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ORIGINAL PAPER

# Decreasing role of HCV and HBV infections as aetiological factors of hepatocellular carcinoma in Italy

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## Abstract

**Background** The epidemiology of hepatocellular carcinoma (HCC) is characterized by a dynamical temporal trend of well-established and emerging risk factors.

**Methods** We evaluated the temporal trend of aetiological factors of HCC over the last two decades in Italy. HCC cases were recruited from two previously published national studies in 1996 and in 2008 and HCC cases were also enlisted from two national surveys in 2001 and in 2014 enrolling consecutive subjects with chronic liver disease (CLD) referring to more than 80 liver units scattered all over the country for a 6-monthperiod.

**Results** Out of the 9997 subjects with CLD recruited in 2001 and the 2408 recruited in 2014, 3.3% and 5.7% ($P < 0.001$), respectively, had HCC. The temporal trend of HBsAg −/HCV + HCC cases significantly linearly decreased from 71.1% in 1996 to 57.2% in 2014 ($P < 0.001$). Conversely, that of virus-negative cases significantly linearly increased from 12.1% to 28.3% ($P < 0.001$). The proportion of HBV-related HCC cases showed a steady low rate, reflecting the reduced endemicity of the infection in Italy. The proportion of HCC with compensated cirrhosis (i.e., Child–Pugh A) linearly increased over time from 55.6% in 1996 to 76.0% in 2014 ($P < 0.001$) reflecting the growing effectiveness of semi-annual ultrasound surveillance for early detection of HCC.

**Conclusion** In conclusion, with decreasing viral aetiology, an overall decrease in the incidence of HCC might be expected in the future. The proportion of metabolic diseases is conversely increasing being considered as an aetiology. The growing prevalence of metabolic disorders in the general population may further increase this trend in the years to come.

**Keywords** Hepatocellular carcinoma · HBV · HCV · Alcohol · Risk factor

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## Introduction

Hepatocellular carcinoma (HCC) generally arises in the context of liver cirrhosis of any aetiology and the majority of patients worldwide with HCC have underlying cirrhosis [1, 2]. The mortality of HCC is increasing in Europe, North and South America, and Africa, while it is decreasing in East Asia [3–5]. The age-standardized mortality rate of HCC × 100,000 inhabitants in Italy has nearly tripled from 5.7 in 1980 to 16.5 in 2012, whereas the corresponding figures of cirrhosis showed more than a threefold decline over the same period (34.5 in 1980 and 10.8 in 2012) (Fig. 1). A potential explanation of these findings is that improvement in the medical management of non-HCC-related complications of cirrhosis, such as prevention [6] and treatment [7] of variceal bleeding, management of ascites [8], and availability of effective drugs for chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) infections [9, 10] has led to a longer survival of patients with cirrhosis, who in turn are at a greater risk over time of HCC development. In fact, the tumour became the first complication [11] and the leading cause of mortality [12] in cirrhotic patients. The reported increase in the prevalence of cirrhosis among CLD cases from 19.4% in 2001 [13] to 26.7% in 2014 [14] supports this statement.

The epidemiology of HCC is characterized by a dynamic temporal trend of the major established (i.e., HBV, HCV, alcohol) and emerging (i.e., diabetes, obesity, non-alcoholic fatty liver disease [NAFLD]) risk factors. Nowadays in the developed world, a rising proportion of HCC cases is ascribed to metabolic disorders [1].

In two multicentre studies performed in 1996 [15] and in 2008 [16], we showed that HCV infection was the main aetiological factor associated with HCC in Italy, albeit with a decreasing trend from 76.4% in 1996 to 63.0% in 2008. Adding to the data from these previously published studies findings from two cross-sectional national surveys performed in 2001 [13] and in 2014 [14] on the characteristics of subjects with chronic liver disease (CLD) referring to more than 80 liver units scattered all over the country, we have evaluated the temporal trend of HCC aetiology over nearly two decades (1996–2014) in Italy.

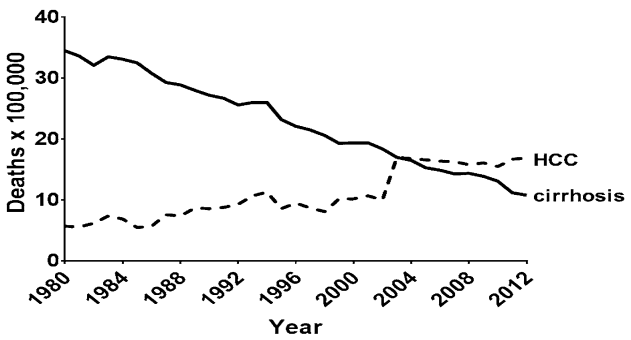


**Fig. 1** Age-standardized mortality rate × 100,000 inhabitants in Italy for liver cirrhosis (solid line) and hepatocellular carcinoma (broken line) in 1980–2012 (Data from the Office of National Statistics, Rome, Italy

## Patients and methods

The two national surveys have been previously described [13, 14]. The first one enrolled 9997 persons with CLD consecutively referring to 79 liver units for a 6-month period in 2001. The second one recruited 2408 CLD cases consecutively referring to 15 liver units for a 6-month period in 2014. Thus, both the studies were cross-sectional surveys with a prospective recruitment of consecutive patients.

Criteria of enrolment were age over 18 years and either altered hepatic biochemistry and/or the presence of etiologic markers of liver diseases. Criteria for recruiting in both surveys were the same. Both inpatients and outpatients were recruited. In both studies, the enrolling liver units were scattered all over the country. Majority of the 15 hospitals participating in the second study had also taken part in the first one. In both the surveys, referral and peripheral hospitals were both represented. Subjects recruited in 2014 were different from those in 2001. The liver units participating in the two surveys collected the data prospectively, had comparable access procedures, used a similar approach, and similar analytical methods.

Two previously published studies [15, 16] recruited only subjects with HCC. In 1996, 1148 HCC cases were recruited in 14 centres over a 1-year period. In 2008, 1733 cases were recruited in 23 centres over a 6-month period. Both surveys were cross-sectional with a prospective enrolment of consecutive subjects.

### Ethics statement

This study (extensive protocol, participating centres and summary grid) was formally and definitively approved by the Ethics Committee of the Coordinating Centre (Prof. Piero Luigi Almasio), Ethics Committee of the University Hospital (Azienda Ospedaliera Universitaria Policlinico Giaccone" of Palermo, Italy) on December 9, 2015 (Protocol number 11/2015, point 18). All procedures applied in the study were in accordance with the international guidelines, with the standards of human experimentation of the local Ethics Committees and with the Helsinki Declaration of 1975, revised in 1983.

At the time of the first observation, each patient signed an informed consent for the collection of personal data, as designated by the Ethics Committee of the coordinating

centre. Patients who agreed to undergo liver biopsy signed an appropriate informed consent before biopsy was performed. Patients were enrolled only once at their first observation. For each patient, a pre-coded questionnaire containing demographic, epidemiological and clinical data was filled out.

### Diagnostic criteria

In both the surveys, the presence of serum hepatitis B surface antigen (HBsAg) was identified as an HBV aetiology and that of the antibody to HCV as an HCV aetiology. The alcohol intake > 40 g/day for males (≥ 3 drinks a day) and > 30 g/day for females (≥ 2 drinks a day) for at least 5 years was considered as an etiologic factor for alcoholic liver disease [17, 18]. Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) were diagnosed based on abnormal serum values of alanine aminotransferase (ALT) associated to the hepatic steatosis identified by liver histology and/or ultrasound (US), in the absence of other known causes of liver disease.

Liver cirrhosis was diagnosed by liver biopsy (LB) or, in the absence, by the presence of characteristic clinical, biochemical, and ultrasound signs [19]. The diagnosis of hepatocellular carcinoma (HCC) was based on histological and/or imaging findings and alpha-1-fetoprotein serum levels [20].

### Serological assays

Serum HBsAg and antibody to HCV were sought using commercial immunoenzymatic assays.

### Data collection

The data were collected in a pre-established electronic CRF database (web-based data collection, e-CRF provided by AirTel®, Airon Telematica, Milan, ITALY).

### Statistical analysis

Continuous variables were summarized as means and standard deviation. Categorical variables were summarized as absolute and relative frequencies. Differences in means and in proportion were evaluated by the Student's *t* test and Chi square test or Fisher's exact test, respectively. The Cochran–Armitage test for trend was used in categorical data analysis to assess the association between a variable with two categories and different years.

A $P$ value < 0.05 was considered significant. All $P$ values were two-tailed.

## Results

Out of the 9997 subjects with CLD recruited in 2001 and the 2408 recruited in 2014, 328 (3.3%) and 138 (5.7%) ($P < 0.001$), respectively, had HCC.

Compared to the subjects enrolled in the study of 2001, those in the study of 2014 were more likely younger (mean age 64.6 years vs. 67.8; $P < 0.001$), with compensated cirrhosis, i.e., Child–Pugh A, (76.0% vs. 54.8%; $P < 0.001$), and with a viral negative aetiology (28.3% vs. 13.1%; $P < 0.001$), but less likely with an HBsAg−/HCV+ aetiology (57.2% vs. 71.3%; $P < 0.001$). No statistical difference between the two studies was observed according to the sex ratio, presence of underlying cirrhosis, HBsAg+/HCV− aetiology. Among subjects with a viral negative aetiology, an alcohol-related aetiology was reported by 60.5% of cases in 2001 and 43.6% in 2014, while the corresponding figures for NAFLD were 13.9% and 56.4%, respectively (Table 1).

Considering the figures from the two previously published studies [15, 16], we can evaluate the temporal trend across nearly two decades (1996–2014). The mean age of HCC cases linearly increased from 64.4 years in 1996 to 68.6 years in 2008, but it decreased to 64.4 years in 2014. The sex ratio was 3.3 in 1996, but it declined to 1.4 in 2014. The proportion of HCC cases with underlying cirrhosis was nearly stable overtime, reaching the lowest rate (87.7%) in 2014. The temporal trend in the prevalence of aetiological factors of HCC shows that the percentage of cases with HBsAg+/HCV− aetiology was quite stable, that of HBsAg−/HCV+ and HBsAg+/HCV+ aetiology significantly linearly decreased ($P < 0.001$), while that of viral negative aetiology significantly linearly increased ($P < 0.001$). (Table 2).

Finally, the proportion of HCC cases with compensated cirrhosis (i.e. Child–Pugh A) linearly increased from 55.6% in 1996 to 76.0% in 2014 ($P < 0.001$) (Fig. 2).

## Discussion

First, the statistically significant growing proportion of HCC cases among subjects with CLD from 3.3% in 2001 to 5.7% in 2014 is in agreement with the reported increase in mortality data of HCC. This finding does not seem to be attributable to the possible differences in the types of centres involved, as both surveys included a nearly similar proportion of tertiary care centres with exclusion of oncology-specific units.

The present study given evidence on a changing pattern over time in the aetiological factors of HCC in Italy. Albeit

**Table 1** Comparison of demographic and clinical features of HCC cases by year of study

| Variables | 2001 Study ($N=328$) | 2014 Study ($N=138$) | $P$ value |
|---|---|---|---|
| Age (years) (mean ± SD) | 67.8 ± 8.6 | 64.6 ± 13.1 | < 0.001 |
| Sex ratio (M/F) | 1.9 | 1.4 | 0.115 |
| Presence of cirrhosis, $N$ (%) (95% CI) | 303 (92.4%) (88.9–94.8) | 121 (87.7%) (81.2–92.2) | 0.113 |
| Child–Pugh score, $N$ (%) (95% CI) | | | |
| A | 166 (54.8%) (49.2–60.3) | 92 (76.0%) (67.7–82.8) | < 0.001 |
| B/C | 137 (45.2%) (39.7–50.8) | 29 (24.0%) (17.2–32.3) | |
| Aetiology, $N$ (%) (95% CI) | | | |
| HBsAg pos/anti-HCV neg | 40 (12.2%) (9.1–16.2) | 18 (13.0%) (8.4–19.7) | 0.878 |
| HBsAg neg/anti-HCV pos | 234 (71.3%) (66.2–75.9) | 79 (57.2%) (48.9–65.2) | < 0.001 |
| HBsAg pos/anti-HCV pos | 11 (3.4%) (1.9–5.9) | 2 (1.4%) (0.4–5.1) | 0.362 |
| HBsAg neg/anti-HCV neg | 43 (13.1%)[a] (9.9–17.2) | 39 (28.3%)[b] (21.4–36.3) | < 0.001 |

In brackets 95% CI

[a]26 (60.5%) cases with alcohol-related aetiology; 6 (13.9%) cases with NAFLD aetiology

[b]17 (43.6%) cases with alcohol-related aetiology; 22 (56.4%) cases with NAFLD aetiology

**Table 2** Temporal trend of characteristics of HCC in Italy

| Characteristic | 1996 Ref. [15] ($N=1083$) | 2001 ($N=328$) | 2008 Ref. [15] ($N=1733$) | 2014 $N=138$ | $P$ value |
|---|---|---|---|---|---|
| Mean age (years) (mean ± SD) | 64.6 (20–87) | 67.8 ± 8.6 | 68.6 ± 9.5 | 64.6 ± 13.1 | < 0.001 |
| Sex ratio | 3.3 | 1.9 | 2.8 | 1.4 | < 0.001 |
| Underlying cirrhosis, $N$ (%) | 1039/1116 (93.1%)[a] | 303 (92.4%) | 1648/1729 (95.3%)[b] | 121 (87.7%) | 0.256 |
| Aetiology, $N$ (%) | | | | | |
| HBsAg pos/anti-HCV neg | 125 (11.5%) | 40 (12.2%) | 230 (13.3%) | 18 (13.0%) | 0.632 |
| HBsAg neg/anti-HCV pos | 771 (71.1%) | 234 (71.3%) | 1,045 (60.3%) | 79 (57.2%) | < 0.001 |
| HBsAg pos/anti-HCV pos | 55 (5.3%) | 11 (3.4%) | 47 (2.7%) | 2 (1.4%) | < 0.001 |
| HBsAg neg/anti-HCV neg | 132 (12.1%) | 43 (13.1%) | 411 (23.7%) | 39 (28.3%) | < 0.001 |

[a]For the other listed variables, information was lacking in 33 cases

[b]For this variable, information was missing in 4 cases

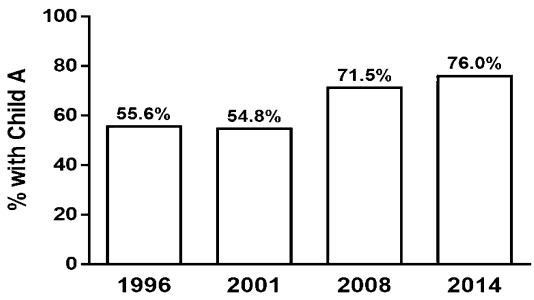


**Fig. 2** Temporal trend of the proportion of Child–Pugh A cirrhosis among HCC cases in Italy. Chi squared for linear trend $P<0.001$

HCV infection is still the more frequent aetiological factor associated with HCC, its role has remarkably declined over the last two decades with a proportional reduction by one-third. This finding confirms the recent reports from ITA.LI.CA. (Italian Liver Cancer), a very large Italian database, showing a 4% quinquennial drop in HCV-related cases during the period 1986–2010 [21].

The progressive decreasing role of HCV infection reflects the vanishing "cohort effect" of the infection. In Italy, many subjects have been exposed to the virus by unsafe injection practices during the 50s and 60s [22], generating a cohort of infected people born before the year 1945 [23]. The role of intravenous drug use is of limited impact, accounting in terms of population attributable risk (PAR) for 12% of all the HCV-positive cases in Italy [23]. A further role can also be ascribed to the achievement of sustained viral response to anti-HCV treatment able to slow down hepatic carcinogenesis [10]. Conversely, the proportion of non-viral cases has significantly increased during the study period in agreement with the ITA.LI.CA findings showing an increasing trend of non-viral factors from 22.5% to 32.4% during the period 2000–2014 [24]. Among these subjects, the decrease in alcoholic aetiology outlines the growing role of NAFLD that represents the hepatic manifestation of metabolic syndrome and may evolve into HCC in the absence of cirrhosis in as many as 50% of cases [25]. An even higher figure (63.0%) of HCC cases without significant fibrosis related to NAFLD

has been recently reported in a surgical referral centre in France [26]; even if it is due to the characteristics of the centre, a referral bias is likely to affect this high rate. The increasing proportion of non-viral-related HCC may also explain the decreasing proportion of cases with underlying liver cirrhosis in the latest year, 2014.

HBV infection accounts for a steady low proportion of cases over time reflecting the reported decreased endemicity of the infection in Italy over the latest decades [27]. It is too early to observe the full impact of HBV compulsory vaccination campaign for 3-month-old infants (started in 1991 and still ongoing) on the burden of the end-stage HBV-related CLD such as HCC. Though vaccination against HBV could prevent HCC, it does not prevent cancer onset in people with chronic infection.

Over time, the linear increase in the proportion of HCC cases arising in compensated cirrhosis (i.e., Child–Pugh A) is due to the effectiveness of semi-annual ultrasound surveillance for HCC detection. It has been shown that the diagnosis was made with ultrasound surveillance in 61.6% of the incident HCC cases in Italy [16].

Currently, ultrasound-based surveillance is recommended [28] for early HCC detection in subjects with liver cirrhosis of any aetiology and in those with chronic B hepatitis of male sex, Orientals, aged over 50 years, HBeAg positive, with high viral load (HBV-DNA) and in whom HCC may arise in up to 15% of cases in the absence of liver cirrhosis.

Subjects with NAFLD, which is now the leading cause of HCC occurring in the absence of significant fibrosis [29, 30], are not yet a targeted population for ultrasound surveillance. As the prevalence of subjects with NAFLD in the Western world [31], as well as in Italy [32], is around 25%, it would be unlikely to recommend surveillance for all NAFLD cases. These points highlight the need for identifying, among NAFLD subjects without cirrhosis, candidates for a cost-effective surveillance to establish earlier diagnosis and offer them effective treatment for HCC.

As a final point, we would like to comment on the limitations and positive aspects of the present study. The factors affecting the observed figures may be poor awareness of a specific disease (the case of metabolic disorders), availability of new antiviral drugs (the case of HBV), and the tendency of patients to seek medical care only once the symptoms have appeared (the case of risky alcohol intake). However, these factors may affect a single point prevalence estimate but not the temporal trend. On the other hand, the strong points should also be considered. All the four studies have enrolled prospectively patients in a given time period (6 or 12 months), which avoided the time-dependent "enrolment bias". Both referral and peripheral hospitals were represented, so that a potential referral bias was minimized. The same clinical approach, analytical methods and facilities to access the participating centres operating in distinct general or academic hospitals were applied. Finally, the geographical distribution of the participating centres throughout the country supports generalization of the findings to the whole of Italy.

In conclusion, a changing pattern of aetiological factors of HCC has been observed over the past two decades in Italy with a shift towards non-viral aetiology. The decrease in viral aetiology is mostly due to a decrease in HCV. The rising prevalence of metabolic disorders, particularly NAFLD, in the general population may further increase this trend in the years to come.

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**Author contributions** All authors contributed equally to this work, designed the study and wrote the manuscript.

## Compliance with ethical standards

**Conflict of interest** All the authors of the manuscript declare they have no conflict of interest in connection with this paper.

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