Hepatitis C Virus Infection and the Temporal Trends in the Risk of Liver Cancer: A National Register-Based Cohort Study in Sweden

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ABSTRACT

Background: In many countries, including Sweden, the birth cohorts with the highest prevalence of hepatitis C virus (HCV) infection have now reached the ages with high risk of primary liver cancer (PLC). The aims of this study were to investigate the temporal trends in PLC incidence and the relative risks of PLC among people diagnosed with HCV infection between 1990 and 2015.

Methods: The HCV cohort ($n = 52,853$) was compared with a matched non-HCV comparison cohort ($n = 523,649$). Both the national Cancer Register (CR) and Cause of Death Register (DR) were used for follow-up. The crude and age-standardized PLC incidence rates were calculated. The relative risk was estimated as standardized incidence ratios (SIR) and as HRs using stratified Cox hazards regression.

Results: There were 1,609 with PLC diagnosis in the HCV cohort; the annual number increased continuously with the crude incidence rate reaching 4.56 per 1,000 person-years in 2013 while remaining low and stable in the comparison cohort. In the HCV cohort, the age-standardized PLC incidence rates per 1,000 person-years remained relatively constant at 2.64 [95% confidence interval (CI), 1.54–3.75] in 2000 and 3.31 (2.51–4.12) in 2014. The highest SIR was 73 (65.9–79.5) among those infected for 35 to 40 years; and the highest HR was 65.9 (55.9–77.6) for men and 62.2 (31.9–121.1) for women.

Conclusions: There was a considerable increase in PLC incidence over time and an extremely high relative risk in the population with HCV infection for more than 35 years.

Impact: The national HCV-associated PLC incidence should be monitored in future studies to evaluate the effect of direct-acting antiviral (DAA) treatment.

Introduction

The global number of people with chronic hepatitis C virus (HCV) infection was recently estimated to be 71 million, corresponding to about 1.0% of the world population (1). The HCV infection is often asymptomatic but is associated with a high risk of long-term complications such as liver cirrhosis and hepatocellular carcinoma (HCC) and also extrahepatic manifestations (2–6).

Primary liver cancer (PLC) is one of the leading causes of cancer-related death in the world and a major cause of death in patients with HCV-associated liver cirrhosis (http://gco.iarc.fr/). The World Health Organization (WHO) has set targets to eliminate HCV and hepatitis B virus (HBV) infection as public health threats, aiming at 90% reduction in new infections and 65% reduction in hepatitis-related mortality by 2030 (https://www.who.int/hepatitis/en/).

The prevalence of HCV infection in Sweden has been estimated to about 0.5%, with a diagnosis rate of approximately 80% (7). In 2008, Strauss and colleagues estimated the risk of PLC in people notified with HCV diagnosis between 1990 and 2004 in Sweden (5). The highest relative risk was among people who had been HCV infected for 25–30 years, with standardized incidence ratio (SIR) of 46 [95% confidence interval (CI), 36–56]. Since this study, the number of people with HCV diagnosis in Sweden has increased by 50%, and the birth cohort with the highest HCV prevalence has now been infected for more than 30 years and reached age 50–70 years with high risk of HCC (8).

Similar trends with aging of the HCV-infected populations exist in other Western countries (8, 9). In the United States, HCV screening is ongoing for those born in 1945–1965, the so-called baby boomers (10). Also, recent studies have demonstrated an underreporting of HCC to the Cancer Register and point out the need for an updated approach to improve completeness when studying HCC-incidence (11, 12).

Until recently, treatment for HCV infection was insufficient. New highly effective therapies with direct-acting antivirals (DAA) will hopefully change the scenario in the future. A decrease in liver transplantations for decompensated cirrhosis has already been reported from some countries, but the effect of DAAs on the incidence of HCC has been debated and not until recently have larger studies demonstrated a decrease among treated patients (13, 14). To achieve the WHO elimination goals, a treatment that effectively decreases HCC incidence and is available for the majority of people with HCV infection is needed. It is therefore important to study the current situation and to follow future temporal trends on a national level.

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Sweden is one of the few countries with possibilities to perform these large, national, population-based studies.

The aim of this study was to investigate temporal trends in PLC incidence and relative risk of PLC in a national cohort of people notified with HCV infection in Sweden between 1990 and 2015.

Materials and Methods

Study population

Every resident in Sweden has a unique personal identification number (PIN) assigned at birth or immigration and used in all national registers (http://www.socialstyrelsen.se/). We used the register for Surveillance of Communicable Diseases at the Public Health Agency to identify all diagnosed HCV infections in Sweden during 1990–2015 (http://www.folkhalsomyndigheten.se/). Information about HBV infection was added to identify potential HCV–HBV coinfections. These infections are notifiable diseases that must be reported by both diagnosing laboratories and clinicians. The basis for HCV notification is a first-time HCV diagnosis, usually based on a positive antibody test (anti-HCV, verified with RIBA or HCV antigen test), and for HBV-notification a first-time HBV diagnosis based on a positive HBsAg test. The notifications include PIN, sex, and presumed route of transmission.

During the years 1990–2015, there were 64,149 HCV notifications recorded at the Public Health Agency. The date of notification was assumed to be the date of HCV diagnosis. The notification data were transferred to Statistics Sweden (http://www.scb.se/) where all PINs were checked and residence in Sweden was confirmed, after that 57,151 people with HCV notifications were eligible for the study. Another 111 individuals were excluded on the basis of HCV diagnosis after inclusion in the matched non-HCV cohort. The HCV population then consisted of 57,040 individuals, of whom 4,038 also were notified with an acute or chronic HBV infection, the HCV–HBV coinfection cohort, and 53,002 constituted the HCV cohort.

A matched comparison cohort consisting of individuals without HCV notifications was obtained from Statistics Sweden. Each HCV-infected subject was matched, on the date of notification, with 10 individuals without an HCV notification from the general population (matching characteristics: birth year, sex, county of residence in Sweden, and alive at date of notification). After excluding comparators with inconsistent data or no observation time, the comparison cohort consisted of 523,672 matched non-HCV subjects.

The HCV cohort and the comparison cohort were followed from notification date using prospectively recorded information for the occurrence of PLC. However, 149 HCV-infected and 23 noninfected comparison individuals were excluded from the analysis due to a PLC diagnosis before or at the same time as the notification date. The HCV cohort then consisted of 52,853 and the comparison cohort of 523,649 subjects for further analysis (**Table 1**).

Table 1. Characteristics of the HCV cohort and the non-HCV comparison cohort.

	HCV cohort	Comparison cohort
Total in the study cohort	52,853	523,649
Total observed person-years	589,294	6,395,003
Mean observed person-years (SD)	11 (7.15)	12 (7.28)
Deceased (%)	12,748 (24.1)	39,292 (7.5)
Male sex (%)	35,414 (67.0)	351,009 (67.0)
Mean age at notification (SD)	40 (13.62)	40 (13.67)
Year of birth (% by cohort)		
<1930	1,227 (2.32)	12,318 (2.35)
1930–1945	4,061 (7.68)	40,657 (7.76)
1945–1960	19,588 (37.06)	194,051 (37.06)
1960–1975	16,707 (31.61)	165,001 (31.51)
>1975	11,270 (21.32)	111,622 (21.32)
Country of origin (% by cohort)		
Nordic countries including Sweden	46,174 (87.36)	426,953 (81.53)
Other	6,679 (12.64)	96,696 (18.47)
Diagnosed with liver cancer (% by cohort)	1,609 (3.04)	408 (0.08)
Males with liver cancer diagnoses	1,303 (3.68)	297 (0.08)
Females with liver cancer diagnoses	306 (1.75)	111 (0.06)
Mean age at liver cancer diagnosis (SD)	61 (8.90)	63 (12.59)
Liver cancer diagnoses by year of birth (% in cohort)		
<1930	115 (7.15)	60 (14.71)
1930–1945	413 (25.67)	134 (32.84)
1945–1960	976 (60.66)	173 (42.40)
1960–1975	102 (6.34)	35 (8.58)
>1975	3 (0.19)	6 (1.47)

Linkage to other registers

The PINs were used to link the HCV-infected and non–HCV-infected subjects to other national registers. Information on dates of death, immigration, emigration, and country of origin was obtained from the Swedish Population register maintained by Statistics Sweden. The National Board of Health and Welfare (http://www.socialstyrelsen.se/) provided information from the national Cancer Register (CR) and Cause of Death Register (DR).

All incident diagnoses of PLC were identified from the CR using the seventh revision of the International Classification of Disease, ICD-7 codes: 155.0 and 156. Information on PLC mortality (listed as the underlying cause of death) was obtained from the DR with ICD-9 codes (used in 1987–1996): 155.0, 155.1, 155.2, and ICD-10 codes (from 1997): C22.0, C22.1, C22.4, and C22.9 (from 2000 divided in C22.90 "primary liver cancer" and C22.99 "liver cancer"). Codes for unspecified (UNS) liver cancer were included because studies have demonstrated that misclassification is common (11, 12). The outcome PLC was primarily identified from the CR but was added from the DR when missing in the CR.

The Prescription Register added information about prescribed drugs from July 2005, when the register started, to the end of 2015. In the HCV cohort, there were 6,070 who had received IFN-based treatment and 2,893 had received DAA therapy (introduced in 2014). There was no information about treatment outcome. Previous studies estimated that in Sweden, from 1990 to 2015, about 7,000 patients had achieved sustained virological response and were considered to be cured (7). Treated patients were included because we wanted to study the national temporal trends of HCV-associated PLC.

Modeling date of infection

For many HCV-infected patients, the date of diagnosis is considerably later than date of infection. We used a previously developed model, based on HCV epidemiology and route of infection, to estimate the date of infection (4).

For individuals infected through intravenous drug use (IDU), sexual, other, or unknown routes of transmission, and (i) born before 1930, the year of infection was set to 1965; (ii) born between 1930 and 1955, the age at infection was set to 35 years when born in 1930 and linearly reducing to age 20 years when born in 1955; and (iii) born after 1955, the age at infection was set to 20 years or equal to age at

notification when younger than 20 years. For transfusion-associated HCV (blood/blood products), the year of infection was set to 1980. For individuals with mother-to-child transmission and adopted children, the date of birth was considered to be the infection date. For nosocomial and occupational routes of transmission, the date of notification was taken as the infection date.

The date of infection was used to estimate time with infection, but was never used as index date for the analyses.

Statistical analysis

The observation time started on the date of notification (same as matching date) and ended at outcome (date of PLC diagnosis), or at censoring due to emigration, death (other causes than PLC), or end of study in December 31, 2015, whichever occurred first. However, for the relative risk analyses (SIR, Cox regression) the first year from the date of notification was excluded for the HCV cohort, that is, starting observation time one year after notification, as part of adjustment for selection bias (15, 16).

For both HCV and comparison cohorts, the temporal trends in PLC incidence and crude incidence rates were assessed. For the HCV cohort, the sex- and age-standardized incidence rates were calculated with standardization according to the Swedish population in the year 2000, using 5-year age groups.

The relative risk for PLC in the HCV cohort, expressed as SIRs, was calculated by dividing the number of observed PLC-diagnoses by the expected number, based on all PLC reported to the CR completed with PLC only reported to the DR. The expected number of PLC-diagnoses was computed from the age-, sex-, and calendar year–specific PLC incidence rates (CR + DR) from the matched comparison-cohort, multiplied by the observed number of person-years (by age, sex, and calendar year) in the HCV cohort. Stratified SIR analyses were performed by estimated duration of HCV infection: less than 10 years, 10–20, 20–25, 25–30, 30–35, 35–40, 40–45, and more than 45 years of infection. Exact 95% CIs were calculated assuming a Poisson distribution of cases. The Poisson trend test was carried out to detect a monotonic relationship between increasing duration of HCV infection and increasing trend in stratified SIR.

For comparison, a supplementary SIR (SIR_{suppl}) was calculated, comparing the HCV cohort to the general population in Sweden using PLC data from the CR only (Supplementary Materials and Methods).

To study the relative effect of duration of HCV infection on the PLC rate for men and women in the HCV cohort in reference to matched cohort, we estimated the HRs for different durations through applying the Cox model with attained age as the time scale, duration of HCV infection as the time-varying cumulative exposure, while adjusting for interaction between the duration and sex, and stratifying on birth cohorts (born before 1930, 1930–1945, 1945–1960, 1960–1975, and later than 1975; refs. 17, 18). Non-HCV individuals of the corresponding sex with duration of HCV infection set at zero were used as baseline reference. The PLCs were identified from both the CR and the DR. The Shoenfeld test of the proportionality assumption in the fitted Cox model was performed (19). The data cleaning and statistical analyses were carried out using the statistical software SAS 9.4, R 3.5, and R package survival (https://CRAN.R-project.org/package=survival).

Ethics

The linkage of the register files was undertaken by the Public Health Agency, Statistics Sweden, and National Board of Health and Welfare. All data were anonymized before they were seen by the research team. This study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Results

Descriptive analyses and incidence rates

There were 57,040 Swedish residents with an HCV notification 1990–2015, of whom 4,038 (7%) also were diagnosed with acute or chronic HBV infection. In total, 1,826 (3.2%) had a PLC diagnosis, of which 1,758 were in the HCV monoinfected cohort. Out of these PLCs, only 1,290 (73.4%) were registered in the CR and the rest were identified from the DR. The PLCs in the CR were further classified as HCC 91%, intrahepatic cholangiocarcinomas (ICC) 3%, and liver cancer UNS 6.3%. Those added from the DR were classified as HCC 43%, PLC/liver cancer 54%, and ICC 2.6%.

The following analyses only comprise the monoinfected HCV cohort that, after exclusion of 149 individuals with PLC diagnosis before HCV notification, consisted of 52,853 persons. Most of the subjects were men (67%) and the majority (87%) originated from Sweden or another Nordic country. The median birth year was 1960 (IQR: 1952; 1972). The matched comparison cohort consisted of 523,649 subjects without HCV diagnosis. **Table 1** summarizes the study population characteristics.

There were 1,609 PLC diagnoses in the HCV cohort and 408 in the comparison cohort, and median age at diagnosis was 60 and 62 years, respectively. The age distribution at PLC diagnosis stratified by sex is demonstrated in **Fig. 1**.

The most commonly reported route of HCV transmission was IDU (21,384; 40%), followed by transfusion of blood/blood products in 2,416 (4.6%) and sexual transmission in 1,396 (2.6%), though missing or unknown in 50% (**Table 2**). The percentage with PLC among those infected through blood/blood products was as high as among those infected through IDU or with missing/unknown route. The PLC count by year of birth demonstrated that 93% of patients with PLC were born before 1960, compared with 47% in the entire HCV cohort.

Between 1990 and 2015, the annual number of PLC-diagnoses in the HCV cohort gradually increased to 161 in 2014, with continuously increasing crude incidence rates reaching 4.56 per 1,000 person-years in 2013, while the crude incidence rates in the comparison cohort were low and stable over years in spite of the aging population (**Fig. 2A** and **B**). The age-standardized PLC incidence rates in the HCV cohort remained relatively constant at 2.64 (95% CI, 1.54–3.75) per 1,000 person-years in year 2000 and 3.31 (95% CI, 2.51–4.12) per 1,000 person-years in 2014 (**Fig. 2C** and **D**).

Risk analyses

Because of adjustment for selection bias, the first year after HCV notification (with 259 new PLC diagnoses) was not included in the risk analyses. Subsequently, the HCV cohort for the risk analyses consisted of 49,445 subjects with an observation time of 538,348 person-years, and 1,350 PLCs remained eligible for further risk analyses. The estimated mean duration of infection at PLC diagnosis was 35.5 (SD: 6.1) years.

The SIR analysis, with PLC incidence from both CR and DR, comparing the HCV cohort to the matched cohort, demonstrated a high relative risk. Those with estimated infection duration of 35–40 years had the highest SIR of 73 (95% CI, 65.9–79.5) followed by SIR 61 (95% CI, 53.0–69.3) for those with 40–45 years of infection (**Table 3**). Supplementary analyses (SIR_{suppl}) with PLC from the CR only is presented in Supplementary Table S1.

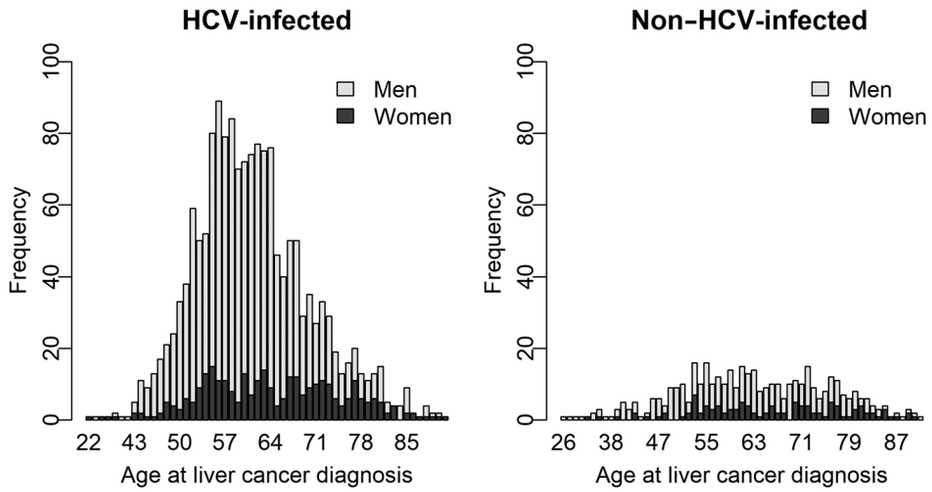

Figure 1.
Age distributions at PLC diagnoses with respect to HCV status and sex. Left graph displays age distributions at PLC diagnoses for individuals in the HCV cohort ($n = 1{,}609$, 81% men), and right is for individuals in the non-HCV comparison cohort ($n = 408$, 73% men).

Using the Cox model, we estimated HRs with 95% CI for different estimated durations of HCV infection and plotted these separately for men and women (**Fig. 3**). The highest HR for men was 65.9 (95% CI, 55.9–77.6) at 35–40 years with HCV infection, whereas for women it reached HR 62.2 (95% CI, 31.9–121.1) after estimated 45 years with HCV infection.

Discussion

There was a continuous increase of HCV-related PLCs with time, in this national cohort of people with HCV diagnosis. This could partly be explained by the growth and the aging of the cohort. However, the increasing incidence rates in the HCV cohort compared with the low and stable incidence rates in the matched non-HCV comparison cohort indicate that duration of the infection plays an important role. The relative risk of PLC in the HCV cohort, estimated as SIR and HR, was very high after an estimated 25 years with infection, with the highest relative risk after 35 years.

The aim was to study the temporal trends of PLC in a national HCV cohort and to provide updated estimates of the relative risk, with more recent and more complete PLC incidence data. As previous studies predicted (7, 20, 21), we observed a continued strong rise in PLC diagnoses among people with HCV diagnosis in Sweden and the increase was even stronger than anticipated. Although there was over a 2-fold increase in total observed person-years in current HCV cohort, 589,294 compared with 246,106 in the 1990–2004 study (5), there were over four times more incident PLCs registered in the CR ($n = 1{,}141$) compared with the previous study ($n = 234$), and over six times more ($n = 1{,}609$) when adding PLCs from the DR. Because the large-scale spread of HCV started in the late 1960s and increased in 1970s (22), this surge

Table 2. Reported routes of transmission by year of birth in the HCV cohort ($n = 52{,}853$) and PLC count ($n = 1{,}609$).

Route of transmission	Total count (%)	Year of birth, number in cohort (% by row)				
		<1930	1930–1945	1945–1960	1960–1975	1975<
Blood/blood products	2,416 (4.57)	223 (9.23)	538 (22.27)	934 (38.66)	529 (21.9)	192 (7.95)
PLC (% in group)	*109 (4.51)*	*23 (10.3)*	*49 (9.1)*	*30 (3.2)*	*6 (1.1)*	*1 (0.5)*
Intravenous drug use	21,384 (40.46)	15 (0.07)	581 (2.72)	5,903 (27.6)	6,963 (32.56)	7,922 (37.05)
PLC (% in group)	*409 (1.9)*	*1 (6.7)*	*60 (10.3)*	*311 (5.3)*	*37 (0.5)*	*0 (0)*
Mother-to-child	147 (0.28)	0 (0)	3 (2.04)	7 (4.76)	19 (12.93)	118 (80.27)
PLC (% in group)	*3 (2.0)*	*0 (0)*	*1 (33.33)*	*1 (14.2)*	*1 (5.2)*	*0 (0)*
Nosocomial	504 (0.95)	17 (3.37)	98 (19.44)	188 (37.3)	125 (24.8)	76 (15.08)
PLC (% in group)	*9 (1.8)*	*0 (0)*	*3 (3.1)*	*5 (2.7)*	*1 (0.8)*	*0 (0)*
Occupational	28 (0.05)	1 (3.57)	4 (14.29)	17 (60.71)	6 (21.43)	0 (0)
PLC (% in group)	*1 (3.6)*	*0 (0)*	*1 (25)*	*0 (0)*	*0 (0)*	*0 (0)*
Other	800 (1.51)	4 (0.5)	50 (6.25)	267 (33.38)	252 (31.5)	227 (28.38)
PLC (% in group)	*26 (3.25)*	*1 (25)*	*7 (14)*	*15 (5.6)*	*3 (1.2)*	*0 (0)*
Sexual	1,396 (2.64)	0 (0)	37 (2.65)	427 (30.59)	495 (35.46)	437 (31.3)
PLC (% in group)	*24 (1.7)*	*0 (0)*	*4 (10.8)*	*16 (3.7)*	*4 (0.8)*	*0 (0)*
Unknown	26,178 (49.53)	967 (3.69)	2,750 (10.51)	11,845 (45.25)	8,318 (31.77)	2,298 (8.78)
PLC (% in group)	*1,028 (3.9)*	*90 (9.3)*	*288 (10.5)*	*598 (5.0)*	*50 (0.6)*	*2 (0.09)*
Total	52,853 (100)	1,227 (2.32)	4,061 (7.68)	19,588 (37.06)	16,707 (31.61)	11,270 (21.32)
PLC (% by row)	*1,609 (100)*	*115 (7.15)*	*413 (25.67)*	*976 (60.66)*	*102 (6.34)*	*3 (0.19)*

Note: Italic text indicates the number/percentage of PLC.

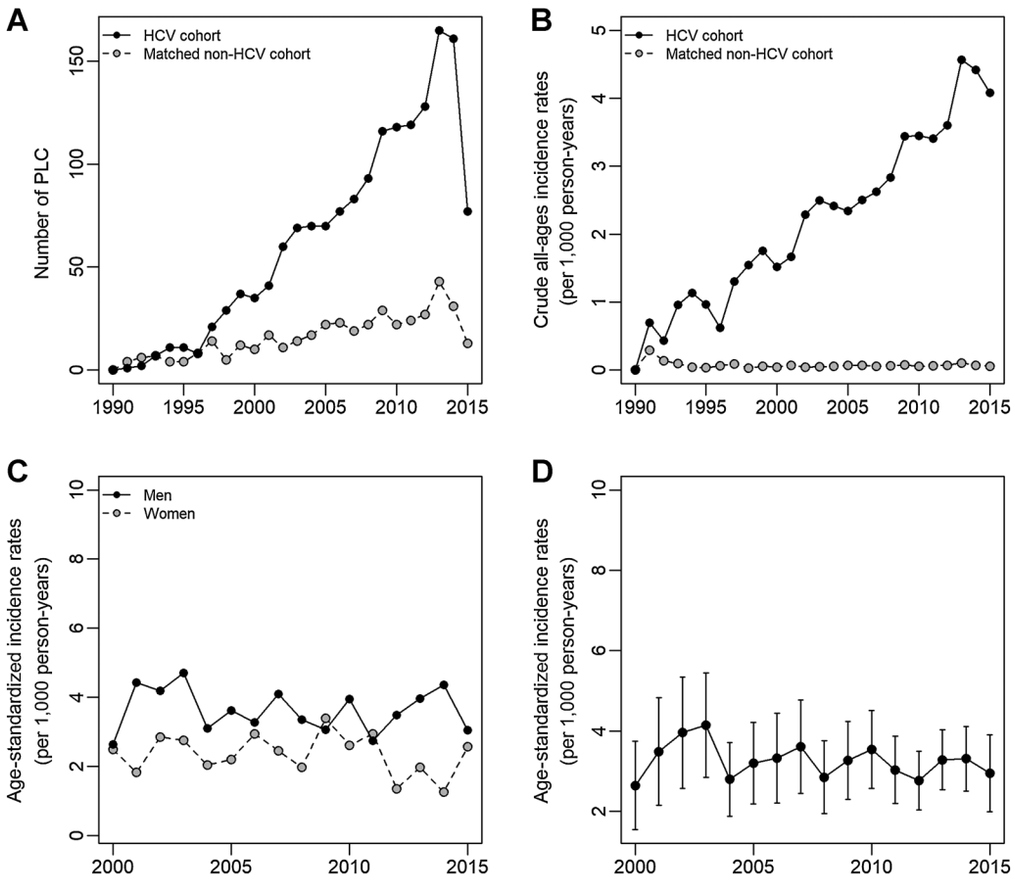

Figure 2.

PLC among people in the HCV cohort and non-HCV comparison cohort. **A,** Crude number of PLC by calendar year. **B,** Crude all-ages PLC incidence rates. **C,** Age- and sex-standardized incidence rates for the HCV cohort, with standard Swedish population in 2000 as reference population. **D,** Age-standardized incidence rates with 95% CIs (indicated by bars) for the HCV cohort, with standard Swedish population in 2000 as reference population.

in new PLCs is probably attributed to the aging of the cohort and the duration of infection. The majority of individuals in the present HCV cohort, born during 1945–1975, showed average estimated infection time of 35.1 (SD: 5.42) years at PLC diagnosis. In spite of the increasing incidence rates, the age-standardized PLC incidences were relatively constant, demonstrating that the risks in different age groups with HCV infection were rather constant over time.

Table 3. Relative risk of PLC for the HCV cohort, expressed as SIRs and stratified by estimated years with HCV infection.

Years with HCV infection	Person-years	Expected	Observed	SIR	95% CI
<10	52,679	0.4	6	15	(5–30)
10–20	117,018	1.5	6	4	(1.4–8.6)
20–25	89,960	2.8	45	16	(11.8–21.7)
25–30	102,969	4.8	190	40	(34.1–45.6)
30–35	93,487	8.3	411	50	(45.0–54.8)
35–40	57,725	6.1	445	73	(65.9–79.5)
40–45	21,937	3.6	219	61	(53.0–69.3)
45+	2,574	0.7	28	40	(25.2–54.8)
Total	538,348	28.2	1350	48	(45.2–50.3)

Note: The reference population was the matched non-HCV comparison cohort. Test for homogeneity of SIR: 230, $P < 0.0001$. Test for trend in SIR: 159.9, $P < 0.0001$.

In addition, the study demonstrates that people infected by transfusion of blood or blood products also were at high risk of PLC (**Table 2**). In a previous study, it was demonstrated that this group had very few hospital admissions related to drug or alcohol use (21). These results confirm that HCV infection is related to a high risk of PLC also in people without alcohol or drug dependency.

The median age at PLC diagnosis was 60 years, most patients diagnosed after the age of 50 years. This is in line with a recent study of people with HCV notification 1995–2011/2012/2013 from Canada/Australia/Scotland, respectively, concluding that older age was the strongest predictor of HCC diagnosis (23). In that study, HCC was identified from hospital admission data 2001–2012/2013/2014, respectively, and 1.1%–1.3% of the study populations were identified with a HCC diagnosis. This is a difference from our study, with 3.0% of the HCV cohort diagnosed with PLC after notification, despite rather similar sex and age distributions. Some possible explanations are that they ended follow-up 2–4 years earlier, missing the last years when the incidence was very high, and they identified the HCCs from hospital discharge diagnoses and used C22.0 (ICD-10) for HCC. This may have underestimated the incidence by excluding people without hospital

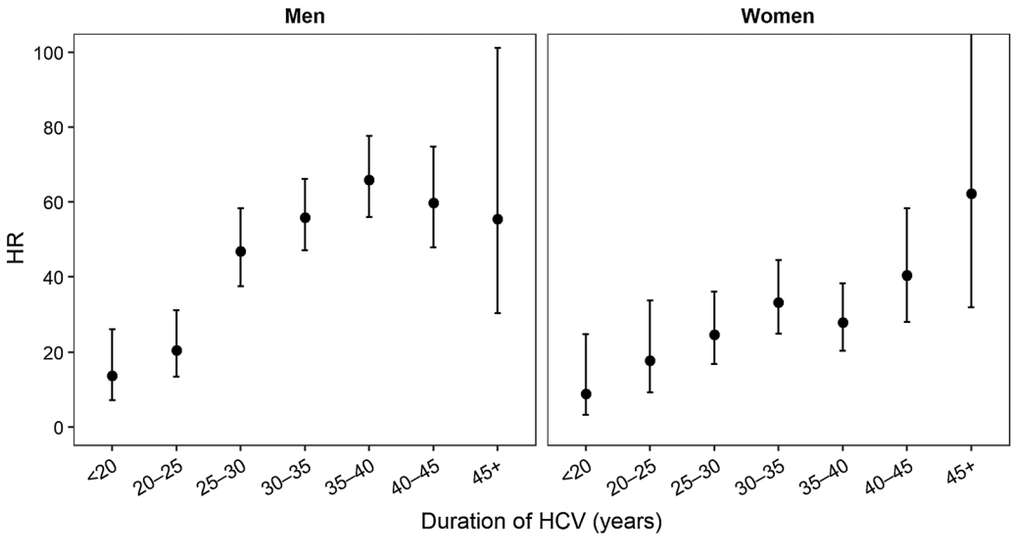

Figure 3.
The relative risk of PLC in the HCV cohort compared with the non-HCV comparison cohort, estimated as HRs. The HRs with 95% CIs (indicated by bars) were estimated using the Cox regression model and plotted separately for men and women for different estimated durations of HCV infection.

admissions and those with HCC classified as liver cancer UNS. Another study from Australia estimated the HCC incidence to be 2-fold higher than reported by CR data, only HCCs with histologic verification (about 40%) were classified as HCC in the CR, approximately 35% were classified as liver cancer UNS, and 25% were not reported to the CR at all (12). A study of the Swedish CR confirmed the underreporting of HCCs without histologic verification (11).

Because of the difficulties with accurate ICD coding and the underreporting to the CR, our study identified PLCs reported to the CR and completed with PLCs from the DR when missing in the CR (27%). Using CR + DR probably identifies about 90% of all PLCs (11). In the DR, PLCs are classified as HCCs only when clearly stated on the death certificate, most PLCs (including many HCCs) are classified as PLC/liver cancer UNS (11). Analysis of all PLCs in the study demonstrated that 80% were classified as HCC (91% in CR, 43% in DR), 19% as PLC/liver cancer UNS (mainly from the DR), and only 2.9% were ICC (to compare with about 20% of PLC in the general population). Accordingly, the vast majority of PLCs in this high-risk population were probably HCCs.

In the previous Swedish study of people notified with HCV diagnosis 1990–2004, those with estimated 25–30 years of HCV infection had the highest relative risk of PLC with SIR 46 (95% CI, 36–56) when compared with the general population and using PLC incidence from the CR only (5). When analyzing the current study population with HCV diagnosis 1990–2015 the same way, individuals with estimated 30–35 years of infection had the highest SIR_{suppl} of 40 (Supplementary Table S1). However, these analyses underestimate the relative risk. Bias arises both from the fact that the general population includes those with HCV infection (representing 20%–30% of PLC diagnoses in Sweden), as well as from the underreporting of PLC to the CR (11, 12). To overcome this, we used a large matched non-HCV comparison cohort and identified incident PLC from both the CR and the DR. This SIR-analysis showed that individuals with estimated 35–40 years with HCV infection had about 73 times more than expected PLCs (**Table 3**). This is thus an updated and probably more accurate estimate of the relative risk for PLC in an aging national cohort of people with HCV diagnosis. This high relative risk was confirmed in the HR analysis (**Fig. 3**). There was a decrease in relative risk for the strata with the longest durations of HCV infection; one possible explanation is the high mortality in the HCV cohort with less people surviving to reach these strata compared with the noninfected cohort.

A recent modeling study predicted the total burden of PLC in 30 countries around 2030, and projected an overall 35% increase in the annual number of new PLC compared with 2005 (24). For Sweden, the projected increase was 118% among men (293 PLC in 2005 and 639 in 2030) and 40% (172 to 241) among women. The predictions were based on data from CRs 1993–2007. In Sweden, the annual number of PLC reported to the CR used to decrease but from 2009 there has been a continuous increase, especially among men (http://www.socialstyrelsen.se/). This is probably due to the dramatic increase in HCV-associated PLC, which may change with the use of efficient DAA therapy. However, other emerging risks for PLC like obesity with nonalcoholic fatty liver disease (NAFLD; ref. 25) and the increasing number of immigrants with chronic hepatitis B may influence the temporal trends up to 2030.

The essential advantages of this study are the large national population-based cohort, the completeness of the HCV surveillance register, the possibility to use PINs to link to other national registers, and to produce a matched population-based comparison cohort, as well as the prospectively collected register data reported by all health care providers in the country, the long observation time, and the possibility to study the future national temporal trends during DAA therapy. Another strength of the study is the methodology that, as discussed above, probably has resulted in more accurate estimates and is recommended for future monitoring of HCV-related PLC incidence.

There are some potential limitations to mention. First, we lack information about viremic HCV infection or not. The HCV cohort includes patients that have been treated and cured and some people with spontaneously resolved infections. This may result in an underestimation of the HCV-related PLC risk. Second, stage of fibrosis was

not recorded in the registers, stratification on estimated years with infection was used in the SIR analyses, but we could not study the risk of PLC by stage of fibrosis. Third, we included diagnoses from the DR to ensure more complete identification of PLC, this may have resulted in inclusion of some diagnoses that are due to metastases from other organs. Finally, the "date of infection" model has been used in several studies and seems to predict duration of HCV infection rather well (4, 5). However, it is hard to model the often random date of infection for those infected by transfusion of blood/blood products (about 5%). In this study, there were a few PLC in the stratum with estimated duration of HCV infection less than 10 years, which probably is a misspecification in the "date of infection" model.

It was estimated that about 7,000 people in the HCV cohort were treated and cured from HCV infection during the study period, yet there was a dramatic increase in PLC incidence, which demonstrates the insufficient effect of treatment so far. With new DAA therapies, introduced in 2014, more than 95% of those who are treated will be cured. This will hopefully change the scenario and dramatically reduce HCV-related complications including PLC (13, 14). However, to reduce PLC on a national level and to achieve the WHO goals until 2030, the treatment uptake needs to increase and prevention of infection/reinfection has to improve. Since 2005, there is information about prescribed drugs on an individual level in the Swedish National Prescription Register, and it will be possible to study these patients in the future. However, it will also be important to monitor the PLC incidence in the whole HCV cohort, irrespective of treatment and cure, to study the effect of DAA on a national level.

To conclude, this study demonstrated a substantial increase in PLC incidence over the past decade, with an extremely high relative risk in an aging population with HCV infection for more than 35 years. Also, we verified that incidence data were more complete with information from both the CR and the DR, and recommend this approach for future studies of temporal trends of PLC during the DAA era.

Disclosure of Potential Conflicts of Interest

N. Batyrbekova is a statistician at Scandinavian Development Services AB. S. Aleman reports receiving commercial research grants from Gilead and AbbVie and speakers bureau honoraria from AbbVie, Gilead, Bristol-Myers Squibb, and MSD. C. Lybeck reports receiving speakers bureau honoraria from MSD. A.-S. Duberg reports receiving speakers bureau honoraria from AbbVie, Gilead, and MSD and is a consultant/advisory board member for Gilead and AbbVie. No potential conflicts of interest were disclosed by the other author.

Authors' Contributions

Conception and design: N. Batyrbekova, S. Aleman, S. Montgomery, A.-S. Duberg
Development of methodology: N. Batyrbekova, S. Aleman, A.-S. Duberg
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Aleman, A.-S. Duberg
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N. Batyrbekova, C. Lybeck, A.-S. Duberg
Writing, review, and/or revision of the manuscript: N. Batyrbekova, S. Aleman, C. Lybeck, S. Montgomery, A.-S. Duberg
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N. Batyrbekova, A.-S. Duberg
Study supervision: S. Aleman, A.-S. Duberg

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