide cohort

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ABSTRACT

OBJECTIVE To estimate the rate of breast cancer associated with use of vaginal oestradiol tablets according to duration and intensity of their use.

DESIGN Registry based, case-control study, nested in a nationwide cohort.

SETTING Based in Denmark using the civil registration system, the national registry of medicinal product statistics, the Danish cancer registry, the Danish birth registry, and statistics Denmark.

PARTICIPANTS Women aged 50-60 years in year 2000 or turning 50 years during the study period of 1 January 2000 to 31 December 2018 were included. Exclusions were a history of cancer, mastectomy, use of systemic hormone treatment, use of the levonorgestrel releasing intrauterine system, or use of vaginal oestrogen treatments other than oestradiol tablets. To each woman who developed breast cancer during follow-up (18 997), five women in the control group (94 985) were incidence density matched by birth year.

MAIN OUTCOME MEASURE The main outcome was pathology confirmed breast cancer diagnosis.

RESULTS 2782 (14.6%) women with breast cancer (cases) and 14 999 (15.8%) women with no breast cancer diagnosis (controls) had been exposed to vaginal oestradiol tablets with 234 cases and 1232 controls having been in treatment for at least four years at a high intensity (›50 micrograms per week). Increasing durations and intensities of use (cumulative dose/cumulative duration) of vaginal oestradiol tablets was not associated with increasing rates of breast cancer. Compared with never-use, cumulative use of vaginal oestradiol for more than nine years was associated with an adjusted hazard ratio of 0.87 (95% confidence interval 0.69 to 1.11). Results were similar in women who had long term use (≥four years) and with high intensity of use (›50-70 micrograms per week) with an adjusted hazard ratio 0.93 (95% confidence interval 0.81 to 1.08).

CONCLUSIONS Use of vaginal oestradiol tablets was not associated with increased breast cancer rate compared with never-use. Increasing duration and intensity of use was not associated with increased rates of breast cancer.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While systemic oestrogen treatment has been associated with increased risk of breast cancer development, use of vaginal oestrogen has been suggested to be risk-free

⇒ The effect of duration and intensity of vaginal oestrogen use on breast cancer risk is uncertain

WHAT THIS STUDY ADDS

⇒ In this nationwide study, use of vaginal oestradiol tablets was not associated with a significant increased risk of breast cancer

⇒ This finding remained even in women who were in treatment for ›nine years and in women who used the drug long term at high intensity (›50 micrograms per week)

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ The findings add reassurance to the breast cancer safety of vaginal oestrogen use in women

Introduction

Breast cancer is the most common cancer in women, affecting around 7.8 million women worldwide with 2.3 million incidences and 700 000 deaths annually.[1] Knowledge about external risk factors would potentially enable preventive actions.

Vaginally administrated oestrogen is the primary pharmaceutical treatment for the genitourinary syndrome of menopause, a condition caused by the physiological oestrogen deficiency following menopause.[2] Around 50% of postmenopausal women will have the syndrome with symptoms such as vaginal irritation, recurrent urogenital infections, and dyspareunia.[2] While systemic menopausal hormone treatment with oestrogen has been linked to an increased risk of breast cancer, use of vaginal oestrogen has been suggested to be risk-free.[3] However, studies have not been able to account for both duration and intensity of vaginal oestrogen use when assessing the association with breast cancer risk, which is highly relevant considering the variation in dosage and time of use among women in need of vaginal oestrogen.[3 4] Furthermore, vaginal oestrogen treatment has previously been associated with an increased risk of endometrial cancer.[4–6] This link to an oestrogen sensitive cancer further necessitates high quality evidence on the breast cancer safety of vaginal oestrogen treatment, especially considering the rise in use.[7]

Nested in a Danish, nationwide, female population, we aimed to investigate the risk of breast cancer among women using vaginal oestradiol tablets.

Methods

Study population

In Denmark, access to healthcare is freely available to all Danish citizens. We conducted a nationwide, nested, case-control study using the following Danish national registries: (1) the civil registration system, which contains information about sex and vital status of all Danish citizens; (2) the national registry of medicinal product statistics, which includes information about all redeemed prescriptions at Danish pharmacies since 1 January 1995; (3) the Danish cancer registry, which includes all cancer cases since 1 January 1943; (4) the national registry of patients, which comprises information about discharge diagnoses and surgical codes on all somatic hospital admissions since 1 January 1976; (5) the Danish national birth registry, which holds information about all live and death births since 1 January 1973; and (6) statistics Denmark, which provides a yearly update on the education and income status of all Danish citizens.[8–12]

We identified incident breast cancer cases and randomly chose controls with no breast cancer who had been matched by birth year. Women were chosen if they were recorded between 1 January 2000 and 31 December 2018 in a nationwide population of all Danish women aged 50-60 years on 1 January 2000 or turning 50 years throughout the study period. Women had no history of cancer (except non-melanoma skin cancer), mastectomy, or prior use of systemic hormone treatment, the hormone-releasing intrauterine system, other vaginal oestrogen treatments than oestradiol tablets, and anti-oestrogen medications.

Data sources and definitions of exclusion criteria are provided in online supplemental table S1. The personal identification number given to all Danish citizens at birth or immigration allowed reliable linkage between data sources. The year of initiation of the study period and the age restriction of the study population were defined to ensure almost complete exposure history of local and systemic hormone treatment on all included women.

Breast cancer

The cancer registry contains records of all incidences of malignant neoplasms in the Danish population from 1943 and onwards.[10] A woman was considered a case with incident breast cancer from the date of a first time invasive breast cancer diagnosis in the Danish cancer registry (the International Classification of Diseases, 10th revision, codes C500-C509).[10] On the date of diagnosis, five women with no breast cancer (controls) were incidence density matched by birth year to each case of breast cancer. The national pathology registry provided information on oestrogen receptor positivity of the breast cancers (systemised nomenclature of medicine code F29521).

Vaginal oestradiol tablets

The exposure of interest was treatment with the vaginal oestradiol tablet as this form is by far the most commonly used type of vaginal oestrogen among Danish women.[7] During the study period, use of any vaginal oestradiol drug formulation required a prescription from a physician. Vaginal oestradiol tablets were available in doses of 10 µg and 25 µg.

Daily updated, individual level information about prescription redemption of vaginal oestradiol tablet was provided by the national registry of medicinal product statistics, which holds information on all prescriptions filled by the Danish population since 1995.[9] The registry receives its information electronically from the digital accounting systems of Danish pharmacies that primarily use the systems to secure reimbursement from the national health service.[9]

A woman was considered to be using vaginal oestradiol tablets if she redeemed at least one prescription of the drug. Using the anatomical therapeutic chemical code (ATC) of oestradiol drug formulations (G03CA03) and conditioning on vaginal tablet administration, information on exposure status was obtained from the national registry of medicinal product statistics.[9] This national registry provided information on the date of redeemed prescription, size of drug unit, as well as size and number of redeemed packages.[9] This information was updated daily for each woman during the study period.

Vaginal oestradiol tablets are recommended to be taken once a day for the first two weeks of treatment followed by a maintenance dose of two tablets per week. However, the dosage may be regulated up or down according to the urogenital symptoms of the woman. The validated programme “medicinMacro”, accessible from Github (www.github.com) in the “tagteam/heaven” R package, was used to calculate the most likely daily dose. As such, also calculated was duration and time of use and non-use of vaginal oestradiol tablets according to information on date and amount of purchased drug, recommended default, minimum, and maximum dosages, and the prescription pattern of up to five most recent prescriptions.[13 14]

Potential confounders

Potential confounding factors, such as educational level and yearly income, was obtained from statistics Denmark. Information about polycystic ovary syndrome, endometriosis, and chronic obstructive pulmonary disease (a surrogate measure for health threatening smoking) was identified from the national registry of patients, and data for redeemed prescriptions on bisphosphonates and diabetes mellitus medication was provided by the national registry of medicinal product statistics.[9 11] Information about parity was extracted from the national birth registry.[12]

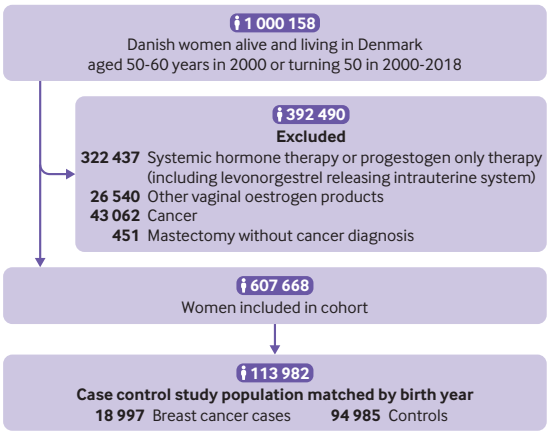

Figure 1 | Study flowchart

Statistical analysis

Conditional logistic regression models provided adjusted hazard rate ratios and corresponding 95% confidence intervals of breast cancer according to duration, intensity, and user status of vaginal oestradiol tablets at time of index date (date of diagnosis or matching). Duration was calculated as the cumulative duration of use at time of the index date without consideration to breaks in treatment. In a sensitivity analysis, duration was categorised according to the maximum length of continuous use without treatment breaks. Intensity of use was calculated as the cumulative dose of vaginal oestradiol tablets redeemed at time of index divided by the cumulative duration of use and categorised into low (≤25 µg/week), medium (>25-50 µg/week), high (>50-70 µg/week), and very high (>70 µg/week) intensity of use. User status was categorised into current use (use within 0-2 months prior to index date), recent use (use 2-24 months prior to index date), and previous use (>24 months prior to index date).

Table 1 | Characteristics of the study population and its use of vaginal oestradiol tablets

	Cases with breast cancer (n=18 997)	Controls (n=94 985)
Age at diagnosis/index (years), median (interquartile range)	61 (55-66)	61 (55-66)
Year of diagnosis/index, median (interquartile range)	2011 (2007-15)	2011 (2007-15)
Highest educational level, n (%)		
Elementary school	6508 (34.3)	34 559 (36.4)
Secondary school	534 (2.8)	2303 (2.4)
Skilled worker	7502 (39.5)	37 009 (39.0)
Theoretical education	3631 (19.1)	17 463 (18.4)
Research education	822 (4.3)	3651 (3.8)
Household income, n (%)		
Low (‹first quartile)	4632 (24.4)	23 865 (25.1)
Medium (first quartile–median)	4747 (25.0)	23 749 (25.0)
High (›median)	9618 (50.6)	47 371 (49.9)
Diabetes mellitus, n (%)	1354 (7.1)	6237 (6.6)
Chronic obstructive pulmonary disease, n (%)	787 (4.1)	3830 (4.0)
Bisphosphonates, n (%)	716 (3.8)	4522 (4.8)
Polycystic ovary syndrome, n (%)	28 (0.1)	93 (0.1)
Endometriosis, n (%)	326 (1.7)	1496 (1.6)
Parity, n (%)		
Nullipara	6888 (36.3)	33 993 (35.8)
Primopara	4888 (25.7)	23 858 (25.1)
Multipara	7206 (37.9)	37 006 (39.0)
Grandmultipara	15 (0.1)	128 (0.1)
Total number of users (%)	2782 (14.6)	14 999 (15.8)
Current user, n (%)*	1031 (37.1)	5261 (35.1)
Recent user, n (%)†	615 (22.1)	3291 (21.9)
Previous user, n (%)‡	1136 (40.8)	6447 (43.0)
Women who used tablets with a drug unit size of 10 µg, n (%)	322 (11.6)	1747 (11.7)
Women who used tablets with a drug unit size of 25 µg, n (%)	2019 (72.6)	10 965 (73.1)
Women who used mixed 10 µg and 25 µg tablets, n (%)	441 (15.9)	2287 (15.3)
Age at treatment initiation (years), median (interquartile range)	57 (54-61)	57 (53-61)
Duration of use (months), median (interquartile range)	8.6 (3.2-29.6)	8.1 (2.8-27.4)
Cumulative dose of use (µg), median (interquartile range)	1875 (750-6356)	1620 (750-5625)
Intensity of use (µg/week), median (interquartile range)	50.5 (48.4-54.7)	50.5 (49.5-55.0)

*0-2 months prior to index date.
†2-24 months prior to index date.
‡›24 months prior to index date.

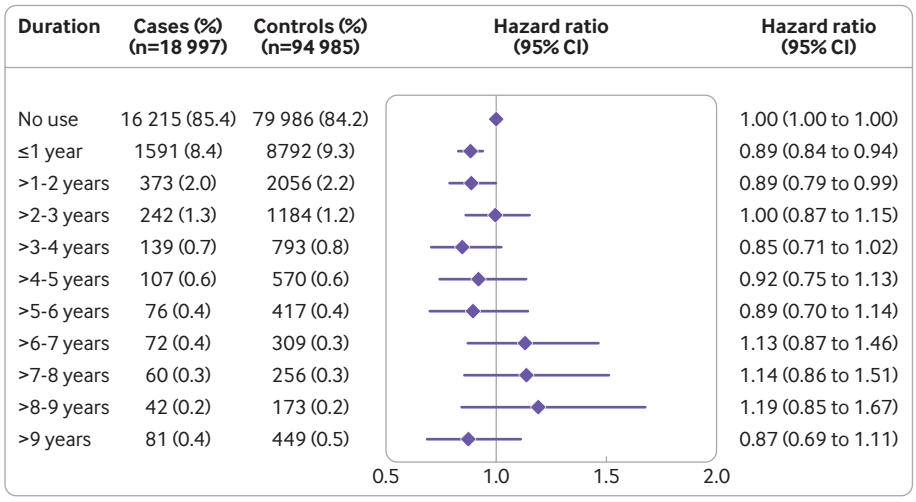

Figure 2 | Rate of breast cancer according to duration of use of vaginal oestradiol tablets. Adjusted for educational level; yearly income; history of polycystic ovary syndrome, endometriosis, chronic obstructive pulmonary disease, use of bisphosphonates, or diabetes mellitus; and parity at index date

Women who had never used vaginal oestradiol tablets and other hormone treatments constituted the reference group in all analyses. The potential confounding factors described above were included in the statistical models.

Sensitivity analyses were conducted on the subpopulation of cases with breast cancers positive for oestrogen receptors and their matched controls as well as on the subpopulation of women with a Charlson comorbidity index score of zero (definition in online supplemental table S1).

All analyses were repeated with one year lag time. The level of statistical significance was set at P<0.05. Data was analysed using R statistical software (RStudio version 4.2.1).[15]

Patient and public involvement

No patients or members of the public were involved in the design, analysis, or writing up of the study because the research project was undertaken by a small research group without funds or staff for patient and public involvement measures. The results of the study will, nevertheless, be disseminated to the public and health professionals by press releases and presentations at scientific conferences.

Results

A total of 18 997 women with breast cancer and 94 985 women in the control group were identified (figure 1). Characteristics of cases and controls are presented in table 1. The overall prevalence of vaginal oestradiol use was 2782 (14.6%) among women with breast cancer and 14 999 (15.8%) among population controls. In the control group, 5261 (5.5%) of 94 985 women currently used, 3291 (3.5%) recently used, and 6447 (6.8%) previously used vaginal oestradiol tablets. The corresponding prevalence estimates were similar in women with breast cancer (table 1). Median age at initiation of vaginal oestradiol tablets was 57 years (interquartile

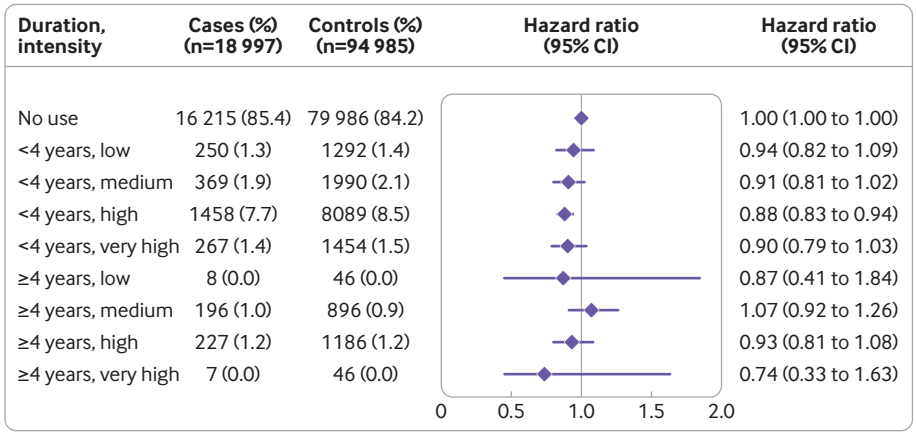

Figure 3 | Rate of breast cancer according to duration and intensity of use of vaginal oestradiol tablets. Intensity categories were low (≤25 µg/week), medium (>25-50 µg/week), high (>50-70 µg/week), and very high (>70 µg/week). Adjusted for educational level, yearly income, polycystic ovary syndrome, endometriosis, chronic obstructive pulmonary disease, use of bisphosphonates, diabetes mellitus, and parity at index date

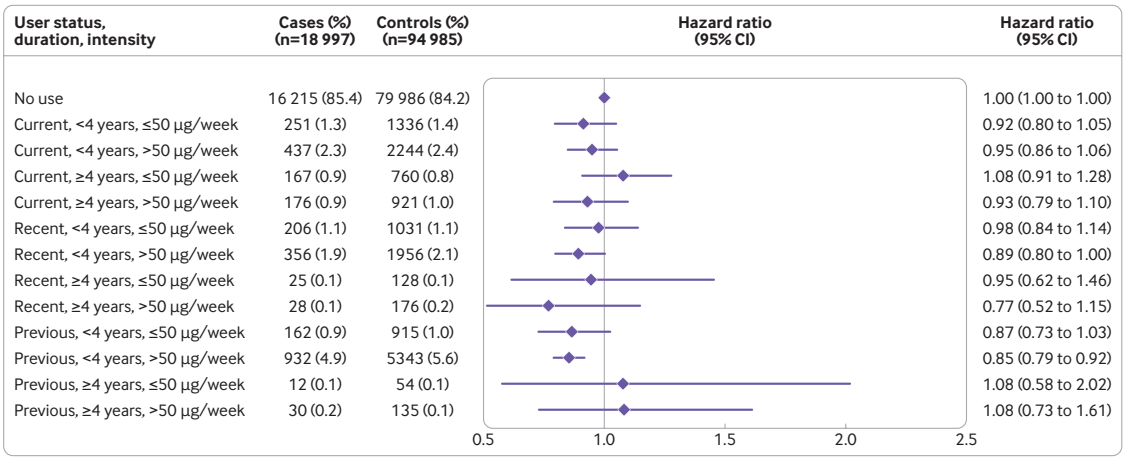

Figure 4 | Rate of breast cancer according to timing, duration, and intensity of use of vaginal oestradiol tablets. Timing of use: current use (0-2 months within index date), recent use (2 months-2 years within index date), previous use (>2 years prior to index date). Adjusted for educational level, yearly income, polycystic ovary syndrome, endometriosis, chronic obstructive pulmonary disease, use of bisphosphonates, diabetes mellitus, and parity at index date

range 53-61) among women in the control group, median cumulative duration of use was 8.1 months (2.8-27.4), median cumulative dose was 1620 µg (750-5625), and the median intensity of use was 50.5 µg/week (49.5-55.0). The characteristics of vaginal oestradiol use were similar in breast cancer cases (table 1).

table 1

Use of vaginal oestradiol tablets was not associated with a significant increase in breast cancer rate compared with never-use (figure 2). Increased cumulative duration of use did not imply increased rates of breast cancer (figure 2), the adjusted hazard ratio of more than nine years of cumulative use was estimated to be 0.87 (95% confidence interval 0.69 to 1.11). The absence of association with duration of use persisted when only considering consistent, uninterrupted use (online supplemental figure S1).

No consistent association was observed between intensity of use and rate of breast cancer (figure 3). A total of 227 cases and 1186 controls were exposed to vaginal oestradiol tablets for more than four years with an intensity of more than 50-70 µg/week, which is above the recommended maintenance dose of 20-50 µg/week. In these users, the adjusted hazard ratio of breast cancer was found to be 0.93 (95% confidence interval 0.81 to 1.08) compared with never-use.

Results remained robust when stratifying according to user status at time of diagnosis or matching (figure 4).

The lack of consistent association between duration and intensity of use of vaginal oestradiol tablets and breast cancer rate persisted in the subpopulation of oestrogen-receptor positive breast cancer cases (online supplemental figure S2) and in healthy women with a Charlson comorbidity index score of zero (online supplemental figure S3), respectively.

Sensitivity analyses including a one year lag time did not materially change the main estimates (online supplemental figure S4).

Discussion

In this real-world, nationwide, Danish population, increasing duration and intensity of use of vaginal oestradiol tablets was not found to be associated with an increased risk of breast cancer.

Several studies have found orally administrated oestrogen-only treatment to be associated with an increased risk of breast cancer.[3] A meta-analysis of individual participants worldwide reported a hazard ratio of 1.33 in current users of oral oestrogen-only treatment compared with no use.[3] The meta-analysis reports a hazard ratio of 1.09 with use of vaginal oestrogen without further consideration to intensity of use.[3] Similarly, a prospective cohort study by the Women's Health Initiative of 45 663 postmenopausal women did not find any association between vaginal oestrogen use and breast cancer risk, but did not investigate the association according to duration or intensity of use.[4] A nationwide observational study from Finland reported that use of vaginal oestrogen for less than five years was not associated with an increased risk of breast cancer, but the study did not have sufficient power to study the effect of use of more than five years or the role of the intensity of use.[16]

The apparent absence of association between use of vaginal oestradiol tablets and development of breast cancer have previously been explained by the low dose of oestradiol absorbed into the blood with vaginal application of low-dose oestrogen.[17 18] Our study suggests that use of >50-70 µg/week for more than four years is not associated with increased breast cancer risk (hazard ratio 0.93 (95% confidence interval 0.81-1.08)) compared with never-use.

Use of >50-70 micrograms per week corresponds to 2.5-fold to 3.5-fold more than recommended weekly maintenance dose of the currently marketed low dose 10 µg vaginal oestradiol tablet.

To our knowledge, our study is the first to report on the breast cancer risk with vaginal oestradiol tablets according to duration and intensity of use. One strength of our study is its nationwide design with a large unselected study population. Additionally, a strength is the use of high quality registry data with accurate and continuously updated data for breast cancer diagnoses and vaginal oestradiol prescriptions as well as medical conditions, reproductive factors, and education. These data allow adjustment for several known risk factors for breast cancer and potential confounders. Use of registries covering the entire Danish population eliminated recall bias, minimised selection bias, provided a long study period, and resulted in no missing data for exposure, outcome, and covariates for all eligible study patients. Thus, no cases or controls were selected on missing data. Cancer diagnoses were from the cancer registry, in which all cancer diagnoses are histologically verified, further enhancing validity.[8] For all women included in the study, we had at least five years of prescription history (establishment of the National Prescription Registry in Denmark was in 1995).

Considering the observational nature of our study, the main limitation is potential existence of bias by unknown or unmeasured confounders. Women who were were adherent users of vaginal oestradiol tablets could potentially be healthier than women who did not use the tablets because adherence to a long term, expensive treatment for a physiological condition might be more likely in women prioritising health and having a favourable socioeconomic status. This potential healthy user bias may have biased our results towards the null. However, the results remained robust in a subpopulation of all healthy women with a Charlson comorbidity index score of zero. Furthermore, as in many other countries, in Denmark, high socioeconomic position has been associated with higher incidence of breast cancer, including in our study (data not shown).[19] Thus, if healthy user bias was present in our study, the direction of the bias would not necessarily cause an underestimation of the association. Finally, we did adjust for education and income in our study.

Despite controlling for several potential confounders, we cannot exclude the occurrence of residual confounding and unmeasured confounding. Obesity has been associated with an increased risk of breast cancer, and obesity is expected to be more common among women who do not use vaginal oestradiol tablets because their oestrogen production in lipid tissue likely decreases the need for exogenous oestrogen.[20] Thus, not adjusting for obesity might have caused an underestimation of the association between vaginal oestradiol and breast cancer. However, obesity is highly (and inversely) correlated with educational status in Denmark, and we did adjust for such.[21]

Conclusions

Alongside recent studies suggesting that vaginal oestrogen treatment may safely be used by many women who have had breast cancer, this study adds reassurance to the breast cancer safety of vaginal oestrogen treatment.[22] However, considering the globally prevalent and often life-long indication and increasing use of vaginal oestrogen by postmenopausal women, further studies, especially in other populations, are warranted to confirm drug safety for all potential patients.

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Contributors LSM and AM designed the study. AM conducted the data management, and NP and CT-P ran the analysis. The manuscript was drafted by AM and LSM, but all authors contributed to the final manuscript. All authors contributed to the interpretation of the findings. All authors approved the final version and made the decision to submit for publication. All authors had access to the statistically analysed data. AM and CT-P had access to and verified the raw data. AM is the guarantor of the overall content, takes responsibility for the work and conduct of the study, and controlled the decision to publish. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted. Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; CTP has received grants from Novo Nordisk and Bayer outside of the current study; AM, EL, and LSM signed an authorship agreement with no financial benefit with Novo Nordisk after submission of this manuscript but before publication.

Ethics approval This study was approved by the Danish Data Protection Agency and the Danish Health Data Board. Registry-based studies are not subject to ethics approval in Denmark.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Raw data used to conduct this study is only accessible through approval from the Danish Data Protection Agency and the Danish Health Data Board. Although anonymised, the data was available on an individual level, making data sharing restricted by the General Data Protection Regulation of EU law.

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjmed-2023-000753).