Risk of diabetes and cardiovascular disease in patients with primary sclerosing cholangitis

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Background & Aims: Primary sclerosing cholangitis (PSC) is associated with increased mortality. Cardiovascular disease is a leading cause of death in the Western world. We examined the risk of cardiovascular disease and diabetes (type 1 and type 2) in patients with PSC and their first-degree relatives.
Methods: This prospective multicentre cohort study included 678 individuals with PSC diagnosed between 1970 and 2004, and 6347 non-PSC reference individuals matched for age, and sex. Through linkage of the Swedish Multigeneration Register we identified 3139 first-degree relatives to PSC patients and 30,953 first-degree relatives to the matched comparison cohort. We retrieved data on cardiovascular disease and type 1 and type 2 diabetes (T1D and T2D) from the National Patient Register, and then examined the association with PSC or having a family history of PSC using Poisson regression.
Results: During 125,127 person-years of follow-up, 203 individuals with PSC had a diagnosis of cardiovascular disease. This corresponded to a 3.34-fold increased relative risk (RR) of cardiovascular disease in individuals with PSC (95% CI = 2.86–3.91). The highest risk estimates were seen for diseases of the arteries, veins, and lymphatic vessels while the RR was neutral for ischemic heart disease (0.90) or only slightly elevated for cerebrovascular disease (1.74). Meanwhile, PSC first-degree relatives were at no increased risk of cardiovascular disease (RR = 0.87; 95% CI = 0.80–0.95). Individuals with PSC (RR = 7.95; 95% CI = 4.82–13.12), and to some extent also their first-degree relatives (RR = 1.73; 95% CI = 1.19–2.52) were at increased risk of T1D. Also for T2D were the RR is higher in individuals with PSC (RR = 2.54; 95% CI = 1.56–4.13) than in PSC first-degree relatives (RR = 0.81; 95% CI = 0.65–1.02).
Conclusions: PSC was associated with T1D, T2D, and non-ischemic cardiovascular disease. In contrast, first-degree relatives to PSC patients were only at a moderately increased risk of T1D, and at no increased risk of either cardiovascular disease or T2D.
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Introduction

Primary sclerosing cholangitis (PSC) occurs in about 4–15/100,000 people [1–3]. It is an idiopathic cholestatic disorder with intra- and extrahepatic fibrosis and inflammation [4]. This causes duct destruction and ultimately biliary cirrhosis and liver failure. There is no available treatment that influences disease progression, and the prognosis of PSC is poor [1,5]. An older Swedish study with 305 PSC patients found a median survival from time of PSC diagnosis to either death or liver transplantation of 12 years [5], and in a recent paper by de Valle et al. from Western Sweden, PSC was associated with a 4-fold increased risk in mortality [6]. Similar mortality risks have also been reported from the British General Practice Research Database [1].

Bile duct cancer is more prevalent in PSC patients and contributes to the excess of both overall mortality and morbidity in PSC [1,5,6]. Less is however known about PSC and the risk of cardiovascular disease and type 1 and type 2 diabetes (T1D and T2D). In a recent paper from the Netherlands, Lamberts et al. reported that 9 out of 241 patients (3.7%) with PSC developed T1D [7]. Although the authors did not calculate any relative risk for T1D, a prevalence of 3–4% is likely to constitute a substantial risk increase since the prevalence of T1D in the general population of the Netherlands is at the most 1% (proportion of individuals in the Netherlands who receive insulin treatment for diabetes: T1D and T2D) [8], and there is a need for more precise estimates of the T1D risk in PSC.

Cardiovascular disease is the leading cause of death in the Western world [9], and some 500,000 people die from ischemic

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heart disease each year in the US, with additional deaths from stroke (stroke being the second most common cause of death [10]). Despite the impact of cardiovascular disease on public health, and observations of dyslipidemia in PSC [11–13] we are not aware of any population-based study on the risk of cardiovascular disease in PSC.

The purpose of this study was to investigate the risk of cardiovascular disease and diabetes (type 1 and 2) in patients with PSC and their first-degree relatives. We hypothesized that individuals with PSC would be at increased risk especially of T1D since this latter disease shares several of the immune-mediated traits of PSC. Furthermore we expected to see an increased risk of cardiovascular disease in PSC, but less so in their first-degree relatives, since the latter are not exposed to PSC-related inflammation.

Patients and methods

Through the personal identity number [14] we linked data on clinically verified PSC and nationwide data on cardiovascular disease, T1D and T2D from Swedish registers.

PSC definition

Hepatologists representing ten Swedish university hospitals have prospectively reported cases of PSC to the *Swedish Internal Medicine Liver Club* since 1970. The ten university hospitals include three transplantation centres. In this study the PSC diagnosis was based on a combination of biochemical, clinical, and cholangiographic data in accordance with Wiesner and LaRusso [15]. In addition, the PSC diagnosis was confirmed against patient charts. We defined the onset of PSC as equal to the first cholangiographic examination with signs of PSC (the patients should also have additional proof of PSC) [16].

We initially identified 700 individuals with PSC. Of these, we excluded 22 (because they had emigrated from Sweden and were no longer available for matching), leaving 678 PSC patients for the main analyses of this study. Detailed characteristics of these individuals have been described previously [16], but in short some 465 (69%) were male, and 545 (80%) had a concomitant diagnosis of IBD (most often ulcerative colitis (n = 463, i.e., 68% of the PSC cohort)). The mean age at onset at diagnosis was 36 years (SD: ±12), and 142 individuals had a liver transplantation during follow-up (21%).

Comparison cohort

Each case with PSC was matched with up to ten individuals from general population for age and calendar year (exact years), sex, and county (n = 6347).

First-degree relatives

In order to explore if potential associations between PSC, cardiovascular disease and diabetes (T1D or T2D), were mediated by active disease rather than through genetic factors, we also examined the association with cardiovascular disease and diabetes in 3139 first-degree relatives (offspring: n = 930, siblings: n = 1030, and parents: n = 1170 (Table 1)). First-degree relatives were identified through the Swedish Multigeneration Register [17]. This register contains data on all individuals born in Sweden since 1932 who were alive in 1961. Similarly we also identified first-degree relatives to the comparison cohort, yielding 30,953 individuals. Their characteristics are given in Table 1. Both relatives to PSC patients and relatives to the comparison cohort had a mean follow-up time of close to 30 years.

Follow-up time

Start of follow-up was defined as birth date, immigration or 1965, whichever occurred later. We excluded relatives who died or emigrated before follow-up (n = 204). Due to data irregularities that resulted in uncertain follow-up, another 9% (n = 602) of first-degree relatives were also excluded. Follow-up ended with death, a positive outcome (cardiovascular disease, T1D or T2D respectively), emigration or end of study (Dec 31, 2004), whichever occurred first. Data on emigration were obtained from the government agency Statistics Sweden, while data on death date were retrieved from the Cause of Death Register maintained by the National Board of Health and Welfare. The Cause of Death Register is regularly

Table 1. Characteristics of first-degree relatives.

	Relatives of PSC[1] patients	Relatives of subjects without PSC
Total	3139	30,953
Offspring	930	9773
Male (%)	496 (53.3)	5035 (51.5)
Siblings	1030	10,529
Male (%)	540 (52.0)	5352 (50.8)
Parents	1170	10,651
Male (%)	576 (49.2)	5211 (48.9)
Mean age at first record of CVD[2] (SD)		
Offspring	24 (13)	25 (13)
Siblings	48 (13)	47 (13)
Parents	68 (13)	68 (13)
Mean follow-up time (SD)	29.6 (12)	29.3 (12)

[1]Primary sclerosing cholangitis.
[2]Cardiovascular disease.

audited against vital status data from the National Tax office to ensure that 100% of all deaths are recorded. In the cardiovascular analyses, the first CVD event was used to define overall relative risk and for each specific group of CVD diagnoses; and the first event from that group of CVD diagnoses was used to define relative risk in subanalyses.

Outcome measures

Data on outcome measures were obtained from inpatient diagnoses in the Swedish Patient Register [18]. This register started in 1964, and became nationwide in 1987. An extensive validation of 132 validation studies on a large range of diagnoses found that the positive predictive value (PPV) of most diagnoses in the register is between 85 and 95% [18], though slightly higher for ischemic heart disease and atrial fibrillation (95–100%), and slightly lower for heart failure (82–88%). No data are available for T1D or T2D specifically but one study found that 235/236 (99%) patients with a diagnosis of diabetic ulcer actually had both diabetes and ulcers [19]. When Zachrisson and co-workers examined some 6000 individuals aged 0–18 years with a diagnosis of diabetes, >99% of these had T1D (as opposed to T2D or other forms of diabetes) [20].

Outcome measures were defined according to relevant international classification of disease (ICD) codes (cardiovascular diseases: ICD-10 = I00–I99 and diabetes: ICD-10: E10 for T1D and E11 for T2D (and corresponding ICD-7-9 codes, Supplementary Table 1)). We also examined six subgroups of cardiovascular disease (I) hypertensive diseases, (II) ischemic heart diseases, (III) pulmonary heart disease and diseases of pulmonary circulation, (IV) cerebrovascular diseases, diseases of arteries, (V) arterioles and capillaries, (VI) diseases of veins, lymphatic vessels and lymph nodes. Relevant ICD-codes and definitions are listed in Supplementary Table 1. As there were no separate codes for T1D and T2D before 1997 and the introduction of ICD-10, we defined T1D by retrieving patients whose age of first hospital admission for diabetes was <20 years. In total, 12 exposed and 104 unexposed individuals had records of both T1D and T2D, using ICD-10. These 116 individuals were excluded from the analyses.

Statistics

The main analyses compared the PSC and non-PSC cohorts. We used Poisson regression to calculate relative risks (RRs) with 95% confidence intervals (CIs). We adjusted all analyses for follow-up duration, year at entry, with further adjustment for age at entry, county and sex to consider the matching factors. In separate analyses we stratified for calendar year of entry (before or after 1987), follow-up (0–5, 6–10, ⩾11 years) and age at end of follow-up (<40, 40–49, 50–59, ⩾60 years).

The offspring, siblings, and parents were the units of analysis and these groups were investigated separately to estimate the risk of cardiovascular disease, T1D and T2D among first-degree relatives of the PSC cohort compared with relatives of the comparison cohorts.

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