

Estrogen Use and Porphyrria Cutanea Tarda

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[+ Supplemental content](#)

IMPORTANCE Estrogen-containing therapy is considered a risk factor for porphyria cutanea tarda (PCT), but the evidence is limited to clinical series and case reports.

OBJECTIVE To investigate whether estrogen-containing therapy is associated with incident PCT, overall and according to estrogen-containing therapy type and route of administration.

DESIGN, SETTING, AND PARTICIPANTS In this matched case-control study using data from Danish nationwide registries conducted from January 1, 1995, through November 1, 2024, female individuals with a first-time hospital diagnosis of PCT were matched 1:100 with population control patients on age, sex, and index date.

EXPOSURE At least 1 redeemed prescription of estrogen-containing therapy within 1 year before the index date.

MAIN OUTCOMES AND MEASURES Odds ratios (ORs) with 95% CIs for incident PCT were calculated from conditional logistic regression. Analyses were stratified by estrogen-containing therapy type and route of administration. Analyses were adjusted for PCT-related comorbidities: HIV infection; liver disease, viral hepatitis, or iron overload; smoking-related diagnosis or treatment; and alcohol or drug misuse diagnosis or treatment.

RESULTS The study included 438 female case patients with incident PCT (median age, 61.16 years [IQR, 51.08-69.17 years]) and 43 800 age-matched female control patients. In total, 154 cases (35.16%) and 9433 control patients (21.54%) had been exposed to any estrogen-containing therapy within 1 year before the index date (adjusted OR, 2.03; 95% CI, 1.66-2.49). Estrogen-containing contraceptives were associated with incident PCT (adjusted OR, 2.52; 95% CI, 1.67-3.82) as were estrogen-only therapy (adjusted OR, 1.58; 95% CI, 1.23-2.03), and combined estrogen and progestogen therapy (adjusted OR, 2.18; 95% CI, 1.53-3.11). When stratified by route of administration, oral therapy was associated with PCT (adjusted OR, 2.44; 95% CI, 1.66-3.59), whereas nonoral routes were not.

CONCLUSIONS AND RELEVANCE This nationwide matched case-control study found that estrogen-containing therapy was associated with incident PCT. In route-specific analyses, only oral therapy was associated with PCT, suggesting that route of administration should be considered when evaluating estrogen exposure as a potential risk factor for PCT.

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Porphyrria cutanea tarda (PCT) is a rare skin disorder characterized by blistering, erosions, and vesicles in sun-exposed areas, particularly the dorsal hands, forearms, and face.¹ The disorder results from the accumulation of photosensitizing porphyrins in the skin and liver due to reduced activity of hepatic uroporphyrinogen decarboxylase (UROD), an enzyme involved in heme biosynthesis.² Reduced UROD activity may result from inherited mutation of the UROD gene or acquired inhibition, but additional precipitating factors are usually required for disease to occur.³ Considered precipitating factors include HIV infection, liver disease, viral hepatitis, iron overload, smoking, alcohol, genetic susceptibility, and estrogen exposure.⁴ Estrogens are considered a risk factor for PCT, possibly through direct reduction of UROD activity or induction of reactive oxygen species in the liver.⁵⁻⁷ However, evidence for the association between

estrogen use and PCT has previously been based on case reports and clinical series.⁸⁻²³ Population-based comparative studies estimating the association between estrogen-containing therapy and PCT are lacking, and whether the findings differ by therapy type or route of administration remains unclear. Therefore, we conducted a Danish nationwide matched case-control study to examine whether estrogen-containing therapy was associated with incident PCT, overall and according to therapy type and route of administration.

Methods

This study was approved by the Danish Data Protection Agency and the Danish Health Data Authority. Since this

study only included anonymized and registry-based data, there was no requirement of informed consent from included patients per the Ministry of the Interior and Health.²⁴ To comply with Danish data protection restrictions, results based on fewer than 5 individuals were not reported. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.²⁵

Data Sources

Data were extracted from 4 Danish nationwide registries: the Danish National Patient Registry,²⁶ the Danish Civil Registration System,²⁷ the Danish National Prescription Registry,²⁸ and the Clinical Laboratory Information Register.²⁹ The Danish National Patient Registry is a detailed nationwide registry with inpatient and outpatient hospital data of patients in Denmark since 1993. In this registry, diagnoses are given according to the *International Classification of Diseases, Tenth Revision (ICD-10)* and can only be assigned by hospital physicians, thus ensuring a high diagnostic certainty. The Danish Civil Registration System contains information on date of birth, sex, vital status, and dates of death or emigration when applicable for all Danish residents. The Danish National Prescription Registry includes data on all redeemed prescriptions dispensed by pharmacies in Denmark since 1994.²⁸ The Clinical Laboratory Information Register contains individual-level laboratory test results from Danish hospitals and general practices, including Nomenclature for Properties and Units codes, measurement units, and reference limits. Data collection was initiated regionally in 2013 and expanded to nationwide coverage through 2015.²⁹ In combination, linked through the unique personal identification number assigned to all Danish residents, these registries provided individual-level data on hospital diagnoses, redeemed prescriptions, and laboratory test results.

Case Patients

We identified all female individuals aged 1 to 99 years with a first-time hospital diagnosis of PCT in the Danish National Patient Registry from January 1, 1995, through November 1, 2024. PCT was defined by *ICD-10* code E80.1. The *ICD-10* code does not distinguish PCT subtypes. The index date was defined as the date of diagnosis. We excluded individuals with less than 1 year of residency in Denmark before the index date and individuals with a PCT diagnosis before 1995.

Among cases diagnosed from 2016 through 2024, we assessed available urinary porphyrin analyses in the Clinical Laboratory Information Register, including uroporphyrin, heptacarboxylporphyrin, hexacarboxylporphyrin, and pentacarboxylporphyrin, each normalized to creatinine. A PCT diagnosis was considered laboratory confirmed if at least 1 of these results exceeded the locally reported upper reference limit during the available laboratory observation period. The included laboratory analyses and Nomenclature for Properties and Units codes are listed in eTable 1 in [Supplement 1](#). Mortality among Danish patients with PCT has previously been examined and reported, but, to our knowledge, their use of estrogen has not.³⁰

Key Points

Question Is estrogen-containing therapy associated with incident porphyria cutanea tarda (PCT)?

Findings In this nationwide Danish case-control study including 438 female individuals with incident PCT and 43 800 matched female control patients, estrogen-containing therapy was associated with incident PCT. The association was observed across estrogen-containing contraceptives, estrogen-only therapy, and combined estrogen and progestogen therapy.

Meaning Results of this study suggest that estrogen-containing therapy is a risk factor for incident PCT.

Control Patients

Each case patient was matched 1:100 with live population control patients from the Danish population with the same eligibility criteria but without PCT. We used risk set sampling based on age, sex, and index date in the selection of control patients.

Exposures

All exposures were defined as at least 1 redeemed prescription of the relevant hormonal therapy within 1 year prior to the index date. In the primary analysis, exposure was defined as any estrogen-containing therapy, which included any exposure to estrogen-containing contraceptives, estrogen-only therapy, or combined estrogen and progestogen therapy. In exploratory analyses, we examined associations according to hormonal therapy type and route of administration and conducted a specificity analysis of nonestrogen reproductive hormonal therapies.

Exposures were subdivided into specific hormonal therapy groups. Premenopausal therapies included estrogen-containing contraceptives, classified within the Anatomical Therapeutic Chemical Classification (ATC) system as G03AA/G03AB. Postmenopausal therapies were classified as estrogen-only therapy (G03C) and combined estrogen and progestogen therapy (G03F). Additionally, among individuals exposed according to the primary exposure definition, we summarized the number of redeemed prescriptions within 1 year before the index date and during available preindex prescription history. Because prescription data were available from 1994 onward, the length of preindex history varied by index date and should not be interpreted as treatment duration or lifetime exposure. Given the diversity of administration routes for postmenopausal estrogen-containing therapy, we further categorized estrogen-only exposure according to route of administration: oral, vaginal, or other nonoral routes, with the latter including transdermal, parenteral, and other nonvaginal formulations. As a specificity analysis, we also investigated exposure to nonestrogen reproductive hormonal therapies classified within ATC group G03, which included androgens, gonadotropins, and progestogens. The ATC codes used to define each hormonal therapy group are provided in eTable 2 in [Supplement 1](#).

PCT-Related Comorbidities

We identified PCT-related comorbidities before the index date using available registry history from hospital diagnoses

Table 1. Characteristics of the Study Population at the Index Date

Characteristic	Patients, No. (%)		Odds ratio (95% CI)
	Case (n = 438)	Control (n = 43 800)	
Age, median (IQR), y	61.16 (51.08-69.17)	61.21 (50.94-69.12)	NA
Sex, female	438 (100)	43 800 (100)	NA
Year of birth, median (IQR)	1947 (1939-1957)	1947 (1939-1957)	NA
Index year, median (IQR) ^a	2007 (2001-2014)	2007 (2001-2014)	NA
HIV infection	<5 (<1.14)	11 (0.03)	NA
Liver disease, viral hepatitis, or iron overload	29 (6.62)	419 (0.96)	7.50 (5.06-11.11)
Smoking related diagnosis or treatment	28 (6.39)	1649 (3.76)	1.76 (1.20-2.63)
Alcohol or drug misuse diagnosis or treatment	23 (5.25)	1321 (3.02)	1.79 (1.17-2.73)
Any listed PCT-related comorbidities ^b	76 (17.35)	3114 (7.11)	2.83 (2.19-3.66)

Abbreviations: NA, not applicable; PCT, porphyria cutanea tarda.

^a Index year refers to the year of PCT diagnosis among case patients and the corresponding matched index year among control patients.

^b Defined as any of the listed PCT related comorbidities: HIV infection; liver disease, viral hepatitis, or iron overload; smoking-related diagnosis or

treatment; or alcohol or drug misuse diagnosis or treatment. PCT-related comorbidities were identified before the index date using hospital-based diagnoses and redeemed prescriptions and did not include hormonal therapy exposures.

in the Danish National Patient Registry and redeemed prescriptions in the Danish National Prescription Registry. These included HIV infection (*ICD-10*: B20-B24, Z21); liver disease, viral hepatitis, or iron overload (*ICD-10*: K70-K77, B18, E83.1); smoking-related diagnosis or treatment, defined by chronic obstructive pulmonary disease, emphysema, or smoking cessation therapy (*ICD-10*: J44, J43; ATC: N07BA); and alcohol or drug misuse diagnosis or treatment, defined by alcohol or drug misuse diagnoses or treatment for alcohol or opioid dependence (*ICD-10*: F10-F19; ATC: N07BB, N07BC).

Statistical Analysis

Characteristics of the study population were summarized using medians and IQRs for continuous variables and proportions for categorical variables. Odds ratios (ORs) with 95% CIs were estimated using conditional logistic regression. Statistical significance was based on 95% CIs. Because control patients were selected using risk-set sampling, the ORs can be interpreted as incidence rate ratios. Exposure categories and confounders were modeled as separate binary variables. Estimates are presented as both crude and adjusted ORs, with adjustment for the PCT-related comorbidities. Route-specific analyses were conducted separately for oral, vaginal, and other nonoral estrogen-only therapies. In addition, we directly compared oral and vaginal estrogen-only therapy, presenting crude estimates and estimates adjusted for PCT-related comorbidities and concomitant use of other estrogen-containing therapies. As a specificity analysis, we evaluated nonestrogen reproductive hormonal therapies classified within ATC group G03, including progestogens, androgens, gonadotropins, and other nonestrogen sex hormones and modulators of the genital system. To assess whether observed associations were independent of concomitant hormonal therapy use, we fitted a multivariable conditional logistic regression model including all hormonal therapy groups and PCT-related comorbidities. Estimates were derived using the same modeling approach described previously. All analyses were performed using SAS version 9.4 (SAS Institute, Inc).

Results

During the study period from 1995 to 2024, approximately 4.3 million women lived in Denmark, contributing to a total of 83 million person-years of observation. Within this population, we identified 438 incident female case patients with PCT (median age, 61.16 years [IQR, 51.08-69.17 years]). Each case patient was matched with 100 control patients, resulting in a total of 43 800 age-matched female control patients. PCT-related comorbidities, including HIV infection, liver disease, viral hepatitis or iron overload, smoking-related diagnosis or treatment, and alcohol or drug misuse diagnosis or treatment, were more prevalent among case patients than control patients. Further details on study population characteristics are provided in **Table 1**. Using laboratory data available for a subsample of the cohort, at least 82% of PCT diagnoses were laboratory confirmed (eTable 1 in **Supplement 1**).

Any Estrogen-Containing Therapy and Risk of PCT

In total, 154 (35.16%) cases had received any estrogen-containing therapy within 1 year prior to diagnosis compared with 9433 (21.54%) among control patients (OR, 2.04; 95% CI, 1.66-2.49) (**Table 2**). After adjustment for the PCT-related comorbidities, effect estimates were not materially changed for estrogen-containing contraceptives (OR, 2.52; 95% CI, 1.67-3.82), estrogen-only therapy (OR, 1.58; 95% CI, 1.23-2.03), and combined estrogen and progestogen therapy (OR, 2.18; 95% CI, 1.53-3.11).

Specific Estrogen-Containing Therapies and Risk of PCT

With regard to premenopausal settings, 40 case patients (9.13%) had used estrogen-containing contraceptives within 1 year before the index date compared with 2248 control patients (5.13%), corresponding to an OR of 2.47 (95% CI, 1.64-3.74). For postmenopausal settings, 38 cases (8.68%) had used combined estrogen-progestogen therapy within 1 year before the index date compared with 1865 control patients (4.26%), corresponding to an OR of 2.27 (95% CI, 1.60-3.24). Estrogen-

Table 2. Estrogen-Containing Therapy Use Within 1 Year Before the Index Date and Risk of Incident PCT^a

Setting	Therapy	Exposed, No. (%)		Odds ratio (95% CI)	
		Case patients (n = 438)	Control patients (n = 43 800)	Crude	Adjusted ^b
Any	Any estrogen-containing therapy	154 (35.16)	9433 (21.54)	2.52 (1.67-3.82)	2.03 (1.66-2.49)
Premenopausal	Estrogen-containing contraceptives	40 (9.13)	2248 (5.13)	2.47 (1.64-3.74)	2.52 (1.67-3.82)
Postmenopausal	Estrogen-only therapy	80 (18.26)	5563 (12.70)	1.57 (1.22-2.02)	1.58 (1.23-2.03)
	Combined estrogen and progestogen therapy	38 (8.68)	1865 (4.26)	2.27 (1.60-3.24)	2.18 (1.53-3.11)

Abbreviation: PCT, porphyria cutanea tarda.

^a Each participant may have been exposed to more than 1 therapy.^b Adjusted for PCT-related comorbidities: HIV infection; liver disease, viral

hepatitis, or iron overload; smoking-related diagnosis or treatment; and alcohol or drug misuse diagnosis or treatment.

Table 3. Route of Administration of Estrogen-Only Therapy and Risk of PCT^a

Route of administration	Exposed, No. (%)		Odds ratio (95% CI)	
	Case patients (n = 438)	Control patients (n = 43 800)	Crude	Adjusted ^b
Oral	30 (6.85)	1300 (2.97)	2.48 (1.69-3.64)	2.44 (1.66-3.59)
Vaginal	46 (10.50)	4010 (9.16)	1.17 (0.86-1.61)	1.19 (0.87-1.63)
Other nonoral routes ^c	7 (1.60)	414 (0.95)	1.71 (0.80-3.66)	1.65 (0.77-3.54)

Abbreviation: PCT, porphyria cutanea tarda.

^a Each participant may have been exposed to more than 1 therapy. Routes were modeled as separate binary variables, with nonuse of each route as the reference.^b Adjusted for PCT-related comorbidities: HIV infection; liver disease, viral hepatitis, or iron overload; smoking-related diagnosis or treatment; and alcohol or drug misuse diagnosis or treatment.^c Including transdermal, parenteral, and other nonvaginal formulations.

only therapy had been used by 80 case patients (18.26%) and 5563 control patients (12.70%), corresponding to an OR of 1.57 (95% CI, 1.22-2.02).

In a multivariable regression model including all of the PCT-related comorbidities, hormonal therapy groups, estrogen-containing contraceptives, estrogen-only therapy, and combined estrogen-progestogen therapy were also associated with PCT (eTable 3 in Supplement 1). The number of prescriptions of estrogen-containing therapies among exposed individuals within the 1-year exposure window was generally similar among case and control patients (eTable 4 in Supplement 1).

Route of Administration and Risk of PCT

In route-specific analyses of estrogen-only therapy, an association was found in oral estrogen-only therapy (OR, 2.48; 95% CI, 1.69-3.64), whereas vaginal estrogen-only therapy showed a similar prevalence among case and control patients (OR, 1.17; 95% CI, 0.86-1.61) (Table 3). Adjustment for PCT-related comorbidities did not substantially affect the estimates for oral therapy (OR, 2.44; 95% CI, 1.66-3.59) and vaginal therapy (OR, 1.19; 95% CI, 0.87-1.63). Oral therapy was associated with higher odds of PCT than vaginal therapy (crude OR, 2.09; 95% CI, 1.28-3.44; adjusted OR, 2.05; 95% CI, 1.25-3.38).

Specificity Analysis

Among nonestrogen reproductive hormonal therapies, progestogen-only therapy was the only group with sufficient exposed case patients to estimate an association. In total, 9 case patients (2.05%) and 424 control patients (0.97%) were exposed to progestogen-only therapy, corresponding to a crude OR of 2.19 (95% CI, 1.11-4.32). However, in the multivariable model the findings were not statistically significant (OR, 1.84; 95% CI, 0.91-3.72). For the remaining nonestrogen reproductive

hormonal therapy groups, too few case patients were exposed to calculate estimates (eTable 3 in Supplement 1).

Discussion

This nationwide matched case-control study spanning almost 30 years found that estrogen-containing therapy was associated with incident PCT and provides risk estimates for specific estrogen-containing therapies. Our findings support estrogen-containing therapy as a risk factor for PCT in both premenopausal and postmenopausal treatment settings. Adjustment for PCT-related comorbidities did not materially change the estimates.

Previous clinical series have reported estrogen use in approximately one-third to three-quarters of female patients with PCT,^{8,9,14,15,17-21,31} but these studies did not include population-based control groups. Furthermore, previous studies did not provide comparative route-specific estimates, and our study indicates that oral estrogen therapy was associated with higher odds of PCT than the vaginal route. Oral estrogen undergoes first-pass hepatic metabolism, resulting in greater hepatic exposure compared with nonoral routes.^{32,33} This raises the question of whether the first-pass hepatic metabolism may play a central role in the development of estrogen-induced PCT.³⁴ Consistent with this interpretation, Bulaj et al¹³ reported no relapse of PCT during 1 year of transdermal estrogen therapy in a small series of 7 women previously treated for PCT.

At a population level, the risk of PCT associated with estrogen-containing hormonal therapies is negligible. However, in patients with PCT, this study supports current recommendations to avoid estrogen when possible and adds that oral

estrogen-containing therapy may be more clinically relevant than nonoral routes.³⁵

Limitations

This study has limitations. Exposure was defined by redeemed prescriptions and actual medication use could not be confirmed. Detection bias is possible, as female individuals receiving estrogen-containing therapy may have more health care contact than nonusers.

However, the route-specific pattern argues against non-specific confounding or detection bias. Adjustment for selected PCT-related comorbidities did not materially change the estimates. Although HIV infection and liver disease are likely well recorded in Danish registries, smoking and alcohol use were incompletely captured by our diagnosis- and treatment-based measures, and residual confounding cannot be excluded.

By design, we did not identify case patients with milder PCT managed exclusively outside the hospital setting,³⁶

which may limit generalizability to all patients with PCT. This would bias the findings only if the likelihood of hospital-based diagnosis or registration differed by estrogen exposure. Finally, because the study included only female individuals, the findings may not be generalizable to male individuals.

Conclusions

In this case-control study, we found evidence supporting estrogen-containing therapy as a clinically relevant risk factor for incident PCT. In route-specific analyses, the association was observed only for oral estrogen-containing therapy, whereas nonoral estrogen-containing therapy routes were not associated with PCT. These findings refine the clinical interpretation of hormone-associated PCT and may support more nuanced counseling for female individuals with PCT who require estrogen-containing therapy.

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Acquisition, analysis, or interpretation of data: All authors.

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