Increased mortality in patients with porphyria cutanea tarda—A nationwide cohort study

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Background: Porphyria cutanea tarda (PCT) is a rare hepatocutaneous disease for which the prognosis is largely unknown.

Objective: To compare all-cause and cause-specific mortality between a nationwide cohort of patients with PCT and a matched population sample.

Methods: We included all Danish patients who received a diagnosis of PCT from 1989 through 2012. Each patient was matched by age and sex to 10 random population control individuals. We compared survival and cause-specific mortality between patients and control individuals and adjusted for confounding from alcohol-related diseases, hepatitis, hemochromatosis, HIV, diabetes, acute myocardial infarction, stroke, cancer, chronic obstructive pulmonary disease, and cirrhosis.

Results: The 20-year survival was 42.9% (95% confidence interval [CI], 36.9-48.7) for patients with PCT compared with 60.5% (95% CI, 58.6-62.4) for matched control individuals. All-cause mortality hazard ratio (HR) was 1.80 (95% CI, 1.56-2.07) before adjustment and 1.22 (95% CI, 1.04-1.44) after adjustment. The cause-specific mortality was markedly increased for nonmalignant gastrointestinal diseases (HR, 5.32; 95% CI, 2.71-10.43) and cancers of the gut (HR, 2.05; 95% CI, 1.24-3.39), liver/gallbladder (HR, 11.24; 95% CI, 4.46-28.29), and lungs (HR, 2.17; 95% CI, 1.41-3.33).

Limitations: We had no data on lifestyle factors.

Conclusions: Patients with PCT have increased mortality, primarily explained by an increased mortality from gastrointestinal diseases and from cancers of the gut, liver/gallbladder, and lungs. (J Am Acad Dermatol 2020;83:817-23.)

Key words: epidemiology; liver; mortality; porphyria; porphyria cutanea tarda; skin.

Porphyria cutanea tarda (PCT) is a metabolic disease where the fifth enzyme in the heme synthesis, uroporphyrinogen decarboxylase (UROD), has reduced activity. Reduced enzyme activity results in accumulation of porphyrins, heme intermediates, primarily in the liver and skin. Porphyrins are phototoxic, resulting in cutaneous symptoms such as blisters, sores, hyperpigmentation, and hypertrichosis on sun-exposed areas.[1]

PCT is the most prevalent porphyria disease worldwide, with a prevalence in Denmark of approximately 1/10 000,[2] yet little is known about its prognosis. In addition to a mutation in the gene coding for UROD, several factors are known to

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reduce enzyme activity and thus facilitate porphyrin accumulation: high alcohol intake, smoking, iron overload, hepatitis C, human immundeficiency virus (HIV), and estrogen use in women.[3,4] Consequently, these characteristics are common among patients with PCT and may explain why they have an increased risk of liver cancer and, possibly, other cancers.[5-9] Moreover, patients with PCT also have an increased prevalence of impaired glucose tolerance and diabetes mellitus. The association between PCT and impaired glucose metabolism is not fully understood but possibly implicates iron overload; a previous study[10,11] showed that patients with PCT with persistently high ferritin levels were more likely to develop impaired glucose metabolism and diabetes.

CAPSULE SUMMARY

- There are limited studies concerning mortality in patients with porphyria cutanea tarda.
- We found that patients with porphyria cutanea tarda have increased all-cause mortality and risk of death due to gastrointestinal diseases and cancer of the gut, liver/gallbladder, and lungs. Clinicians treating these patients must pay special attention to lifestyle and lifestyle-related comorbidities.

Only 2 studies have focused on the mortality of patients with PCT. One small study[12] from 2005 did not find a higher mortality, whereas a 20-year-old study by Linet et al[5] found increased all-cause mortality and increased mortality from cancer, chronic obstructive pulmonary disease (COPD), and liver cirrhosis. Linet et al followed Danish and Swedish patients with PCT from 1965 to 1993 and compared mortality among these patients with the mortality in the general population using standardized mortality rates. Since then, new diagnostic tools and treatment modalities have emerged, and the general population survival has improved. Whether these changes have influenced the survival of persons with PCT is not known; however, such information is important to the patients and the clinicians caring for them. Consequently, we investigated the mortality and causes of death among 659 Danish patients diagnosed with PCT between 1989 and 2012.

PATIENTS AND METHODS

This historical cohort study includes all Danish patients biochemically diagnosed with PCT from September 1989 until December 2012. The date of the PCT diagnosis (index date) was set as the first date the person was biochemically investigated for porphyria. From 1989 through 2012, the porphyrin analyses were performed at the Department of Clinical Biochemistry at Viborg Regional Hospital (Denmark). We defined the biochemical diagnosis of PCT as either urine urocarboxylporphyrin/creatinine greater than 6 μmol/mol creatinine, plasma fluorescence emission peak at 615 to 620 nm, or fecal heptacarboxylporphyrin greater than 2 nmol/g (dry weight). When measured, fecal coproporphyrin III/I ratio was less than 2, fecal protoporphyrin was less than 62 nmol/g dry weight, and the excretion of porphobilinogen in urine was less than 1.5 μmol/mmol creatinine and/or porphobilinogen was less than 10 μmol/L. Analyses for genetic mutations in the UROD gene were not performed routinely, and if performed, the results were not available for this study.

Patients with PCT were matched to random control individuals from the general population by sex, age, and birth year. Each patient with PCT was matched to 10 control individuals except a 94-year-old woman, for whom we could match only 6 control individuals. All control individuals were alive on the index date of their matched patient with PCT.

Danish registers

Since 1968, all Danish citizens have been assigned a civil registration number. Each civil registration number is unique, and it is used for all contacts with the public system. Individual-level data from all Danish registers can be linked through the civil registration number.

The National Patient Registry contains data from all hospital admissions since 1977 and, from 1995, outpatient and emergency department visits as well. The International Classification of Diseases, eighth revision (ICD-8) was used in the period from 1977 through 1993, and from 1994, the tenth revision (ICD-10) was used.[13] From the National Patient Registry, we extracted diagnosis codes and dates of hospitalization. Dates of death or emigration were extracted from the Central Person Register.[14] Data on cancers was received from the Cancer Register, which contains data on cancer diagnoses, including the type of cancer and date of diagnosis.[15] From 1977 until 2003 the ICD-7 codes were used, and from 2004 the ICD-10 codes were used. Causes of death were retrieved from the Cause of Death Register; this register contains data on causes of death for all decedents since 1970 and is currently updated through 2015.[16]

Abbreviations used:

AMI:	acute myocardial infarction
CI:	confidence interval
COPD:	chronic obstructive pulmonary disease
HIV:	human immundeficiency virus
HR:	hazard ratio
ICD:	International Classification of Diseases
PCT:	porphyria cutanea tarda
UROD:	uroporphyrinogen decarboxylase

Statistical analysis

Follow-up began 6 months after the index date because patients are typically screened for comorbid diseases shortly after the PCT diagnosis is made. Follow-up ended at death, in censoring at emigration, or on April 30, 2017, whichever came first. For each person, we extracted the date of the first diagnosis code for PCT risk factors (alcohol-related diseases, hepatitis C, hemochromatosis, and HIV) and for selected comorbidities (diabetes, acute myocardial infarction [AMI], stroke, cancer, COPD, and cirrhosis).

First, we used the Kaplan-Meier method to estimate survival time for patients with PCT and control individuals. Cox regression was used to estimate hazard ratios (HRs) for patients with PCT versus control individuals, and we adjusted for differences in alcohol-related disease, hepatitis C, hemochromatosis, HIV, diabetes, AMI, stroke, cancer, COPD, and cirrhosis. These confounders were included as time-dependent binary variables in the analysis—for example, a patient with PCT (or a control individual) who was diagnosed with diabetes (or with hemochromatosis, etc) 2 years after the index date counted as a nondiabetic participant for the first 2 years of follow-up and as a diabetic participant after that. The Cox regression was repeated after exclusion of persons (control individuals, patients with PCT and their matched control individuals) and risk factors/comorbidities, excluding cancers that were diagnosed before 1995. This additional analysis was performed to see the effect of registering outpatient visits from 1995 and forward.

Second, we repeated the Kaplan-Meier analysis of survival time, except we excluded persons (control individuals, patients with PCT and their matched control individuals) who had been diagnosed with any of the potentially confounding diseases before the beginning of follow-up. The purpose was to describe the survival time of patients with PCT who were presumably healthy except for PCT at the time of PCT diagnosis.

Third, we used the cumulative incidence function to compute the 20-year cumulative mortality for patients with PCT and control individuals for the following competing causes of death: cancer (this was subsequently divided by cancer site), cardiovascular disease, cerebrovascular disease, COPD, respiratory diseases excluding COPD, infection, endocrinologic disease, gastrointestinal disease, alcohol-related death, neurological disease, kidney/bladder disease, accident, suicide, other causes, and missing cause of death. In addition, we used Cox regression to estimate cause-specific mortality HR for patients with PCT versus control individuals. These analyses did not adjust for confounding factors from comorbid diseases.

Ethical considerations

This study was approved by the Danish Data Protection Agency (record number 17/26696). According to Danish law, it did not need approval from the local ethics committee because it was a purely registry-based study.

RESULTS

From September 1989 through December 2012, 659 patients were diagnosed with PCT: 358 men with a mean age of 58 years and 301 women with a mean age of 60 years. The control group consisted of 3580 men and 3006 women. Total follow-up time for the PCT group was 6404.7 years and for the control group was 72 522.7 years. Patients with PCT were sicker than control individuals from the time of inclusion; they had a higher prevalence of all PCT-related risk factors, with alcohol-related diagnoses being most prevalent at 8.3%. The prevalences of stroke and AMI were nearly the same for patients with PCT and control individuals, but all other comorbidities were more prevalent in the PCT group, with the prevalence of cancer highest at 14.4% (Table I).

The primary Kaplan-Meier analysis included 637 patients with PCT and 6519 control individuals; 22 patients with PCT had died, 1 control individual was lost to follow-up, 6 control individuals had emigrated, and 60 control individuals had died less than 6 months after the index date. The median survival time was 17 years for the PCT group. The 20-year survival probability was 42.9% (95% confidence interval [CI], 36.9-48.7) for the PCT group and 60.5% (95% CI, 58.6-62.4) for the control group (Fig 1).

In the second Kaplan-Meier analysis, we excluded 283 patients with PCT and 3622 control individuals who had comorbid diseases (alcohol-related disease, hepatitis C, hemochromatosis, HIV, diabetes, AMI, stroke, cancer, COPD, or cirrhosis) diagnosed before the start of follow-up. We found that the 20-year

Table I. Characteristics of patients with PCT and control individuals at the time of inclusion

Characteristics	Patients	Control individuals
Total, n	659	6586
Sex, n (%)		
Male	358 (54.3)	3580 (54.4)
Female	301 (45.6)	3006 (45.6)
Age in years, mean (range)		
Male	58 (10-85)	58 (10-85)
Female	60 (20-94)	60 (20-94)
PCT risk factors, n (%)*		
Alcohol	55 (8.3)	165 (2.5)
Hepatitis C	38 (5.8)	19 (0.3)
Hemochromatosis	17 (2.6)	1 (0.02)
HIV	10 (1.5)	4 (0.06)
Comorbidities, n (%)*		
Diabetes	44 (6.7)	289 (4.4)
AMI	29 (4.4)	332 (5.0)
Stroke	29 (4.4)	254 (3.9)
Cancer	95 (14.4)	583 (8.9)
COPD	51 (7.7)	245 (3.7)
Cirrhosis	18 (2.7)	33 (0.5)

AMI, Acute myocardial infarction; *COPD*, chronic obstructive pulmonary disease; *HIV*, human immunodeficiency virus; *PCT*, porphyria cutanea tarda.
*PCT risk factors and comorbidities were identified before the start of follow-up.

survival probability was 52.8% (95% CI, 44.7-60.2) for the PCT group and 70.3% (95% CI, 67.8-72.8) for the control group.

When we adjusted for comorbid diseases (including those diagnosed during the follow-up), we found that the all-cause mortality HR for patients with PCT versus control individuals was 1.22 (95% CI, 1.04-1.44); without adjustment, it was 1.80 (95% CI, 1.56-2.07) (Fig 2). Thus, the excess mortality for patients with PCT was partially, but not fully, explained by the comorbid diseases we considered. Restricting the study period to 1995 through 2012 did not affect our findings considerably (adjusted mortality HR, 1.33; 95% CI, 1.12-1.59).

Patients with PCT had significantly increased mortality from cancer (HR, 2.21; 95% CI, 1.76-2.76) and gastrointestinal diseases (HR, 5.32; 95% CI, 2.71-10.41) (Fig 2). The hazard rates for the other specific causes of death were generally higher for patients with PCT, except for the rate of death from cardiovascular disease, which was similar in the 2 groups, and the rate of death from a neurological disease, which was lower in patients with PCT (Figs 2 and 3). Patients with PCT had a higher rate of death from "other causes" (Fig 2), which for the PCT group consisted of 14 deaths: 7 deaths from poorly defined causes and 7 deaths from sarcoidosis, rheumatic disease, psychiatric disease, or anemia. The cause of death was missing for 32 decedents in the PCT group (7.7% of deaths) and for 193 decedents in the control group (5.5% of deaths) (Fig 2).

The distribution of the 20-year mortality risks showed that cancer was the most likely cause of death (21.2% risk of death from cancer within 20 years for patients with PCT vs 11.9% for control individuals). Except for death from cardiovascular, cerebrovascular, or neurologic diseases, all cause-specific mortality risks were higher in the PCT group (Fig 4).

DISCUSSION

This nationwide cohort study showed that patients with PCT had higher mortality than matched population control individuals, and their higher prevalence of comorbid diseases could not fully explain this excess. We found that they had an increased risk of death from gastrointestinal diseases versus control individuals (20-year mortality, 3.8% vs 0.9%, respectively) and cancer (21.2% vs 11.9%, respectively), particularly cancers of the gut, liver/gallbladder, and lungs. Additionally, we found that the most frequent causes of death for patients with PCT were cancers and cardiovascular and gastrointestinal diseases and that their risk of death from cardiovascular disease was not increased (5.9% vs 6.3% for control individuals).

The primary strength of our study is the large number of patients with PCT included; studies of patients with PCT are often small because the disease is rare. Another strong point is that because all patients had PCT biochemically diagnosed, we did not include patients with pseudoporphyria or PCT-like symptoms, which could be the case in the study of Linet et al.[5] However, we cannot exclude the possibility that a few patients in our study may have one of the acute porphyrias. Because the prevalence of the acute porphyrias in Denmark is very low and those patients are often identified from other systemic symptoms, we believe that the number of misdiagnosed cases is minimal and not significant in the results of our study.

We found that our patients with PCT had increased all-cause mortality, also after adjusting for comorbidities. This finding is consistent with the findings by Linet et al[5] but contradicts the study by Rossmann-Ringdahl and Olsson,[12] who performed a retrospective study of 84 patients with PCT, of whom 21 died. By comparing their mean age of death, 86 years for women and 76 years for men, with that of the general local population, they found that the deceased patients with PCT had a normal life expectancy. However, no statistical analysis was

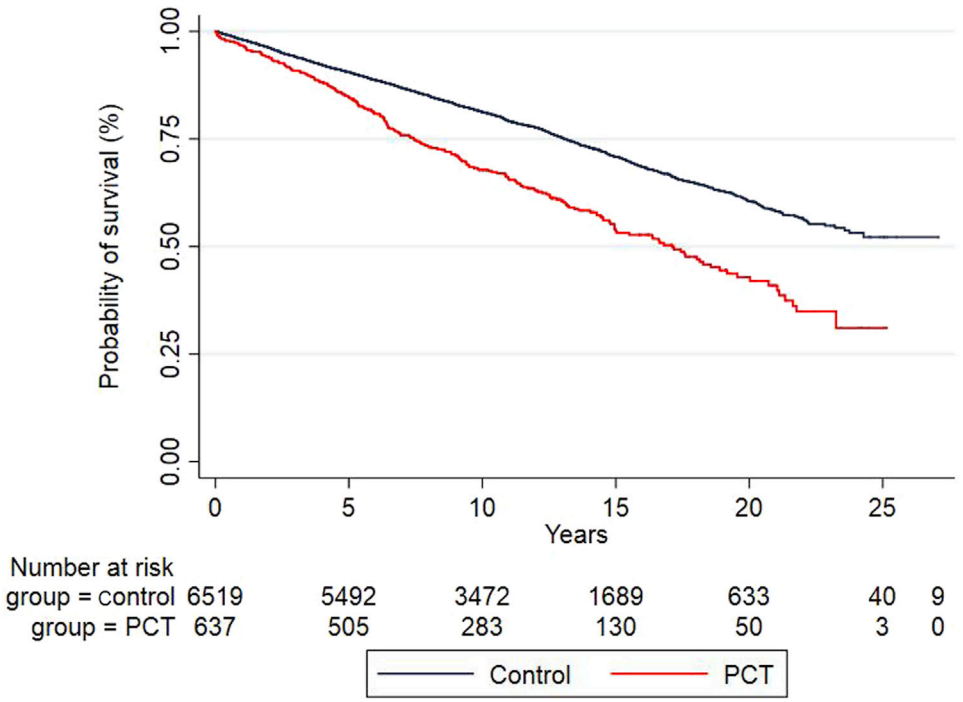

Fig 1. Survival time for patients with PCT and their matched control individuals. *PCT*, Porphyria cutanea tarda.

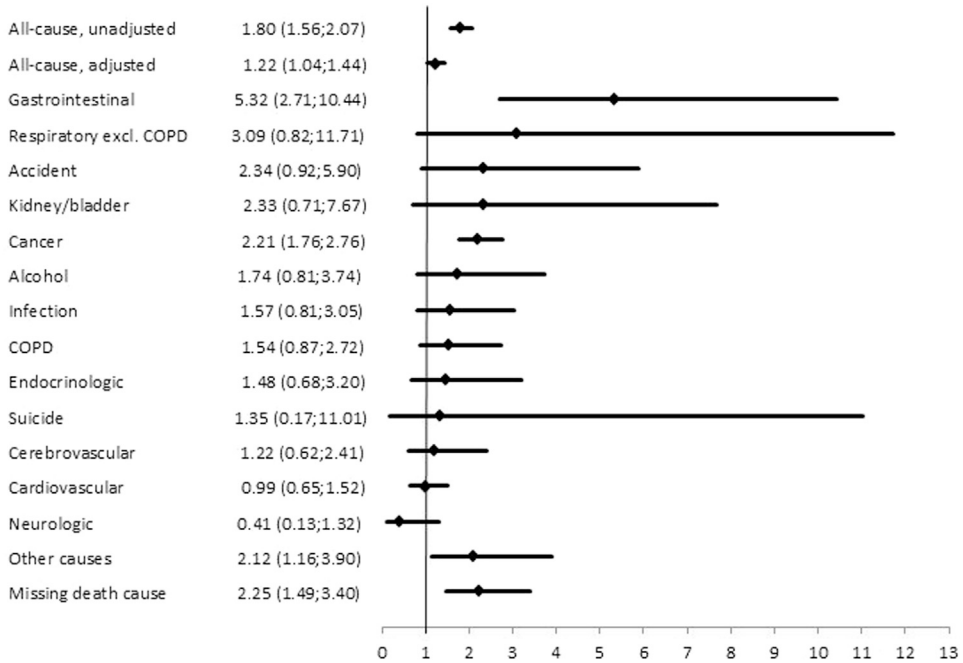

Fig 2. Hazard ratios: unadjusted and adjusted all-cause mortality hazard ratios (95% confidence intervals) and unadjusted cause-specific hazard ratios. *COPD*, Chronic obstructive pulmonary disease; *excl.*, excluding.

performed in that small study, and we believe that our larger matched cohort study provides a more precise and accurate estimate of the association between PCT and mortality.

Like Linet et al,[5] we found that the mortality from cancer was increased for patients with PCT. We extended this finding by showing that our patients with PCT had higher mortality from cancer in the

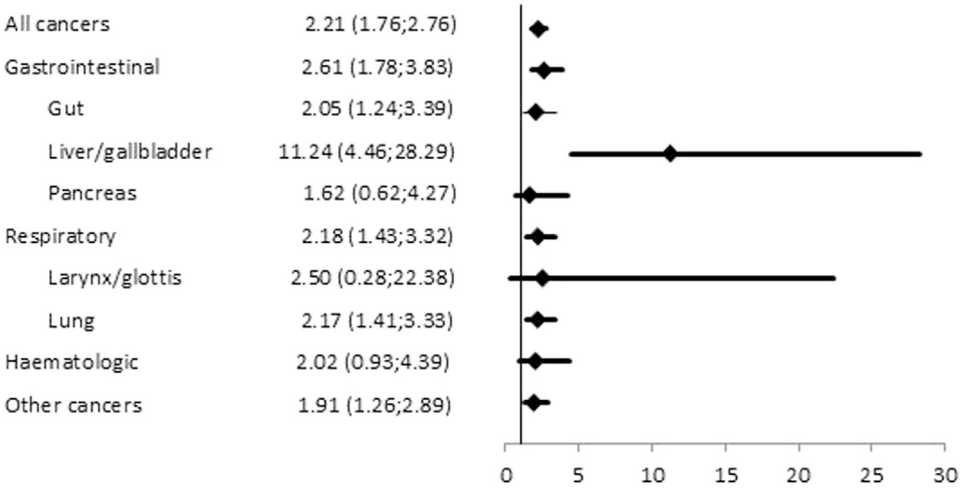

Fig 3. Hazard ratios (95% confidence intervals) for death from all cancers and death from cancers subdivided into 4 main groups.

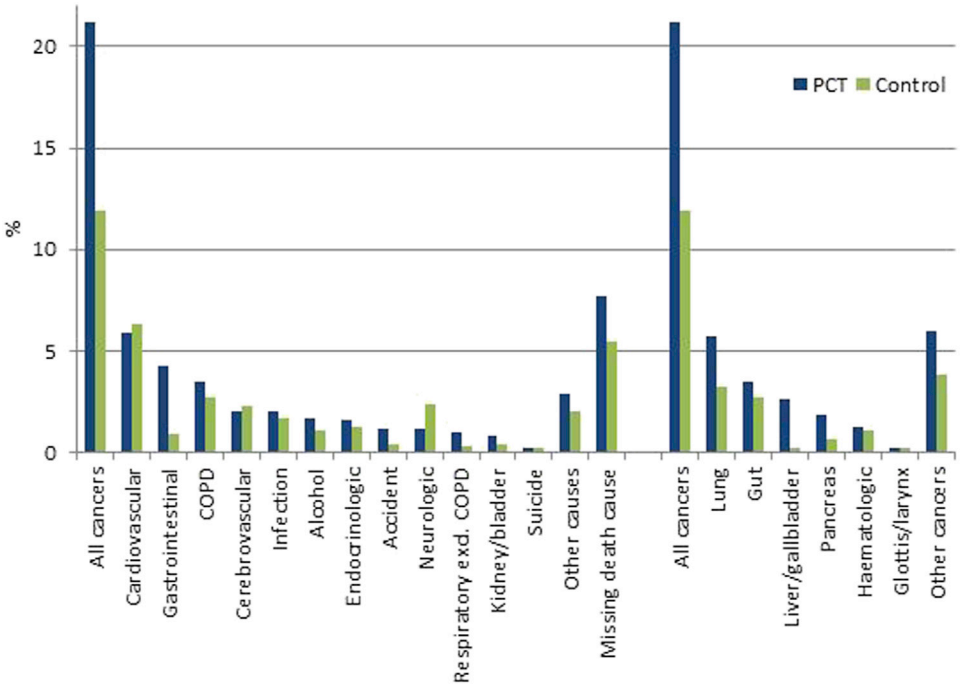

Fig 4. The 20-year risk of specific death causes for patients with PCT and matched control individuals. *COPD*, Chronic obstructive pulmonary disease; *excl.*, excluding; *PCT*, porphyria cutanea tarda.

liver/gallbladder and the gut. Also, our patients with PCT had increased mortality from lung cancer and COPD, although the latter did not reach statistical significance. These associations are consistent with previous findings that patients with PCT have an increased prevalence of tobacco smoking.[4,5] Finally, our patients with PCT had increased mortality from gastrointestinal diseases, likely explained by high alcohol intake and liver cirrhosis.[5] We had expected to see an increased mortality from cardiovascular and cerebrovascular disease, too, but the mortality was not increased. Our expectation was based on previous studies showing that patients with PCT had a high prevalence of diabetes and high risk of stroke. We cannot explain this discrepancy between older studies and ours.[10-12,17]

We showed that a large part of the excess mortality in patients with PCT was due to lifestyle factors and comorbidity, and this conclusion is corroborated by their higher risk of death from alcohol-related

causes, accidents, and suicide. It is possible that the 1.22-fold higher mortality in our PCT group is in fact due to residual confounding from lifestyle factors, that is, we could not measure those factors with sufficient accuracy to fully eliminate confounding. However, it is also possible that PCT itself increases mortality. This hypothesis that porphyrins are toxic is supported by a study from 1992 that showed that patients with PCT who developed hepatocellular carcinoma had a longer untreated symptomatic period.[9] Unfortunately, we do not have the data to fully clarify the causes of the higher mortality among our patients with PCT.

In conclusion, this historical cohort study has shown that patients with PCT have higher mortality and increased risk of death, mostly related to respiratory and gastrointestinal causes. The study emphasizes that patients with PCT and clinicians treating these patients must pay special attention to lifestyle and lifestyle-related comorbidities.

REFERENCES

1. Horner ME, Alikhan A, Tintle S, et al. Cutaneous porphyrias part I: epidemiology, pathogenesis, presentation, diagnosis, and histopathology. *Int J Derm*. 2013;52(12):1464-1480.
2. Christiansen AL, Aagaard L, Krag A, et al. Cutaneous porphyrias: causes, symptoms, treatments and the Danish incidence 1989-2013. *Acta Derm Venereol*. 2016;96(7):868-872.
3. Bissell DM, Anderson KE, Bonkovsky HL. Porphyria. *New Engl J Med*. 2017;377(9):862-872.
4. Jalil S, Grady JJ, Lee C, et al. Associations among behavior-related susceptibility factors in porphyria cutanea tarda. *Clin Gastroenterol Hepatol*. 2010;8(3):297-302.
5. Linet MS, Gridley G, Nyren O, et al. Primary liver cancer, other malignancies, and mortality risks following porphyria: a cohort study in Denmark and Sweden. *Am J Epidemiol*. 1999;149(11):1010-1015.
6. Elder GH. Porphyria cutanea tarda. *Semin Liver Dis*. 1998;18(1):67-75.
7. Fracanzani AL, Taioli E, Sampietro M, et al. Liver cancer risk is increased in patients with porphyria cutanea tarda in comparison to matched control patients with chronic liver disease. *J Hepatol*. 2001;35(4):498-503.
8. Salata H, Cortes JM, Enriquez de Salamanca R, et al. Porphyria cutanea tarda and hepatocellular carcinoma. Frequency of occurrence and related factors. *J Hepatol*. 1985;1(5):477-487.
9. Siersema PD, ten Kate FJ, Mulder PG, et al. Hepatocellular carcinoma in porphyria cutanea tarda: frequency and factors related to its occurrence. *Liver*. 1992;12(2):56-61.
10. Munoz-Santos C, Guilabert A, Moreno N, et al. The association between porphyria cutanea tarda and diabetes mellitus: analysis of a long-term follow-up cohort. *Br J Derm*. 2011;165(3):486-491.
11. Christiansen AL, Bygum A, Hother-Nielsen O, et al. Diagnosing diabetes mellitus in patients with porphyria cutanea tarda. *Int J Derm*. 2018;57(7):763-769.
12. Rossmann-Ringdahl I, Olsson R. Porphyria cutanea tarda in a Swedish population: risk factors and complications. *Acta Derm Venereol*. 2005;85(4):337-341.
13. Schmidt M, Schmidt SA, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidimiol*. 2015;7:449-490.
14. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549.
15. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry—history, content, quality and use. *Dan Med Bull*. 1997;44(5):535-539.
16. Helweg-Larsen K. The Danish Register of Causes of Death. *Scand J Public Health*. 2011;39(7 Suppl):26-29.
17. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *Lancet*. 2017;389(10085):2239-2251.