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Extrahepatic Cancers Are the Leading Cause of Death in Patients Achieving Hepatitis B Virus Control or Hepatitis C Virus Eradication

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Data on extrahepatic cancers (EHCs) in compensated viral cirrhosis are limited. The objective of the prospective multicenter Agence Nationale de Recherche sur le SIDA et les Hépatites virales CO12 CirVir cohort was to assess the occurrence of all clinical events in patients with compensated viral cirrhosis, including all types of cancer. Patients with the following inclusion criteria were enrolled in 35 French centers: (1) biopsy-proven hepatitis B virus (HBV) or hepatitis C virus (HCV) cirrhosis, (2) Child-Pugh A, or (3) absence of previous liver complications including primary liver cancer (PLC). Patients were followed up prospectively every 6 months. The standardized mortality ratio (SMR) was calculated according to age and gender using 5-year periods. The impact of sustained viral response (SVR) in HCV patients and maintained viral suppression in HBV patients were assessed using time-dependent analysis. A total of 1,671 patients were enrolled between 2006 and 2012 (median age, 54.9 years; men, 67.3%; HCV, 1,323; HBV, 317; HCV–HBV, 31). Metabolic features and excessive alcohol and tobacco consumption were recorded in 15.2%, 36.4%, and 56.4% of cases, respectively. After a median follow-up of 59.7 months, 227 PLCs were diagnosed (5-year cumulative incidence [CumI] 13.4%) and 93 patients developed EHC (14 patients with lymphoid or related tissue cancer and 79 with solid tissue cancer; 5-year EHC CumI, 5.9%). Compared to the general French population, patients were younger at cancer diagnosis, with significantly higher risk of EHC in HCV patients (SMR, 1.31; 95 confidence interval [CI], 1.04-1.64; $P = 0.017$) and after SVR (SMR = 1.57; 95% CI, 1.08-2.22; $P = 0.013$). EHC was the fourth leading cause of death in the whole cohort and the first in patients with viral control/eradication. *Conclusion:* Compared to the general French population, HCV cirrhosis is associated with a higher risk of EHC and the first cause of death in patients with viral cirrhosis who achieve virological control/eradication. (HEPATOLOGY 2018; 68:1245-1259).

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Cirrhosis related to hepatitis B (HBV) and hepatitis C (HCV) viral infection is responsible for significant morbidity and mortality throughout the world. The leading cause of death in these patients is liver-related and includes the occurrence of primary liver cancer (PLC),[1] namely hepatocellular carcinoma (HCC) and cholangiocarcinoma.[2] However, only retrospective studies or registers are currently available with respect to extrahepatic cancers (EHCs). HBV and HCV are associated with

Abbreviations: ANRS, Agence Nationale de Recherche sur le SIDA et les Hépatites virales; AVT, antiviral treatment; CI, confidence interval; CumI, cumulative incidence; DAA, direct-acting antiviral agent; EHC, extrahepatic cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; ICC, intrahepatic cholangiocarcinoma; IFN, interferon; IQR, interquartile range; MVR, maintained virosuppression; NHL, non-Hodgkin's lymphoma; PLC, primary liver cancer; PY, persons per year; SMR, standardized mortality ratio; SVR, sustained virological response.

the development of hematological malignancies such as non-Hodgkin's lymphoma (NHL), predominantly of the B-cell type.[3-5] Some studies have also suggested that chronic HCV infection, whatever the severity of the underlying liver disease, may be associated with an increased risk of other solid malignancies affecting the pancreas, rectum, lung, mouth, breast, thyroid, or kidneys.[6,7] A sustained viral response (SVR) in HCV patients and maintained viral suppression (MVR) by nucleos(t)ide analogues in HBV patients have changed the clinical course of viral cirrhosis during recent decades. Several studies have suggested a lower incidence of liver-related complications as well as the regression of NHL following viral control or eradication.[8-10] The long-term follow-up of patients with a negative HBV viral load and SVR is now the next challenge as these patients are going to live for longer and will therefore be exposed to extrahepatic complications like EHC, as is observed in the general population.

Prospective quality data regarding the onset of EHC in patients with viral cirrhosis are necessary to cover the whole spectrum of malignancies in this population and their impact on prognosis. The aim of this study was therefore to report the incidence and characteristics of all cancers observed in the Agence Nationale de Recherche sur le SIDA et les Hépatites virales (ANRS) CO12 CirVir prospective cohort and to make an accurate comparison with the general French population.[2,10-12] A further aim was to identify risk factors for the development of EHC and analyze the impact of virological control or eradication following antiviral treatment (AVT) on the occurrence of these malignancies.

Patients and Methods

PATIENTS

The sponsor of the study was the ANRS. Informed consent was given by all of the patients involved. The protocol complied with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by an ethics committee (Comité de Protection des Personnes, Aulnay-sous-Bois, France). Thirty-five French liver centers participated in the study. The inclusion criteria were age over 18 years; histologically proven cirrhosis, whatever the timing of the biopsy; serum hepatitis B surface antigen or HCV antibody–positive, whatever the level of viral replication; no previous complications of cirrhosis such as ascites, bleeding, or HCC; Child-Pugh A classification; and no severe uncontrolled extrahepatic disease resulting in an estimated life expectancy of less than 1 year. No patients

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had a history of PLC before their inclusion. For all patients, past medical history, metabolic syndrome, and past and ongoing alcohol and tobacco consumption were recorded. Missing biological data were determined from frozen serum samples provided by the Liver Disease Biobank (Groupe Hospitalier Paris Seine-Saint-Denis BB-0033-00027). Ethnicity was defined by a predictive panel of 26 single-nucleotide polymorphisms assessed on peripheral DNA. Samples were classified as European, African, or Asian based on the closest 1000 Genomes population in a principal component analysis.[13]

FOLLOW-UP

Standard clinical and biological data were recorded every 6 months by the senior hepatologist responsible for a given patient. According to the guidelines of the European Association for the Study of the Liver and the European Organisation for Research and Treatment of Cancer,[14] Doppler ultrasonography was performed by an experienced operator every 6 months to detect the development of any PLC. In the event of focal lesions, the echogenicity and the number and diameter of nodules, as well as their anatomic localization according to the Couinaud classification, were reported. According to the Baveno consensus, regular endoscopic examinations were performed, associated with preventive therapy whenever needed. All treatments recorded at inclusion and any modifications during follow-up were noted. AVTs were monitored, with particular focus on the regimen and viral response, according to international recommendations. Patients who underwent liver transplantation were censored for analysis at the date of transplantation. During the observation period, all events, liver-related or not, were recorded and confirmed by two senior hepatologists (authors V.B. and P.N.). All cancers

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were recorded and classified as PLC (including HCC and cholangiocarcinoma) or EHC (including lymphoid and related tissue cancers, as well as solid tissue cancers).

With respect to EHC, the design of the study did not propose any specific screening strategy, surveillance being left to the choice of the senior hepatologist in charge of the patient, in line with French guidelines.[15] Surveillance strategies in France are guided by the type of cancer, past medical history, and family history of cancer. For example, in the case of colorectal cancer, if there is no family history, a stool test is recommended every 2 years between the ages of 50 and 74 years. The same strategy is proposed for breast cancer when no risks factors have been identified, with a mammogram being performed every 2 years between the ages of 50 and 74 years. In risky situations, special screening strategies have been developed, adapted to each patient.

When a cancer was diagnosed during follow-up, treatment was specified, as was the outcome of the patient. EHCs diagnosed and treated before inclusion were excluded from the calculation of incidence and analysis of *de novo* EHCs. If a patient died, the cause was defined and classified as being liver-related (PLC, liver failure, bacterial infection, gastrointestinal bleeding) or not (malignancies other than PLC, cardiovascular diseases, other). All information recorded during follow-up was secondarily monitored by the same panel of three clinical research associates from the Service d'Hépatologie, Hôpital Jean Verdier, Université Paris 13, Bondy, France.

STATISTICAL ANALYSES

The characteristics of the patients were presented as means ± standard deviation or medians (interquartile range [IQR]) for continuous variables and as numbers (percentages) for categorical data. Characteristics were compared between groups using the Student *t* test or Wilcoxon's rank-sum test for continuous variables. Categorical variables were compared using the χ^2 test or Fisher's exact test if necessary.

Incidence rates were expressed per 100,000 person-years of observation. In the ANRS CO12 CirVir cohort, incidence rates were computed from inclusion to cancer diagnosis or the last date of follow-up or death. Eight recurrent cancers occurring during follow-up were excluded from the analysis of incidence rates; their characteristics are available in the Supporting Table S1.

The results of cancer incidence and cancer-related mortality estimates between 1980 and 2012, based on 14 French tumor registries from the France Cancer Incidence et Mortalité FRANCIM réseau,, were used to calculate incidence rates, age at cancer diagnosis, and age at cancer-related death of the French general population.[16,17] These registries, which have collected cancer incidence and mortality data for all cases diagnosed from 1980, cover approximately 24% of the French general population, including the following French departments: Ardennes, Calvados, Côte-d'Or, Doubs, Finistère, Gironde, Hérault, Isère, Loire-Atlantique, Manche, Marne, Orne, Bas-Rhin, Haut-Rhin, Saône-et-Loire, Somme, Tarn, and Vendée (Supporting Table S2).

Comparisons of these cancer incidence rates with those from the general French population were performed by calculating the standardized morbidity ratio (SMR), both overall and according to virological status. This feature was considered time-dependent in HCV patients included in the CirVir cohort as patients without SVR at inclusion could be retreated and this retreatment could result in SVR, while in HBV patients, MVR could occur during follow-up and at different time points. MVR was defined as persistently undetectable HBV DNA after achieving a complete virological remission. Non-MVR was defined by persistent detectable HBV DNA, whatever the level of viral replication, or intermittent episodes of <2,000 IU/mL detectable HBV DNA after complete virological remission. The 95% confidence intervals (CIs) for the SMR and corresponding *P* values were calculated using conventional approaches or the Byar method, as appropriate.[18] Statistical differences between the CirVir cohort and the general French population in terms of mean age at cancer diagnosis and at cancer-related death were determined using the Student *t* test.

Features associated with the occurrence of EHC were assessed using univariate and multivariate Cox proportional hazards regression models. All variables were evaluated on their baseline levels, except for SVR in all patients with HCV and HBV viral load in HBV patients. SVR status was included as a time-dependent covariate, and HBV viral load was studied at endpoint in all Cox models. Predictors associated with EHC in univariate analysis at the $P < 0.20$ level were entered in the multivariate model, with a backward stepwise procedure applied to retain significant features at the $P < 0.05$ level in the final model.

All statistical analyses were performed using Stata 13.0 (StataCorp, College Station, TX). $P < 0.05$ was considered statistically significant.

Results

BASELINE CHARACTERISTICS OF THE POPULATION

The inclusion of patients started in March 2006 and lasted until July 2012, at continuous and stable rates. A total of 1,822 patients were included from 35 French centers. Of these, 151 were secondarily excluded from the analysis after the revision of individual data, owing either to noncompliance with the inclusion criteria (n = 142) or to withdrawal of consent (n = 9). Analyses were thus performed in 1,671 patients with a median follow-up of 59.7 months (IQR, 37.2-80.7). The patients were mainly male (67.3%), with a median age of 54.9 years. Cirrhosis was due to HCV in 79.2%, HBV in 18.9%, and both HCV and HBV in 1.9% of patients. Patients with HCV presented with more cancer risk factors than patients with HBV (Table 1).

PLC

During follow-up, 227 PLCs were diagnosed in 225 patients (HCC, n = 214; intrahepatic cholangiocarcinoma [ICC], n = 9; HCC and ICC, n = 2). The PLC 5-year cumulative incidence (CumI) in the whole cohort was 13.4% (95% CI, 11.6-15.4) and was significantly higher in HCV than in HBV or HCV–HBV patients (HCV, 14.4%; 95% CI, 12.4-16.8, HCV–HBV 10.7%; 95% CI, 3.6-29.6, HBV 9.4%; 95% CI, 6.3-13.7; $P = 0.010$). Compared to the general French population, in patients with viral cirrhosis we observed a higher age-adjusted incidence of PLC (SMR = 103; 95% CI, 90.00-117.41; $P < 0.001$) with a diagnosis being made at a younger age (62.3 versus 67.7 years; $P < 0.001$) (Table 2). Using 5-year periods, incidence of PLC was higher after 60 years in men and after 75 years in women, like in the general population (Supporting Table S3). Among the 11 patients with ICC, 81.8% were men with a median age of 63.9 years and most of them had HCV cirrhosis (72.7%). The ICC 5-year CumI was 0.6% (95% CI, 0.3-1.2). In HCV patients, 50.0% had a positive viral load, whereas an MVR was observed in all HBV patients at the time of ICC diagnosis. Regarding PLC, 81.4% of patients were diagnosed within the Milan criteria, 79.9% of non-SVR and 88.5% SVR HCV patients ($P = 0.42$, missing data = 20).

EHCs

EHCs were classified as lymphoid and related tissue cancers or solid tissue cancers, as listed in Table 2. During follow-up, 93 patients presented with EHC, with a 5-year EHC CumI of 5.9% (95% CI, 4.7-7.3). Age was significantly higher, and presence of diabetes and achievement of SVR were more frequent at time of EHC diagnosis compared to the time of inclusion (Supporting Table S4). Fifteen patients had several malignancies. Eight of them experienced a PLC first of all and then an EHC, 5 first an EHC and then a PLC, and no patient developed at the same time a PLC and an EHC. Two patients suffered from two different EHCs during the follow-up period. Incidence rates using 5-year periods showed a peak of EHCs in men between 65 and 70 years of age and in women older than 75 years (Supporting Table S5). Age at the diagnosis of EHC was younger in the Cir-Vir cohort compared to the general French population (63.6 versus 67.7 years; $P < 0.001$), and we observed an SMR of 1.20 (95 CI, 0.97-1.47; $P = 0.09$) for the age-adjusted incidence of EHC in the whole cohort and an SMR of 1.18 (95% CI, 0.77-1.73; $P = 0.47$) in patients without any cancer risk factors such as tobacco and alcohol consumption, metabolic syndrome and human immunodeficiency virus (HIV) infection (Supporting Table S6). If only HCV patients were considered, we observed a higher risk of EHC (SMR = 1.31; 95% CI, 1.04-1.64; $P = 0.017$) compared to the general French population (Table 3). The results did not reach a level of significance among HBV patients.

Lymphoid and Related Tissue Cancers

During follow-up, 14 patients developed lymphoid and related tissue cancers, with a 5-year CumI of 1.0% (95% CI, 0.6-1.7) (NHL type B, n = 5; other lymphomas, n = 2; myelodysplasia, n = 2; multiple myeloma, n = 2; acute leukemia, n = 1; Hodgkin's lymphoma, n = 1; chronic lymphocytic leukemia, n = 1). All patients presented with HCV cirrhosis (genotype 1, n = 6; genotype 2, n = 1; genotype 3, n = 4; genotype 4, n = 2; not determined, n = 1). A positive viral load at diagnosis was observed in 8 patients, none of whom had HIV coinfection. Compared to the general French population, the age-adjusted incidence of hematological malignancies in the study population was higher (SMR = 2.03; 95% CI, 1.11-3.41; $P = 0.023$) with more diagnoses in younger patients (61.7 versus 70.3 years old; $P = 0.013$). Under univariate analysis, no factors were identified to predict the

TABLE 1. Baseline Characteristics of the CirVir Cohort

Baseline Characteristics	Number of Patients	HBV (n = 317)	HCV (n = 1,323)	HBV–HCV (n = 31)	Total (n = 1,671)	*P**
Male gender	1,671	261 (82.3)	839 (63.4)	24 (77.4)	1,124 (67.3)	<**0.001**
Age (years)	1,671	53.0 (43.4-61.8)	55.4 (48.9-64.4)	52.6 (48.8-57.8)	54.9 (48.2-63.7)	<**0.0001**
Ethnic origin (SNPs)	1,400	(n = 272)	(n = 1103)	(n = 25)	(n = 1400)	<**0.001**
EUR		160 (58.82)	1,001 (90.8)	20 (80.0)	1,181 (84.4)	
AFR		70 (25.74)	82 (7.4)	2 (8.0)	154 (11.0)	
EAS		42 (15.44)	20 (1.8)	3 (12.0)	65 (4.6)	
Past excessive alcohol intake	1,590	(n = 295)	(n = 1266)	(n = 29)	(n = 1590)	<**0.001**
Yes		31 (10.5)	406 (32.1)	5 (17.2)	442 (27.8)	
No		264 (89.5)	860 (67.9)	24 (82.8)	1,148 (72.2)	
Ongoing alcohol consumption	1,545	(n = 291)	(n = 1225)	(n = 29)	(n = 1545)	0.11
0		225 (77.3)	918 (74.9)	20 (69.0)	1,163 (75.3)	
<10		50 (17.2)	193 (15.8)	3 (10.3)	246 (15.9)	
10-50		13 (4.5)	91 (7.4)	6 (20.7)	110 (7.1)	
50-100		2 (0.7)	18 (1.5)	—	20 (1.3)	
>100		1 (0.3)	5 (0.4)	—	6 (0.4)	
Tobacco consumption	1,553	(n = 294)	(n = 1229)	(n = 30)	(n = 1553)	<**0.001**
Never		178 (60.5)	491 (39.95)	8 (26.67)	677 (43.6)	
Past		66 (22.5)	276 (22.46)	11 (36.67)	353 (22.7)	
Current		50 (17.0)	462 (37.59)	11 (36.67)	523 (33.7)	
BMI (kg/m^2)	1,458	24.9 (22.8-27.7)	25.8 (23.0-28.8)	23.9 (21.8-26.6)	25.5 (22.9-28.6)	**0.004**
BMI (class)	1,458	(n = 267)	(n = 1162)	(n = 29)	(n = 1458)	**0.009**
<25		137 (51.3)	487 (41.9)	17 (58.6)	641 (43.96)	
25-30		96 (36.0)	457 (39.3)	8 (27.6)	561 (38.48)	
≥30		34 (12.7)	218 (18.8)	4 (13.8)	256 (17.56)	
Diabetes	1,671	35 (11.0)	253 (19.1)	3 (9.7)	291 (17.4)	**0.001**
Dyslipidemia	1,671	23 (7.3)	69 (5.2)	1 (3.2)	93 (5.6)	0.16
Arterial hypertension	1,671	72 (22.7)	373 (28.2)	8 (25.8)	453 (27.1)	**0.049**
HCV viral load	1,351	—	(n = 1320)	(n = 31)	(n = 1345)	—
Negative		—	389 (29.5)	16 (51.6)	405 (30.0)	
Positive		—	931 (70.5)	15 (48.4)	946 (70.0)	
HCV genotype	1,272	—	(n = 1250)	(n = 22)	(n = 1272)	—
1		—	849 (67.92)	15 (68.2)	864 (67.9)	
2		—	69 (5.52)	3 (13.6)	72 (5.7)	
3		—	195 (15.60)	1 (4.55)	196 (15.4)	
4		—	115 (9.20)	1 (4.55)	116 (9.1)	
5		—	18 (1.44)	1 (4.55)	19 (1.5)	
6		—	4 (0.32)	1 (4.55)	5 (0.4)	
Anti-HBc antibodies	1313	—	(n = 1313)	—	—	—
Negative		—	846 (64.4)	—	—	
Positive		—	467 (35.6)	—	—	
HBV viral load	348	(n = 317)	—	(n = 31)	(n = 348)	—
Negative		229 (72.2)	—	23 (74.2)	252 (72.4)	
Positive		88 (27.8)	—	8 (25.8)	96 (27.6)	
HDV coinfection	347	(n = 316)	—	(n = 31)	(n = 347)	—
Negative		285 (90.2)	—	21 (67.7)	306 (88.2)	
Positive		31 (9.8)	—	10 (32.3)	41 (11.8)	
HIV coinfection	1,655	(n = 315)	(n = 1309)	(n = 31)	(n = 1655)	0.71
No		300 (95.2)	1,253 (95.7)	27 (87.1)	1,580 (95.5)	
Yes		15 (4.8)	56 (4.3)	4 (12.9)	75 (4.5)	
Past or ongoing AVT at inclusion	1,666	(n = 314)	(n = 1321)	(n = 31)	(n = 1666)	0.91
No		21 (6.7)	86 (6.5)	2 (6.4)	109 (6.5)	
Yes		293 (93.3)	1,235 (93.5)	29 (93.6)	1,557 (93.5)	

*HBV versus HCV. Bold indicates significance.
Abbreviations: AFR, African; anti-HBc, antibody to HBV core antigen; BMI, body mass index; EAS, Asian; EUR, European; HDV, hepatitis D virus; SNP, single-nucleotide polymorphism.

TABLE 2. Age-Adjusted Cancer Incidence and SMR, Age at the Time of Cancer Diagnosis, and Age at Cancer-Related Death in the Whole CirVir Cohort Compared to the General French Population

		Age-Adjusted Incidence per 100 000 PY					Mean Age at Cancer Diagnosis			Mean Age at Cancer-Related Death			
Cancers	No. of Cases, n (%)	CirVir	General Population	SMR	(95% CI)	*P*	CirVir	General Population	*P*	Deaths, n	CirVir	General Population	*P*
PLC	**225 (13.5)**	**2910.7**	**28.3**	**103**	**(90.00-117.41)**	**<0.001**	**62.3**	**67.7**	**<0.001**	53	63.2	nd	NA
EHC	**93 (5.6)**	1181.2	985.8	1.20	(0.97-1.47)	0.09	**63.4**	**67.7**	**<0.001**	23	65.6	nd	NA
Solid tissue cancers													
Oral cavity cancer	**12 (0.7)**	**148.4**	**54.9**	**2.70**	**(1.39-4.72)**	**0.005**	**55.4**	**63.7**	**0.013**	2	63.2	66.4	0.70
Colorectal cancer	12 (0.7)	148.3	115.5	1.28	(0.66-2.24)	0.46	68.0	71.5	0.30	**3**	**61.3**	**76.1**	**0.026**
Lung cancer	11 (0.7)	135.7	137.0	0.99	(0.49-1.77)	0.91	63.5	66.6	0.35	3	68.4	68.7	0.96
Pancreatic cancer	5 (0.3)	61.6	33.1	1.86	(0.60-4.35)	0.27	66.4	71.3	0.35	3	69.7	nd	NA
Breast cancer	9 (1.7)	335.9	289.8	1.16	(0.53-2.20)	0.75	62.9	63.2	0.96	2*	56.7	71.8	NA
Melanoma	1 (0.1)	12.3	28.1	0.44	(0.01-2.44)	0.67	69.4	63.6	NA	2	59.3	69.7	0.30
Prostate cancer	**6 (0.5)**	**111.2**	**315.9**	**0.35**	**(0.13-0.77)**	**0.011**	65.6	69.3	0.30	—	NA	NA	NA
Uterine cancer	3 (0.6)	111.6	54.0	2.07	(0.42-6.03)	0.36	67.3	65.7	0.84	—	NA	NA	NA
Ovarian cancer	2 (0.4)	74.0	30.0	2.46	(0.28-8.90)	0.39	81.9	67.3	0.11	1	87.3	73.9	NA
Thyroid	1 (0.1)	12.3	18.0	0.69	(0.01-3.81)	0.85	69.7	57.1	NA	1	70.9	75.6	NA
Skin cancer	9	—	—	—	—	—	—	—	—	—	—	—	—
Stomach cancer	2	—	—	—	—	—	—	—	—	—	—	—	—
Mesothelioma	1	—	—	—	—	—	—	—	—	—	—	—	—
Gallbladder cancer	1	—	—	—	—	—	—	—	—	—	—	—	—
Bladder cancer	2	—	—	—	—	—	—	—	—	—	—	—	—
Not determined	2	—	—	—	—	—	—	—	—	—	—	—	—
Lymphoid and related tissue cancers	**14 (0.8)**	**173.5**	**85.4**	**2.03**	**(1.11-3.41)**	**0.023**	**61.7**	**70.3**	**0.013**	2	54.1†	nd	NA

Bold indicates significance.
*With one missing date of death.
†There is one HBV patient who died from a lymphoid cancer developed before inclusion in the CirVir cohort. However, this lymphoid cancer was not counted among EHCs *de novo* in the study.
Abbreviations: NA, not applicable; nd, not determined.

TABLE 3. Age-Adjusted Cancer Incidence and SMR, Age at the Time of Malignant Cancer Diagnosis, and Age at the Time of Cancer-Related Death Among HCV Patients Included in the CirVir Cohort Compared to the General French Population

		Age-Adjusted Incidence per 100 000 PY					Mean Age at Cancer Diagnosis			Mean Age at Cancer-Related Death			
Cancers	No. of Cases, n (%)	HCV Patients	General Population	SMR	(95% CI)	*P*	HCV Patients	General Population	*P*	Deaths, n	HCV Patients	General Population	*P*
PLC	**192 (14.5)**	**3222.7**	**27.8**	**115.79**	**(99.99-133.37)**	**<0.001**	**62.1**	**67.7**	**<0.001**	47	63.3	nd	NA
EHC	**79 (6.0)**	**1300.3**	**988.9**	**1.31**	**(1.04-1.64)**	**0.017**	**63.6**	**67.7**	**0.003**	17	66.2	nd	NA
Solid tissue cancers													
Oral cavity cancer	**10 (0.8)**	**159.7**	**53.9**	**2.96**	**(1.42-5.45)**	**0.005**	**55.1**	**63.7**	**0.007**	1	62.5	66.4	NA
Colorectal cancer	11 (0.8)	175.8	116.8	1.51	(0.75-2.69)	0.24	67.6	71.5	0.27	**3**	**61.3**	**76.1**	**0.025**
Lung cancer	10 (0.8)	159.5	134.3	1.19	(0.57-2.18)	0.67	62.7	66.6	0.27	2	71.5	68.7	0.73
Pancreatic cancer	4 (0.3)	63.7	33.8	1.88	(0.51-4.82)	0.33	66.5	71.3	0.42	2	71.7	nd	NA
Breast cancer	8 (1.7)	342.0	295.4	1.16	(0.50-2.28)	0.77	64.7	63.2	0.77	2*	56.7	71.8	NA
Melanoma	1 (0.1)	15.9	28.4	0.56	(0.01-3.12)	0.94	69.4	63.6	NA	2	59.3	69.7	0.30
Prostate cancer	**3 (0.4)**	**76.4**	**313.2**	**0.24**	**(0.05-0.71)**	**0.012**	65.0	69.3	0.40	—	NA	NA	NA
Uterine cancer	3 (0.6)	128.1	55.8	2.30	(0.46-6.71)	0.29	67.3	65.7	0.84	—	NA	NA	NA
Ovarian cancer	2 (0.4)	84.9	30.9	2.75	(0.31-9.92)	0.33	81.9	67.3	0.11	1	87.3	73.9	NA
Thyroid	1 (0.1)	15.9	18.7	0.85	(0.01-4.74)	0.65	69.7	57.1	NA	1	70.9	75.6	NA
Lymphoid and related tissue cancers	14 (1.1)	224.4	86.5	2.59	(1.42-4.35)	**0.003**	61.7	70.3	**0.013**	1	52.9	nd	NA

Bold indicates significance.
*With one missing date of death.
Abbreviations: NA, not applicable; nd, not determined.

TABLE 4. Age-Adjusted Cancer Incidence and SMR Among HCV Patients Who Achieved SVR in the CirVir Cohort Compared to the General French Population

	No. of Cases, n (%)	Age-adjusted incidence per 100 000 person-years					No. of cases	Age-adjusted incidence per 100 000 person-years				
		SVR Patients	General Population	SMR	(95% CI)	*P*		HCV Patients (SVR IFN)	General Population	SMR	(95% CI)	*P*
PLC	31 (4.8)	1474.9	28.6	51.54	(35.01-73.16)	**<0.001**	30	**1519.7**	**28.1**	**54.02**	**(34.44-77.11)**	**<0.001**
EHC	**32 (4.8)**	**1553.5**	**987.9**	**1.57**	**(1.08-2.22)**	**0.013**	31	**1606.0**	**978.3**	**1.64**	**(1.12-2.33)**	**0.008**
Solid tissue cancers												
Oral cavity cancer	**6 (0.9)**	**280.3**	**56.3**	**4.97**	**(1.82-10.83)**	**0.004**	6	**298.8**	**55.7**	**5.36**	**(1.96-11.67)**	**0.003**
Colorectal cancer	4 (0.6)	186.3	113.7	1.64	(0.44-4.20)	0.46	4	198.5	112.6	1.76	(0.47-4.51)	0.39
Lung cancer	4 (0.6)	185.8	138.7	1.34	(0.36-3.43)	0.70	3	148.3	137.1	1.08	(0.22-3.16)	0.95
Pancreatic cancer	1 (0.2)	46.3	32.6	1.42	(0.02-7.91)	1.00	1	49.4	32.3	1.53	(0.02-8.50)	0.95
Breast cancer	2 (0.9)	266.7	296.3	0.90	(0.10-3.25)	0.70	2	279.1	296.4	0.94	(0.11-3.10)	0.75
Melanoma	—	NA	28.2	NA	NA	NA	0	NA	28.1	NA	NA	NA
Prostate cancer	2 (0.5)	142.7	322.1	0.44	(0.05-1.60)	0.34	2	153.6	318.0	0.48	(0.05-1.74)	0.43
Uterine cancer	2 (0.9)	267.6	54.5	4.91	(0.55-17.73)	0.13	2	280.1	54.6	5.13	(0.58-18.53)	0.12
Ovarian cancer	—	NA	30.1	NA	NA	NA	0	NA	30.1	NA	NA	NA
Thyroid	—	NA	19.0	NA	NA	NA	0	NA	19.1	NA	NA	NA
Lymphoid and related tissue cancers	5 (0.8)	233.2	83.9	2.78	(0.90-6.49)	0.07	5	248.6	83.1	2.99	(0.96-6.98)	0.057

Bold indicates significance.
Abbreviation: NA, not applicable.

occurrence of lymphoid and related tissue cancers. Two patients died, at the ages of 52.9 years and 55.2 years, explaining why the median age at death of patients with lymphoid and related tissue cancer is 54.1 years, younger than the mean age at diagnosis.

Solid Tissue Cancers

Solid tissue cancers are listed in Table 2. Most of them occurred in the setting of HCV cirrhosis, and no statistical difference was observed as a function of the cause of cirrhosis. Among oral cancers, lung cancers, and digestive cancers including esophageal, pancreatic, and colorectal cancers, 30.8% of patients had a history of excessive alcohol intake and 63.2% a history of tobacco consumption as associated cancer risk factors. A positive viral load was present in 56.4% of HCV patients and 18.2% of HBV patients. Compared to the general French population and considering all patients, oral cancers were the only EHC developing more frequently in the event of viral cirrhosis (SMR = 2.70; 95% CI, 1.39-4.72; $P = 0.005$), with an age 8 years younger. The characteristics of the patients with oral cancer did not change between inclusion and time of diagnosis (Supporting Tables S7 and S8). The results were similar for HCV patients, as represented in Table 3. All HBV patients presented with smoking-related EHC, and regarding only patients without any confounding cancer risk factors, the results did not reach significance for all patients (SMR = 0.74; 95% CI, 0.01-4.11; $P = 0.78$) and HCV patients (SMR = 1.12; 95% CI, 0.01-6.22; $P = 0.82$) (Supporting Table S6).

IMPACT OF VIRAL STATUS ON THE OCCURRENCE OF PLC AND EHC

At the time of PLC and EHC diagnosis, among the 1,354 patients with HCV, 1,033 patients had received interferon (IFN)–based treatment alone, among whom 507 achieved SVR (50.4%), 499 did not achieve SVR after IFN and have never received direct-acting antiviral agents (DAAs; 49.6%, 27 missing data), 316 received DAAs after ineffective IFN-based treatment, and 5 received only DAAs. Among patients who received DAAs, 23 were included in randomized controlled trials. Follow-up duration between AVT and PLC or EHC occurrence was 24.4 months (IQR, 15.5-49.0) in patients who achieved SVR after IFN and never received DAAs, 24.3 months (IQR, 14.1-

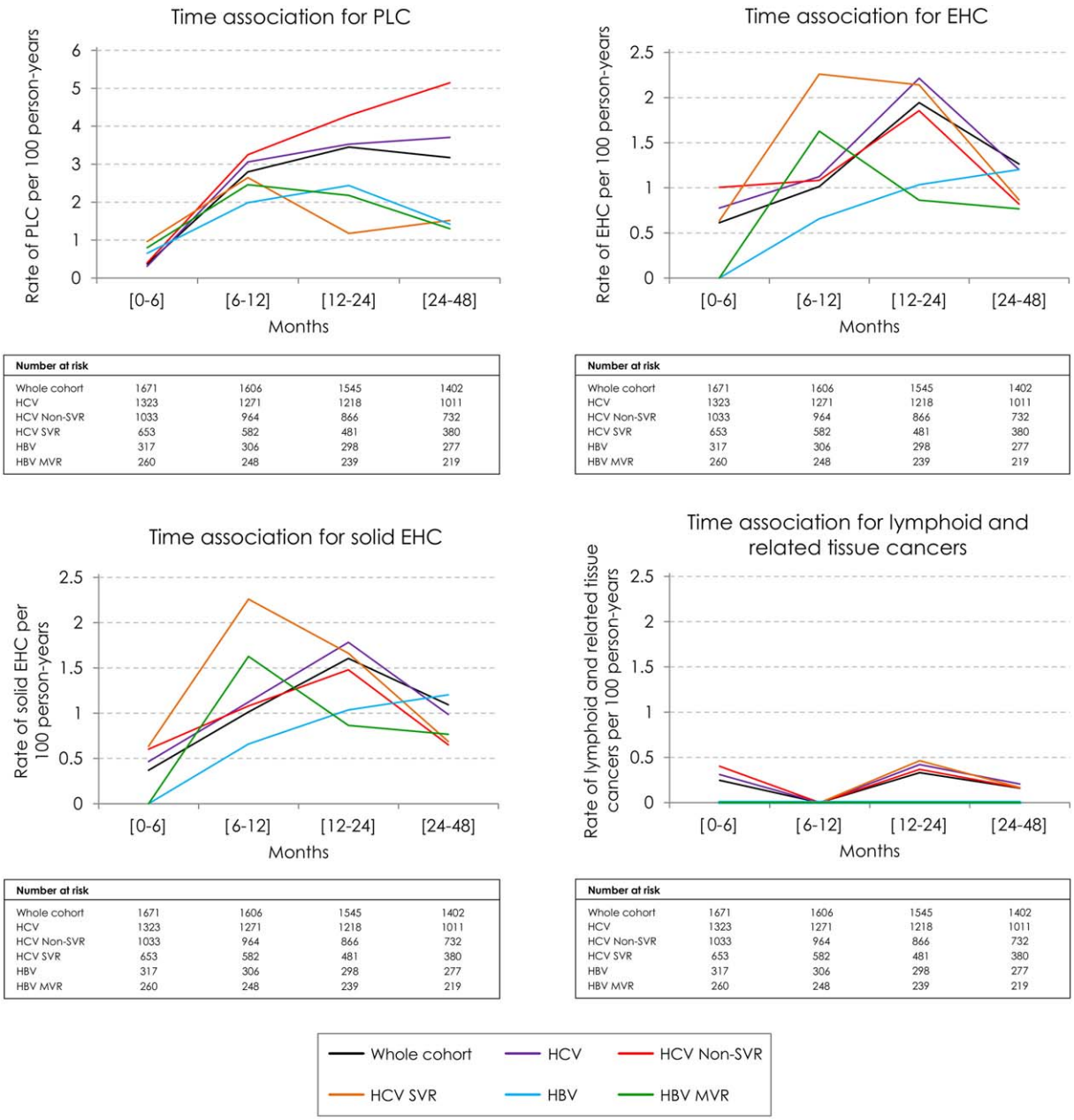
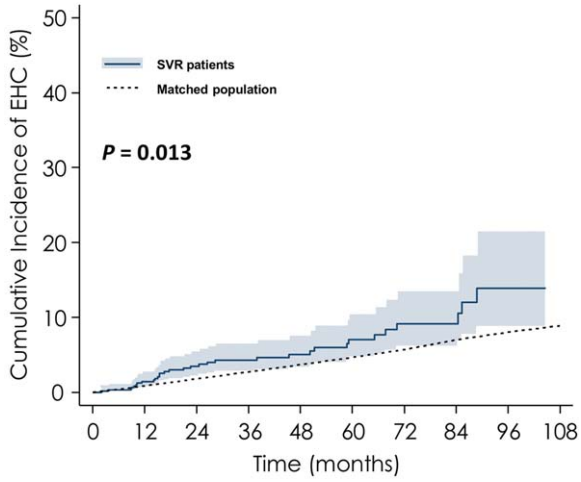


FIG. 1. Time association incidence of PLC, EHC, solid EHC, and lymphoid and related tissue cancers over the first 48 months of follow-up. Start point was time of entering the cohort (whole cohort, HBV, HCV, HCV non-SVR) or time of SVR/MVR achievement (HCV SVR, HBV MVR).

40.3) in patients who did not achieve SVR after IFN and never received DAAs, and 9.1 months (IQR, 5.2-11.4) in patients who experienced DAAs. Among patients who experienced DAAs, 5 non-SVR patients and 2 SVR patients developed PLC and/or EHC ($P = 0.25$). Regarding HBV, 281 patients were under nucleos(t)ide analogues and 81.9% presented MVR.

PLC

The age-adjusted incidence of PLC (SMR = 51.54; 95% CI, 35.01-73.16; $P < 0.001$) was higher in the HCV cohort when compared to the general French population after viral eradication (Table 4). Median follow-up duration between AVT initiation and PLC occurrence was 9.0 months (IQR, 2.9-10.9) in patients



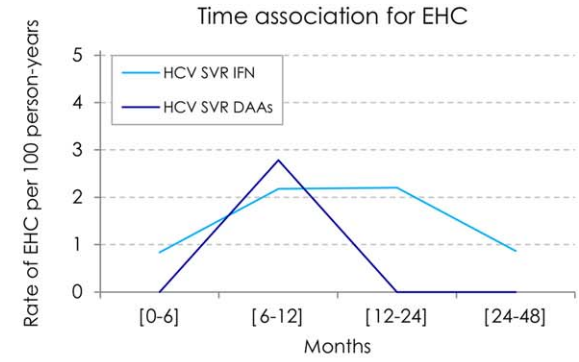
	Number at risk (events)
SVR	663 (8) 483 (9) 374 (3) 287 (2) 216 (4) 165 (3) 115 (0) 69 (3) 25 (0) 3

FIG. 2. CumI of EHC in patients with HCV with SVR included in the CirVir cohort, compared with the age-matched and sex-matched general French population.

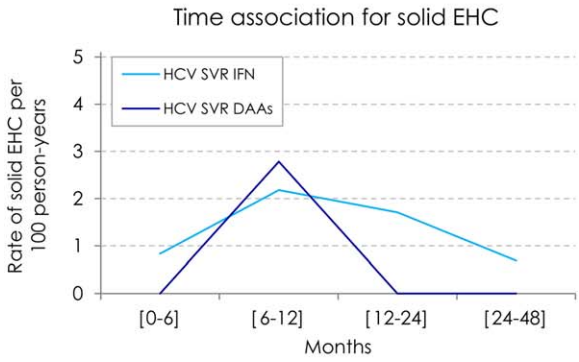
who experienced DAAs, 26.6 months (IQR, 15.6-42.1) in patients who did not achieve SVR under IFN and have never received DAAs, and 26.2 months (IQR, 16.3-49.0) in patients who achieved SVR under IFN. Patients who achieved SVR after IFN (1.46 per 100 persons per year [PY]; 95% CI, 1.02-2.09) developed less PLC compared to patients who experienced DAAs (2.57 per 100 PY; 95% CI, 1.23-5.40; P = 0.014), and a peak was observed between 6 and 12 months for both entities (Supporting Tables S9 and S10). The time-association incidence of PLC in HCV patients whatever the presence of SVR or not over the first 48 months of follow-up is shown in Fig. 1.

EHC

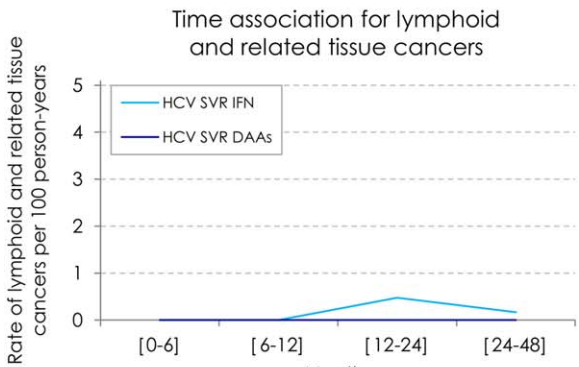
In all patients who experienced HCV treatment, the age-adjusted incidence of EHC compared to the general French population was 1.26 (95% CI, 0.96-1.61; P = 0.08) (Supporting Table S11 and Fig. S1) and was higher in patients who achieved SVR (SMR = 1.57; 95% CI, 1.08-2.22; P = 0.013, Fig. 2) (Table 4). Median follow-up duration between AVT initiation and EHC occurrence was 15.0 months in the only patient who experienced DAAs (lung cancer with a history of tobacco consumption), 20.8 months (IQR, 9.9-29.2) in the 36 patients who did not achieve SVR under IFN and have never received DAAs, and



Number at risk				
HCV SVR IFN	490	468	445	370
HCV SVR DAAs	173	117	37	3



Number at risk				
HCV SVR IFN	490	468	445	372
HCV SVR DAAs	174	117	37	3



Number at risk				
HCV SVR IFN	491	471	453	383
HCV SVR DAAs	176	119	38	3

FIG. 3. Time association in the incidence of EHC, solid EHC, and lymphoid and related tissue cancers for patients with HCV achieving SVR after IFN or DAAs. Start point was SVR achievement defined by the end of HCV treatment leading to SVR.

TABLE 5. Causes of Death as a Function of Viral Status in the Whole Cohort

Causes of death	Total (n = 192)	Viral control (n = 33)	Nonviral Control (n = 150)	*P*
				<0.001
PLC†	53 (30.5)	7 (23.4)	45 (33.3)	
Non-PLC liver-related*	46 (26.4)	4 (13.3)	40 (29.6)	
Severe Infection excluding SBP	22 (12.6)	1 (3.3)	19 (14.1)	
EHC	23 (13.2)	**12 (40.0)**	**9 (6.7)**	
Cardiovascular disease	9 (5.2)	1 (3.3)	8 (5.9)	
Other extrahepatic event	21 (12.1)	5 (16.7)	14 (10.4)	
Missing data	18	3	15	
Time between treatment and death (months)	36.7 (25.2-47.6)	30.2 (14.0-57.6)	36.4 (21.3-56.1)	0.47

Bold indicates significance.
*Including liver failure, renal failure, SBP, digestive bleeding, liver decompensation/alcoholic hepatitis.
†Including HCC and cholangiocarcinoma
Abbreviation: SBP, spontaneous bacterial peritonitis.

24.2 months (IQR, 15.5-58.9) in the 27 patients who achieved SVR under IFN. The time-association incidence of EHC, solid EHC, and lymphoid and related tissue cancers over the first 48 months of follow-up in HCV patients according to viral status and HCV treatment are shown in Figs. 1 and 3, respectively. The incidence of EHC was 1.59 per 100 PY (95% CI, 1.13-2.25) in patients who achieved SVR under IFN and 0.34 per 100 PY (95% CI, 0.05-2.43) in patients who experienced DAAs (Supporting Tables S9 and S13). These results need to be confirmed with a longer follow-up of SVR patients by DAAs. Regarding the 14 HBV patients, 84.6% presented MVR.

Older age (hazard ratio [HR], 1.04; 95% CI, 1.02-1.06; $P = 0.001$) was an independent risk factor for the onset of EHC in the whole cohort. Alcohol consumption (past or ongoing), tobacco consumption, diabetes and body mass index were not associated with EHC occurrence (Supporting Table S14).

In HCV patients, those who were older (HR, 1.04; 95% CI, 1.02-1.06; $P = 0.001$) and those achieving an SVR (HR, 1.61; 95% CI, 1.01-1.56; $P = 0.047$) presented with a higher risk of EHC under multivariate analysis. Older age (HR, 1.06; 95% CI, 1.00-1.12; $P = 0.04$) and tobacco consumption (HR, 4.62; 95% CI, 1.35-15.81; $P = 0.015$) were independent risk factors for the occurrence of EHC in HBV patients. When considering viral status, older age was an independent risk factor for EHC occurrence (HR, 1.05; 95% CI, 1.02-1.08; $P = 0.002$) in HCV patients without SVR and diabetes mellitus (HR, 2.29; 95% CI, 1.08-4.84; $P = 0.031$) in HCV patients with SVR. In HBV patients, only older age was associated with the occurrence of EHC under multivariate analysis in MVR patients (HR, 1.06; 95% CI, 1.00-1.13; $P = 0.046$).

Oral Cancer

Regarding oral cancers, we observed a significantly higher risk after SVR (SMR, 4.97; 95% CI, 1.82-10.83; $P = 0.004$), but no statistical difference was reached in patients without SVR (SMR, 1.75; 95% CI, 0.35-5.12; $P = 0.49$) (Supporting Table S15). By contrast, past excessive alcohol intake (HR, 4.83; 95% CI, 1.41-16.51; $P = 0.021$) and ongoing tobacco consumption (HR, 11.42; 95% CI, 1.43-91.36; $P = 0.022$) were associated with oral cancer occurrence in univariate analysis (Supporting Table S14). AVT of the 12 patients who developed oral cancer is detailed in Supporting Table S16. No statistically significant association was found for other cancer types (data not shown).

SURVIVAL

During a median follow-up period of 59.7 months, 192 patients died. EHC was the fourth leading cause of death (13.2%), after PLC progression (30.5%), non-PLC liver-related progression (26.4%), and bacterial infection except for spontaneous bacterial peritonitis (12.6%). EHC was the leading cause of death in HBV patients (50.0%) and the fifth one in HCV patients (10.8%). In the whole cohort, EHC was the leading cause of death in patients with a negative viral load (40.0%) and was significantly more frequent when compared to patients with a positive viral load (6.7%; $P < 0.001$) (Table 5). The results were similar in patients with HCV (30.4% versus 7.1%) and those

with HBV (71.4% versus 0.0%) (Supporting Table S17).

Discussion

During this study, we analyzed the incidence and characteristics of EHC (lymphoid and related tissue cancers and solid tissue cancers) in a large prospective cohort of 1,671 patients with HCV, HBV, or HCV–HBV cirrhosis. Our findings were supported by the rigorous methodology regarding the exhaustive recording of all events, liver-related or not, that occurred over a long period of follow-up in this well-defined population. These high-quality data were furthermore analyzed within a competing risk framework. Finally, we compared the incidences of PLC and EHC observed in a prospective cohort of patients with virus-induced cirrhosis versus the general French population, considering both cancer risk factors and viral control in a time-dependent analysis. As expected, the 5-year CumI incidence of PLC was high (13.4%) and the age-adjusted incidence was higher in the cohort than in the general French population (SMR, 103; 95% CI, 90.00-117.41; $P < 0.001$), in HBV patients without MVR (SMR, 53.89; 95% CI, 19.68-117.30; $P < 0.001$), and in HCV patients without SVR (SMR, 188.69; 95% CI, 160.33-220.62; $P < 0.001$). Diagnoses were made in younger patients (62.3 versus 69.7 years old, $P < 0.001$), and the risk was reduced but still persistent in patients without any cancer risk factors (SMR, 87.0; 95% CI, 64.96-114.07; $P < 0.001$), after MVR in HBV patients (SMR, 48.02; 95% CI, 30.75-71.45; $P < 0.001$), and after SVR in HCV patients (SMR, 51.54; 95% CI, 35.01-73.16; $P < 0.001$). These results thus confirm a direct impact of viral replication associated with cirrhosis on liver carcinogenesis. This observation underlines the importance of maintaining patients with cirrhosis within HCC surveillance programs after SVR and/or MVR, although the cost-effectiveness issues need to be further discussed.[19]

Few cases of EHC occurred in HBV patients, leading to underpowered analyses. HCV cirrhosis was associated with a significantly higher age-adjusted incidence of EHC in the whole subgroup (SMR, 1.31; 95% CI, 1.04-1.64; $P = 0.017$), particularly after SVR (SMR, 1.57; 95% CI, 1.08-2.22; $P = 0.013$).

Unlike other studies,[6,7] we only observed a higher risk of hematological malignancies and oral cancers in HCV patients. Different hypotheses can be advanced regarding these two types of cancer: a direct impact of viral replication in the case of lymphoid and related tissue cancers and a potential role for other cancer risk factors such as metabolic syndrome and chronic tobacco and alcohol intake in the case of oral cancer.

Our results suggest a role for viral replication in the carcinogenesis of lymphoproliferative disorders, although the mechanism by which HCV may cause hematological malignancies remains unclear. HCV RNA has been detected in hematopoietic cells (particularly B cells and monocytes), but how the virus induces B-cell proliferation also remains unclear.[20] In our population, none of the patients presented with HBV and HIV coinfection and, as in other studies, the age-adjusted incidence of lymphoid and related tissue cancers was higher when compared to the general French population (SMR, 2.03; 95% CI, 1.11-3.41; $P = 0.023$), which also applied to patients without any cancer risk factors (SMR, 2.08; 95% CI, 1.14-3.50; $P = 0.019$) and those without an SVR (SMR, 2.74; 95% CI, 1.18-5.40; $P = 0.021$). In some studies, the clearance of HCV infection was associated with a reduction in hematological malignancies, a better response to chemotherapy, and an improvement in overall survival.[9] Interestingly, the age-adjusted incidence of lymphoid and related tissue cancers was higher when compared to the general French population, independently of the existence of risk factors and SVR achievement. Of note, the SMR is 2.03 in the whole population, 2.08 in the population without risk factors, and 2.99 in SVR patients (following IFN). However, it was necessary to adopt a cautious approach to interpreting these results because the analysis considered all types of hematological malignancies and the small number of cases might have reflected a lack of power. As shown in the study by Allison et al.,[6] a diagnosis of lymphoid and related tissue cancers was made earlier in the cohort than in the general French population (61.1 versus 69.1 years old, $P = 0.043$). But unlike that study, where patients died younger of more aggressive malignancies compared to the general French population, we did not observe any impact on cancer-related deaths.

In terms of solid tissue cancers and more particularly smoking-related cancers (pancreas, rectum, kidney, and lung), our results differed from those of previous studies.[6,7] As described in the literature on HCV patients, we observed a higher age-adjusted incidence of oral cancers (SMR, 2.96; 95% CI, 1.42-5.45; $P = 0.005$); but this risk disappeared after account was taken of confounding factors such as tobacco and

alcohol. Moreover, past excessive alcohol intake and ongoing tobacco consumption were associated with oral cancer in univariate analysis. This higher risk of oral cancer was significantly higher in the case of SVRs (SMR, 4.97; 95% CI, 1.82-10.83; $P = 0.004$), but no statistical difference was observed in patients without SVR (SMR, 1.75; 95% CI, 0.35-5.12; $P = 0.49$). Regarding other solid tissue cancers, the results followed the same trend but did not reach a level of significance. Viral replication alone cannot explain these data, and we hypothesize a potential impact of metabolic syndrome and chronic tobacco and alcohol consumption on the cancer process in this population. During this study, HCV patients presented more cancer risk factors than HBV patients, particularly in the event of overt cirrhosis. Diabetes mellitus was associated with the occurrence of EHC in HCV patients with an SVR. Patients who did not achieve SVR died of end-stage liver disease and PLC; SVR patients will present relatively stable liver disease and will be exposed to complications linked to their comorbidities. Interestingly, patients with cirrhosis often present with decreased androgen production; and as prostate cancer is hormone-dependent, it could explain why CirVir patients present a lower risk of cancer prostate compared to the general French population.[21]

Because DAAs are now being used in larger numbers of HCV-related patients with cirrhosis, the occurrence of PLC is expected to decrease; however, this population will live longer and will be exposed to new types of complications such as EHC, which represented the fourth most common cause of death in the cohort and the leading cause in patients who had achieved viral control. In a recent study focusing on SVR patients who were mostly free of cirrhosis, EHC was the second most frequent cause of death after injected drug–related complications.[22] The screening and surveillance of metabolic syndrome and certain addictive behaviors should therefore be a priority in this patient population.

The data on a controversial potential risk of HCC recurrence after treatment with DAAs[23-25] have already been explored in the CirVir cohort in a previous report.[26] However, the present analyses (Supporting Table S9) and their subsequent update (Nahon et al. Oral presentation 017, ILCA 2017)[27] suggest a higher "crude" HCC incidence in DAA-treated patients compared to those who achieved SVR by means of an IFN-based regimen. Whether such an observation relates to actual temporal evolution patterns in patients under DAAs should be confirmed in future CirVir updates and specific analyses taking into account confounders according to treatment allocation.

Another alarming report suggested a higher incidence of "*de novo*" hematological malignancies following DAA therapy.[28] During our analyses, we observed that one case of EHC developed in a patient who experienced DAAs; consequently, our study mostly reflects the profile of patients who developed EHC after IFN. The median follow-up duration between AVT initiation and EHC occurrence was shorter (15.0 months) compared to patients who did not achieve SVR under IFN and have never received DAAs (20.8 months) and to patients who achieved SVR under IFN (24.2 months). These data may suggest a time association between DAAs and EHC. However, these analyses only included one patient with lung cancer and a history of tobacco consumption within a short follow-up. As a consequence, we are unable to draw any conclusions as to a potential impact of DAAs on EHC occurrence, and longer follow-up of the CirVir cohort is necessary to clarify this issue.

We must acknowledge certain limitations to this study. First, the small number of incidental cases of nonhepatic malignancies may have hampered the statistical analyses, which could have been underpowered. Second, tumor burden at diagnosis of EHC was not recorded in our database, a fact that precluded the conduct of specified analyses dedicated to risk factors for cancer aggressiveness. Finally, the design of the cohort did not enable an accurate assessment of time-dependent analyses relative to alcohol and tobacco consumption or an accurate evaluation of metabolic changes over time.

In summary, compared to the general French population, HCV cirrhosis was associated with a higher risk of EHC. A diagnosis was possible in younger patients, and EHC was strikingly the leading cause of death after viral eradication, probably due to the observed benefits of SVR on liver-related complications. Viral replication may impact hematological malignancies but not the onset of solid tissue cancers. Cancer risk factors such as metabolic features, tobacco consumption, and chronic alcohol intake seem to play a role in EHC carcinogenesis; and specific surveillance must be implemented in this patient population, particularly at a time where most patients will experience viral eradication due to the use of DAAs. How far these observations can be extended to HCV patients without cirrhosis now deserves the conduct of dedicated studies.

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