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Years of life that could be saved from prevention of hepatocellular carcinoma

A. Cucchetti*, F. Trevisani*, L. Bucci*, M. Ravaioli*, F. Farinati†, E. G. Giannini‡, F. Ciccarese§, F. Piscaglia*, G. L. Rapaccini¶, M. Di Marco**, E. Caturelli††, M. Zoli*, F. Borzio‡‡, R. Sacco§§, M. Maida¶¶, M. Felder***, F. Morisco†††, A. Gasbarrini¶, S. Gemini‡‡‡, F. G. Foschi§§§, G. Missale¶¶¶, A. Masotto****, A. Affronti¶¶, M. Bernardi* & A. D. Pinna* for the Italian Liver Cancer (ITA.LI.CA) group[1]

*Bologna, Italy.
†Padova, Italy.
‡Genova, Italy.
§Zingonia, Italy.
¶Rome, Italy.
**Seriate, Italy.
††Viterbo, Italy.
‡‡Milan, Italy.
§§Pisa, Italy.
¶¶Palermo, Italy.
***Bolzano, Italy.
†††Napoli, Italy.
‡‡‡Ancona, Italy.
§§§Faenza, Italy.
¶¶¶Parma, Italy.
****Negrar, Italy.

Correspondence to:
Dr A. Cucchetti, Department of Medical and Surgical Sciences – DIMEC, Alma Mater Studiorum – University of Bologna, Via Massarenti, 9, Bologna 40138, Italy.
E-mail: aleqko@libero.it

[1]Other members of the ITA.LI.CA group are reported in the Appendix 1.

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SUMMARY

Background
Hepatocellular carcinoma (HCC) causes premature death and loss of life expectancy worldwide. Its primary and secondary prevention can result in a significant number of years of life saved.

Aim
To assess how many years of life are lost after HCC diagnosis.

Methods
Data from 5346 patients with first HCC diagnosis were used to estimate lifespan and number of years of life lost after tumour onset, using a semi-parametric extrapolation having as reference an age-, sex- and year-of-onset-matched population derived from national life tables.

Results
Between 1986 and 2014, HCC lead to an average of 11.5 years-of-life lost for each patient. The youngest age-quartile group (18–61 years) had the highest number of years-of-life lost, representing approximately 41% of the overall benefit obtainable from prevention. Advancements in HCC management have progressively reduced the number of years-of-life lost from 12.6 years in 1986–1999, to 10.7 in 2000–2006 and 7.4 years in 2007–2014. Currently, an HCC diagnosis when a single tumour <2 cm results in 3.7 years-of-life lost while the diagnosis when a single tumour ≥2 cm or 2/3 nodules still within the Milan criteria, results in 5.0 years-of-life lost, representing the loss of only approximately 5.5% and 7.2%, respectively, of the entire lifespan from birth.

Conclusions
Hepatocellular carcinoma occurrence results in the loss of a considerable number of years-of-life, especially for younger patients. In recent years, the increased possibility of effectively treating this tumour has improved life expectancy, thus reducing years-of-life lost.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide, representing a frequent cause of cancer-related deaths.[1] It has currently shown an increased incidence due the improved survival of patients with chronic liver diseases and demographical ageing.[1, 2] Representing a leading cause of disability, its diagnosis and treatment often include expensive procedures which are capable of determining a substantial impact on healthcare resources. Thus, a comprehensive knowledge of the impact of HCC on population-mortality rates can give an accurate measure of the burden of the disease. In Italy, the incidence of HCC is relatively high.[3] From National statistics, the number of new cases per year is estimated to be about 13 200 (8900 male + 4300 female) in a population of 59.8 million of persons and, for males aged between 50 and 69 years, HCC ranks third as cause of death from cancers.[4] A mild higher incidence is observed in the South of Italy, mainly related to the higher prevalence of hepatitis B and/or C infection; however, the lower diffusion of surveillance programmes in this area and the greater alcohol consumption in North Italy returns a grossly similar number of incident cases across the country.[4]

The epidemiological weight of cancer is ordinarily measured in number of deaths, and reported as survival rates. However, the number of years of life lost (YLL) may be a more appropriate indicator of its impact on society, since it represents a measure of relative survival which takes into account the age at which the deaths occur.[5] Therefore, it gives greater weight to deaths at a younger age than those occurring at an older age. Years of life lost is a measurement used in public health to compare the relative importance of different causes of premature deaths in a given population, to establish priorities for prevention and to compare the premature mortality experience between populations.[5, 6] It can provide not only an estimate of population-level effect but also an effective health message for individuals who want to clearly understand the severity of their disease.[7, 8] This information is currently lacking for HCC, despite the worldwide incidence of this cancer. In addition, the estimation of YLL gives a precise measurement of the impact of HCC on patient and population life expectancy, and allows assessing its temporal trends regarding demographic ageing, advances in the prevention, diagnosis and treatment of HCC, and liver diseases predisposing to this cancer.

The aim of the present study was to assess YLL due to HCC in a large cohort of adult patients diagnosed with HCC in a setting of clinical practice. Temporal trends and relationships with sex, age, tumour burden and application of surveillance protocols were also explored in order to understand how many years of life could be saved by the prevention of an incident case of HCC.

METHODS

Study population

The Italian Liver Cancer (ITA.LI.CA) database is a prospective registry of HCC patients consecutively diagnosed with HCC between 1986 and 2014 who were followed at 24 Italian medical institutions (North: 14; Central: 6; South Italy: 4). Data entry was checked for consistency by the group coordinator; when clarification or additional informations were deemed necessary, relevant cases were resubmitted to the recruitment centre before final inclusion in the database. The ITA.LI.CA database management conforms to the past and the current Italian legislation regarding privacy, and the present study conforms to the ethical guidelines of the Declaration of Helsinki. Approval for the study was obtained from the Institutional Review Board of the participating centers.

In December 2014, the ITA.LI.CA data set included 6581 HCC patients. The present study population included only patients with a new HCC diagnosis, treated at participating centres with complete availability of data regarding demographics (sex, age and year of diagnosis) and survival after diagnosis. Therefore, 933 patients were excluded because they were referred to participating centres for cancer recurrence and 260 because they were referred after a poor response to initial therapies adopted in other care institutions. An additional 42 patients were excluded due to incomplete demographic or survival data. The final cohort, analysed for lifespan and YLL estimates, was formed of 5346 patients with a newly diagnosed HCC. In this sample, the presence of cirrhosis was histologically confirmed in only 19% of cases, whereas it was made unequivocal in about 95% of the remaining subjects by clinical, endoscopic and radiological signs together with laboratory findings.

The following additional data were considered: modality of HCC diagnosis (during or outside of surveillance), number and diameter of lesions, Child–Pugh class and first-line therapy adopted. The tumour burden was staged according to United Network for Organ Sharing (UNOS) tumour staging and the Milan

criteria.[9, 10] The diagnosis of HCC was made according to the guidelines published at the time of the cancer detection. Liver function tests, alpha-fetoprotein levels and tests for identifying the aetiology of liver disease were determined by conventional methods using commercially available assays. In each centre, the treatment decisions were made by a multidisciplinary team, taking into account tumour burden, liver function, comorbidities and patient willingness. Several therapeutic strategies were therefore used, including resection, liver transplantation, percutaneous ablation, trans-arterial embolisation (TAE), chemo-embolisation (TACE), systemic therapies and best supportive care (BSC).[11]

Statistical analysis

Continuous data were reported as means and standard deviations (SDs) or medians and 95% confidence intervals (CIs) or interquartile ranges (IQRs) depending on the distributions of the variables. Categorical data are presented as counts and percentages. Differences in means were investigated using the ANOVA test, and differences in percentages using the chi-square test; polynomial linear contrast and linear-by-linear association were used for trend analyses. Patient survival was measured from the date of diagnosis until death or the date of the last follow-up.

For a comprehensive interpretation of the results, YLL estimates were reported before and after lead-time bias correction of the survival of those patients diagnosed during surveillance. Lead-time is the time by which the diagnosis is anticipated by screening with respect to the clinical presentation of a disease and artificially prolongs the survival of cases detected during screening, leading to a specious improvement in prognosis with respect to symptomatic cases.[11, 12] However, for HCC patients the weight of lead-time bias becomes negligible for survival rates calculated 3 years after diagnosis.[11] Therefore, the results of the present study, encompassing the entire (extrapolated) post-diagnostic lifespan, could be assumed as barely affected by this bias. Nevertheless, they were reported both without and after lead-time adjustment, which was obtained assuming a tumour-doubling time of 100 days,[11] an exponential tumour growth during the tumour sojourn time and applying the formula proposed by Duffy *et al.*[13] Statistical analyses were carried out using R-project (R Development Core Team – 2008, R Foundation for Statistical Computing, Vienna, Austria). A $P < 0.05$ was considered statistically significant.

Extrapolation of years-of-life lost after cancer diagnosis

The extrapolation of lifespan after tumour diagnosis relies on the concept that HCC patients would die from causes directly related to liver disease in addition to the common causes experienced by the age- and sex-matched general population, assuming a *constant excess hazard* for the HCC cohort.[14]

First, an age-, sex- and year-of-diagnosis-matched reference population was generated from population life tables obtained from the Italian National Institute of Statistics using the Monte Carlo method previously described by Hwang and Wang.[15, 16] Of note, Italian national life tables report a life expectancy from birth which increased linearly from 77 years in 1986 to the current 83 years (80.4 for males and 85.6 years for females).[17] Second, knowing the survival of the cancer cohort and that of the reference population at each time t period, the survival ratio $W(t)$ can be expressed as $S(t)_{\text{HCC cohort}}/S(t)_{\text{reference cohort}}$.[14–16] For lifespan expectancy extrapolation, $W(t)$ was log-transformed: if the cancer-associated *excess hazard* remains *constant* over time, the logit of the $W(t)$ curve would gradually plateau over time, confirming the existence of the *constant excess hazard* and the reliability of the analysis (Figure S1). Third, a linear regression line to the logit of $W(t)$ to the end of the follow-up was fitted and used to predict a long-term survival curve, beyond the follow-up limit of the HCC cohort. In this way, it was possible to estimate the lifespan after tumour diagnosis of the HCC cohort (up to 100 years old corresponding to 600 months).[14–16] Finally, once the post-diagnosis lifespan was obtained, YLL was calculated as the difference in the area between the mean survival curves of the HCC cohort and that of the reference population. The ISQoL (integration of survival and quality of life) package for R-project was used for all the calculations; relative mathematical details have previously been described elsewhere.[14–16] The R-project package can be downloaded free from the following URL: http://www.stat.sinica.edu.tw/jshwang/isqol/

RESULTS

Baseline characteristics of the study population are reported in Table 1. The mean age of the 5346 patients was 67.1 years (s.d.: 10.0), ranging from 18 to 95 years, having a median of 68 years. Male gender largely prevailed (74.2%). The mean age for males was 65.9 years (s.d.: 10.0) and for females was 70.5 (s.d.: 8.6; $P < 0.001$). Four age quartiles were identified: 18–

Table 1 | Clinical characteristics of the whole population (1986–2014) of HCC patients used for estimation of years-of-life lost

Characteristics	No. of patients
Age (years) (n = 5346)	
Mean (s.d.)	67.1 (10.0)
Median (IQR)	68 (61–74)
18–61 years	1419 (26.5%)
62–68 years	1337 (25.0%)
69–74 years	1287 (24.1%)
75–95 years	1303 (24.4%)
Gender (n = 5346)	
Male	3966 (74.2%)
Year of diagnosis (n = 5346)*	
1986–1992	340 (6.4%)
1993–1999	893 (16.7%)
2000–2006	1646 (30.8%)
2007–2014	2467 (46.1%)
Hepatitis C infection (n = 5054)	
Present	3227 (63.9%)
Hepatitis B antigen (n = 4816)	
Positive	777 (16.1%)
Type of diagnosis (n = 5156)	
Surveillance	2853 (55.3%)
Incidental	1536 (29.8%)
Symptoms	767 (14.9%)
Child–Pugh class (n = 4741)	
A	2983 (62.9%)
B	1441 (30.4%)
C	317 (6.7%)
Tumour burden (n = 5266)	
Single <2 cm	543 (10.3%)
Single 2–5 cm/2–3 nodules & Milan In	2373 (45.1%)
Single or multifocal & Milan Out	2350 (44.6%)
First-line therapy (n = 4645)	
TACE/TAE	1486 (32.0%)
Ablation/Ethanol injection	1430 (30.8%)
BSC/Other	833 (17.9%)
Hepatic Resection	590 (12.7%)
Liver Transplantation	155 (3.3%)
Sorafenib	151 (3.3%)

* In the four periods the number of participating centres increased as follows: 1986–1992 = 8; 1993–1999 = 12; 2000–2006 = 18; 2007–2014 = 24. Geographical distribution of patients was as follows: North Italy centres, n = 3922 (73.4%); Central Italy centres, n = 892 (16.7%); South Italy centres, n = 532 (10.0%). The median number of patients recruited for each centre was 176 (further details can be found in the Appendix 1).

61 years (1419 patients), 62–68 years (1337 patients), 69–74 years (1287 patients) and 75–95 years (1303 patients). Four cohorts, based on the year of diagnosis, were also generated: 1986–1992 (340 patients), 1993–1999 (893 patients), 2000–2006 (1646 patients) and 2007–2014 (2467 patients).

The main cause of liver disease was hepatitis C infection (63.9%) and, in 62.9% of cases HCC was found in a setting of well-preserved liver function (Child–Pugh class A). Cancer was detected during a scheduled surveillance in slightly more than half of the cases (55.3%). The 55.4% of patients were diagnosed with an HCC fulfilling the Milan criteria (one single lesion ≤5 cm or no more than three nodules each ≤3 cm, without vascular invasion or extrahepatic spread). The majority of patients underwent trans-arterial or percutaneous loco-regional treatments, each of these approaches accounting for about 30% of cases.

During a median follow-up of 20 months (range: 1 day–24 years) 3414 patients died (63.7%). Median survival of the entire cohort was 30 months (95% CI: 29–31 months). The overall 1-, 3-, 5- and 10-year survival rates were 75.9%, 45.9%, 28.4% and 13.9% respectively.

Years of life lost after tumour diagnosis

Calibration of the long-term survival model (Figure S1) provided evidence for the constant excess hazard assumption (this verification was repeated for each subgroup analysis). For the entire study cohort (Figure 1), the estimated mean lifespan after tumour diagnosis was 4.9 years (95% CI: 4.3–5.4). The matched referent cohort had a mean life expectancy of 16.4 years, resulting in a number of YLL after tumour diagnosis of 11.5 years (95% CI: 10.9–12.1). Detailed survival results and number of YLL, in relationship with age quartiles, sex and year of diagnosis, are reported in Table 2. Notably,

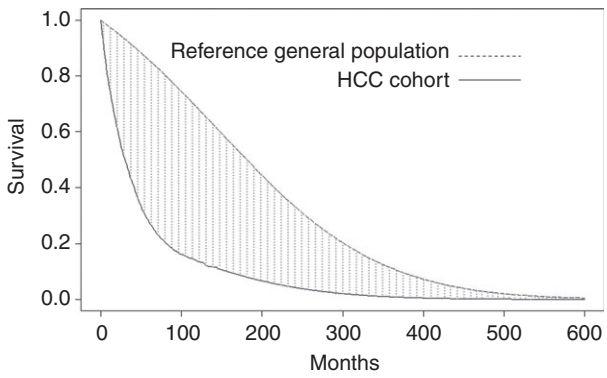

Figure 1 | The number of years of life lost (YLL) estimation derives from the difference between the area under the survival curve of the study population formed by 5346 patients with first diagnosis of hepatocellular carcinoma (continuous line) and that of the age-, year- and sex-matched reference population derived from the Italian National Institute of Statistics (dotted line).

Table 2 | Estimation of the entire lifespan after HCC diagnosis and number of years-of-life lost (YLL) with respect to the general population (data released by the Italian National Institute of Statistics)

	Mean age (s.d.)	Lifespan (years) after diagnosis (95% CI)	Years of life lost (95% CI)
Age			
18–61 years (n = 1419)	54.2 (6.3)	6.9 (5.6–8.2)	19.1 (17.8–20.4)
62–68 years (n = 1337)	65.2 (1.9)	4.4 (3.8–4.9)	12.8 (12.2–13.3)
69–74 years (n = 1287)	71.5 (1.7)	4.0 (3.5–4.5)	9.0 (8.5–9.5)
75–95 years (n = 2467)	78.9 (3.5)	3.4 (2.9–3.8)	5.1 (4.7–5.6)
Males			
All patients (n = 3966)	65.9 (10.1)	4.6 (4.2–5.0)	12.0 (11.5–12.4)
18–61 years (n = 1224)	53.9 (6.4)	6.2 (5.1–7.3)	19.4 (18.3–20.5)
62–68 years (n = 1025)	65.2 (1.9)	4.1 (3.6–4.6)	12.4 (11.9–12.9)
69–74 years (n = 888)	71.4 (1.7)	3.9 (3.5–4.3)	8.2 (7.8–8.6)
75–95 years (n = 829)	78.7 (3.3)	3.4 (2.9–3.9)	4.6 (4.0–5.1)
Females*			
All patients (n = 1380)	70.5 (8.7)	5.1 (4.1–6.1)	11.0 (10.0–12.1)
18–68 years (n = 507)	55.6 (5.3)	6.0 (4.4–7.5)	17.2 (15.7–18.7)
69–74 years (n = 399)	65.2 (1.9)	4.7 (3.8–5.6)	10.2 (9.3–11.1)
75–95 years (n = 474)	71.6 (1.7)	3.2 (2.8–3.6)	6.4 (6.0–6.8)
Year of diagnosis†			
1986–1992 (n = 340)	64.3 (9.0)	3.9 (3.1–4.7)	12.5 (11.7–13.3)
1993–1999 (n = 893)	64.7 (8.5)	4.1 (3.6–4.6)	12.7 (12.2–13.2)
2000–2006 (n = 1646)	67.1 (9.7)	5.7 (4.8–6.5)	10.7 (9.8–11.5)
2007–2014 (n = 2467)	68.4 (10.5)	8.9 (8.1–9.6)	7.4 (6.7–8.2)

For lead-time adjustment, a mean of 3.6 months (range 3.3–4.5 months) has to be subtracted from the total lifespan, or added to the number of YLL, in each subgroup.

* The classes 18–61 years and 62–68 years were grouped because of the small size of each group resulting in unreliable estimates.

† National life tables report a life expectancy from birth that linearly increased from 77 years in 1986 to the current 83 years: 80.4 for males and 85.6 years for females. The ANOVA test for mean age showed P = 0.642 between 1986–1992 and 1993–1999 and P = 0.001 from 2000 onwards having the first period as a contrast.

younger patients had the highest estimated lifespan after HCC diagnosis (6.9 years), but also the highest YLL (19.1 years), the magnitude of which greatly exceeded (12.2 years) estimated survival. All age groups showed this imbalance which, however, progressively faded with ageing so that, in patients over 75 years of age, the difference between lifespan and YLL was <2 years. Males and females experienced similar number of YLL (12.0 and 11.0 years respectively). Temporal analysis showed both a progressive increase in mean age at diagnosis (P = 0.001) and a decrease in YLL, starting from year 2000 onwards.

Other temporal trends were investigated. Figure 2 shows a progressive decline in the use of TACE/TAE over time (P = 0.001), mainly counterbalanced by an increased use of ablative techniques (P = 0.038). Apart from the availability of Sorafenib after 2007, no additional significant differences in treatment allocation were observed. Stratifying patients by Italian regions, it was observed that in the last period (2007–2014) TACE was adopted more frequently (33.1%) in the South Italy centres (recruited in recent years) as compared with both North (29.0%) and Central Italy (19.3%) institutions, already present in the ITA.LI.CA network (see the Appendix 1 for details on the recruitment timing). This could account for the plateau occurring in the last years, following a gradual over time decrease in TACE utilisation (Figure 2).

Figure 3 shows that a progressive increase in tumours diagnosed when single <2 cm or when single 2–5 cm or when 2–3 in number still fulfilling the Milan criteria, was observed over the years (P = 0.001). Figure 4 shows that surgery was most frequently adopted among the youngest patients (P = 0.001), whereas ablation techniques were preferred with ageing patients (P = 0.001); TACE/TAE and other treatment modalities did not show a significant trend over age quartiles.

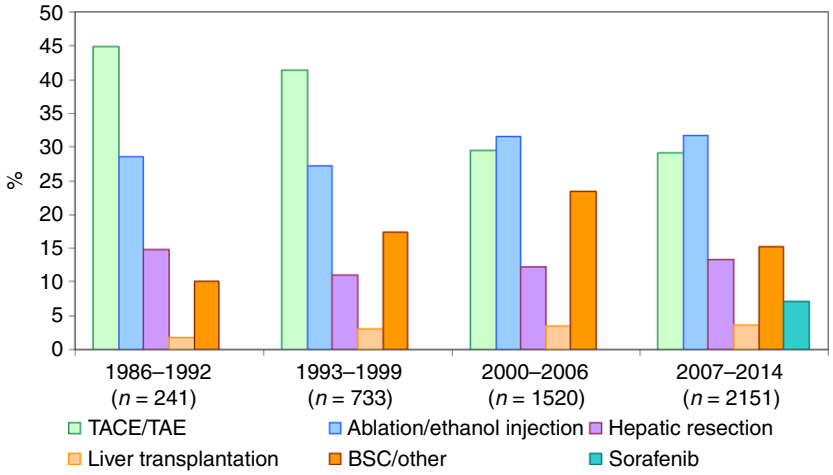

Figure 2 | Temporal trends in the first-line therapeutic modalities adopted during the study period (1986–2014). A progressive decline in the use of TACE/TAE over time was observed (P = 0.001), mainly counterbalanced by an increased use of ablative techniques (P = 0.038).

As an additional finding, the proportion of patients diagnosed under surveillance increased from 51.0% in 1986–1992 to 52.0% in 1993–1999, 55.1% in 2000–2006 and to 57.3% in 2007–2014 (P = 0.001). YLL were calculated according to surveillance in the 1986–1999, 2000–2006 and 2007–2014 periods. In the first period, surveyed patients (n = 635) had 12.2 YLL (95% CI: 11.6–12.9) vs. 13.3 (95% CI: 12.8–13.8) of nonsurveyed patients (n = 593) and in the 2000–2006 period, surveyed patients (n = 852) had 9.9 YLL (95% CI: 8.9–10.8) vs. 11.5 YLL (95% CI: 11.0–12.0) of nonsurveyed patients (n = 694). In order to investigate today's life expectancy and YLL, all the analyses (including surveillance) were repeated in the subset of patients with HCC diagnosed between 2007 and 2014 (contemporary subset).

Years of life lost in the contemporary subset

Baseline characteristics of the 2467 HCC patients diagnosed between 2007 and 2014 are outlined in Table 3. During a median follow-up of 16 months (range: 1 day–8 years), 1088 patients died (44.1%). The median survival of this cohort was 34 months (95% CI: 31–37). The overall 1-, 3-, 5- and 8-year survival rates were 76.4%, 49.2%, 33.3% and 26.0% respectively.

The YLL after tumour diagnosis were 7.4 (95% CI: 6.7–8.2). Lifespan estimates and the number of YLL, in relationship with age class, sex, type of diagnosis and tumour burden, are reported in Table 4. Once again, the youngest patients experienced the highest number of YLL, with males and females having similar figures. Child–Pugh class A and surveilled patients had lower YLL. In particular, YLL of surveyed patients was 6.2 (95% CI: 5.4–7.1) vs. 9.5 (95% CI: 8.4–10.6) of nonsurveyed patients. Of note, patients diagnosed with a single HCC <2 cm and those diagnosed with a single HCC 2–5 cm or with 2–3 nodules still fulfilling the Milan criteria had the lowest figures of YLL (3.7 and 5.0 years respectively). No significant differences were observed among the three Italian regions (P = 0.774; see Appendix 1)

DISCUSSION

The quantification of lifespan after HCC diagnosis and YLL represents advancement in the knowledge of the

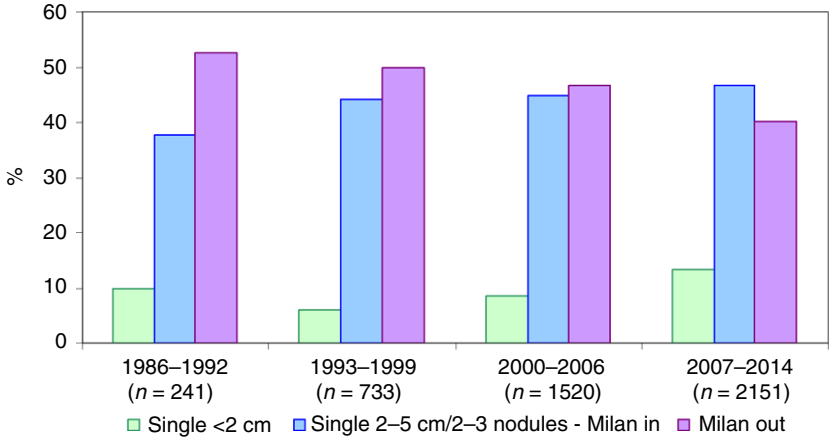

Figure 3 | Stage migration observed in the different time spans. A progressive increase in tumours diagnosed with single <2 cm or with single 2–5 cm or with 2–3 nodules fulfilling the Milan criteria, was observed over the years (P = 0.001).

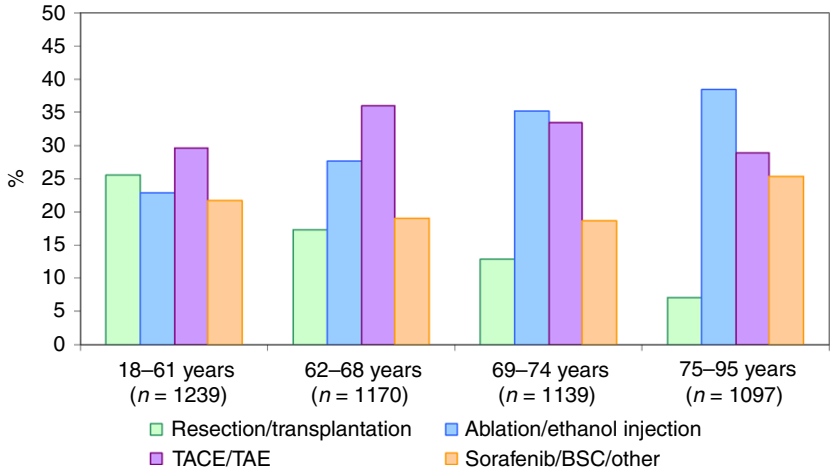

Figure 4 | Adoption of different therapies by age quartiles. Hepatic resection was most frequently pursued in the youngest patients (P = 0.001), whereas ablation techniques were preferred in elderly patients (P = 0.001).

impact of this cancer on patient survival. Reporting life expectancy through these measures allows an immediate and comprehensive health message to the community regarding cancer outcome and the actual value of its prevention.[5]

The present analysis showed that, over the last three decades, the prevention of an incident case of HCC could have saved an average of 12 years of life for each patient. Unfortunately, although this figure is valuable, the prevention of HCC is a very difficult task.[18] Primary prevention includes the screening of blood products, hepatitis B vaccination and policies aimed at reducing alcohol intake and at promoting a correct lifestyle in order to avoid non-alcoholic fatty liver disease (NAFLD) in the general population. Secondary prevention has the aim of slowing, or arresting, the progression of liver disease to cirrhosis, the main risk factor for HCC occurrence, through effective anti-viral therapies or the correction of inappropriate eating, smoking and drinking habits.[18–20] In this regard, the recent advent of anti-viral drugs able to cure hepatitis C in most cases will lead to a great improvement in the life expectancy of patients carrying this infection, due to an increased effectiveness of the secondary prevention of liver cirrhosis and, consequently, HCC.[21]

Several results of the present study require discussion. First of all, the results make evident that younger individuals are the optimal target for primary and secondary prevention of HCC since, despite the highest survival after tumour diagnosis, they also experienced the highest number of YLL (Tables 2 and 4). The value of preventing one HCC case in the first six decades of life is higher than that of preventing one case in subsequent decades. The current possibility of saving 15.5 years of life in the early decades of life (Table 4) surely has a greater social impact than saving 4 or 10 years in older subjects.

Table 3 | Clinical characteristics of the cohort of HCC patients diagnosed between 2007 and 2014 used for estimation of years-of-life lost in the most recent recruitment period (contemporary subset)

Characteristics	No. of patients
Age (years) (n = 2467)	
Mean (s.d.)	68.4 (10.5)
Median (IQR)	70 (62–76)
18–61 years	588 (23.8%)
62–68 years	496 (20.1%)
69–74 years	619 (25.1%)
75–95 years	764 (31.0%)
Gender (n = 2467)	
Male	1811 (73.4%)
Hepatitis C infection (n = 2391)	
Present	1414 (59.1%)
Hepatitis B antigen (n = 2315)	
Positive	777 (13.5%)
Child–Pugh class (n = 2301)	
A	1429 (62.1%)
B	730 (31.7%)
C	142 (6.2%)
Type of diagnosis (n = 2382)	
Surveillance	1366 (57.4%)
Incidental	699 (29.3%)
Symptoms	317 (13.3%)
Tumour Stage (n = 2429)	
Single <2 cm	322 (13.3%)
Single 2–5 cm or 2–3 nodules & Milan In	1131 (46.5%)
Single/multifocal & Milan Out	976 (40.2%)
First-line therapy (n = 2151)	
TACE/TAE	625 (29.1%)
Ablation/Ethanol injection	683 (31.8%)
BSC/Other	326 (15.2%)
Hepatic resection	288 (13.4%)
Liver transplantation	78 (3.6%)
Sorafenib	151 (7.0%)

Geographical distribution was as follows: North Italy centres, n = 1455 (59.0%); Central Italy centres, n = 486 (19.7%); South Italy centres, n = 526 (21.3%).

Table 4 | Estimation of entire lifespan after HCC diagnosis and numbers of years-of-life lost (YLL) in the cohort of 2467 patients diagnosed between 2007 and 2015. YLL were calculated using as reference life tables released by the Italian National Institute of Statistics

	Mean age (s.d.)	Lifespan (years) after diagnosis (95% CI)	Years of life lost (95% CI)
Age			
18–61 years (n = 588)	53.5 (6.6)	12.2 (10.0–14.4)	15.5 (13.3–17.7)
62–68 years (n = 496)	65.3 (1.9)	7.8 (6.4–9.1)	10.3 (8.9–11.7)
69–74 years (n = 619)	71.6 (1.7)	6.2 (5.0–7.3)	7.4 (6.3–8.6)
75–95 years (n = 764)	79.3 (3.6)	4.1 (3.4–4.9)	4.5 (3.8–5.2)
Males			
All patients (n = 1811)	67.0 (10.7)	8.9 (7.9–9.8)	7.8 (6.8–8.7)
18–61 years (n = 513)	53.4 (6.5)	11.4 (8.9–14.0)	15.9 (13.4–18.4)
62–68 years (n = 395)	65.2 (1.9)	7.6 (5.8–9.5)	9.8 (7.9–11.6)
69–74 years (n = 423)	71.5 (1.7)	7.4 (6.3–8.4)	5.4 (4.3–6.5)
75–95 years (n = 480)	79.2 (3.5)	4.5 (3.4–5.6)	3.5 (2.5–4.6)
Females*			
All patients (n = 656)	72.2 (8.9)	8.5 (7.1–9.9)	7.4 (6.0–8.7)
18–74 years (n = 372)	66.5 (7.5)	11.4 (9.5 – 13.3)	8.5 (6.5–10.4)
75–95 years (n = 284)	79.6 (3.8)	3.4 (2.9–3.8)	6.3 (5.8–6.8)
Child–Pugh class (n = 2301)			
A (n = 1429)	69.0 (10.2)	7.4 (4.3–10.4)	8.4 (5.4–11.5)
B-C (n = 872)	67.6 (10.9)	3.7 (2.3–5.0)	13.4 (12.0–14.7)
Type of diagnosis (n = 2382)			
Surveillance (n = 1366)	68.7 (10.0)	9.9 (9.0–10.8)	6.2 (5.4–7.1)
Incidental/symptoms (n = 1016)	68.0 (11.1)	7.1 (6.1–8.2)	9.5 (8.4–10.6)
Tumour burden (n = 2429)			
Single <2 cm (n = 322)	67.0 (10.4)	13.8 (12.3–15.2)	3.7 (2.3–5.1)
Single 2–5 cm/2–3 & Milan In (n = 1131)	69.2 (9.9)	11.6 (10.8–12.4)	5.0 (4.1–5.8)
Single/multifocal & Milan Out (n = 976)	67.9 (11.0)	4.8 (4.0–5.5)	11.8 (11.0–12.5)

For lead-time adjustment, a mean of 3.7 months has to be subtracted from the total lifespan, or added to the number of YLL, in each subgroup, ranging from zero (for incidental/symptomatic patients) to 5.8 months for patients diagnosed because of surveillance.

* 18–61, 62–68 and 69–74 year classes were grouped together because the small size of each group did not result in reliable estimates.

Indeed, focusing on the 2007–2014 data, it can be calculated that the average YLL for the first age quartile is 9114 years (15.5 × 588 patients), representing approximately 41% of the overall YLL (22 241 years). These results can be interpreted from different standpoint: considering the perspective of the entire (from birth) lifespan, it is reasonable that medical resources allocation, rather than saving the most lives, should be aimed at saving the most life-years in order to obtain similar life-expectancies from birth for every individual (fulfilling the concept of prudential lifespan account proposed by the Nobel Prize philosopher Norman Daniels), without incurring into ageism accusation.[22, 23] Of note, this benefit was equal for males and females. There are two reasons for the equivalence of YYL between genders; females have a delayed peak incidence of HCC but also a longer life expectancy in the general population.[17]

A second interesting finding is the decrease in YLL observed in the new century (Table 2). This trend cannot be attributed to older patient age at diagnosis since the general population experienced a parallel increase in their life expectancy.[17] Instead, the favourable stage migration phenomenon observed (Figure 3), attributable to the increasing adoption of surveillance programmes, may have played an important causative role.[24] In particular, in the latest time-period (2007–2015), the number of YLL for very early tumours was very small (3.7 years) as well as for early cases (5.0 years), representing the loss of only approximately 5.5% and of 7.2% of the entire lifespan (from birth) (Table 4). The improved therapeutic results obtained in recent decades, especially with loco-regional therapies which represent the most frequent first-line therapies adopted, have probably played an equally important role. It is also worth noting that, among these

therapies, the curative approach (ablation) has surpassed the palliative one (TACE) in recent years (Figure 2). Moreover, surgical advances, refined retreatment schedules using the same or different approaches and the availability of sorafenib have likely contributed to reducing the YLL in the latest time period. All in all, smaller tumours at diagnosis, which are more efficiently treatable with all therapeutic strategies and refinements of therapies, have resulted in decreasing YLL after HCC diagnosis.

A final brief discussion should be reserved as to what is already known about the subject of the present study. A 2013 report from the Surveillance, Epidemiology and End Results (SEER) program including six different types of cancers, quotes an estimated number of YLL of 16.7 years for 'liver cancer'.[25] This figure is different from the present findings, especially considering that the average life expectancy of the US population is lower than that of the Italian population.[26] This difference may have two explanations. First, in defining 'liver cancer' authors have probably included not only HCCs but also tumours of the biliary tract which have a worse prognosis, thus increasing the number of YLL. Second, our data were generated in centres where expertise regarding HCC management can be considered high. Indeed, all the ITA.LI.CA centres are experts in the management of liver diseases and operate in a setting of collaborative multidisciplinary regional/supraregional networks which include tertiary referral centres (high volume centres) and liver transplant units. Despite the trend toward a more frequent adoption of TACE in South Italy, no significant regional differences in YLL were observed and all these features can explain the better YLL figures observed in the present study in respect to the SEER results. Although based on a very large sample size, the present study is not population-based, but this inherent limitation should be viewed in the light of the complementary utility between population-based statistics and large clinical-based studies, which can provide many more (and verified) data for the analyses. Moreover, to the best of our knowledge, the ITA.LI.CA registry is the largest, multicentric, permanent database of HCC patients available in Europe, adding value to the present results.

Our results should be also interpreted in the light of those generated by country-specific population-based statistics. In Italy, the Global Burden of Disease Study currently shows that ischaemic heart disease and cerebrovascular disease still represent the leading causes of death accounting for about 25% of the total YLL through population, with a considerable reduction (more than 30%) through the last decades, due to medical improvements.[27] Lung and breast cancers, among within the first seven causes of YLL, also showed a reduction in about 20% of the total YLL. Conversely, liver cancer showed an increase in about 16% of the total YLL moving this cancer within the first 10 causes of YLL in more recent period. Present results indicate that even if HCC is not the leading causes of YLL in the whole population, it currently represents a major health problem in Italy,[4]

The present study has at least two potential limitations due to methodological aspects. First, the lifespan calculation is based on the projection of a survival curve, therefore representing an estimated result (based on real-life data) but not an observed result. The most robust method for calculating YLL would rely on observing the cohort until all patients had died. However, this would require an extremely long follow-up, leading to a high risk of resulting in a figure which would be out-of-date at the time of the assessment. The delayed availability of data sharply contrasts with the need to promptly adapt the available resources to the current clinical scenario and its temporal trends. It should also be considered that the mathematical approach adopted in this study is reported to suffer from a very small imprecision ($\pm$1.5%) with respect to the entire observed lifespan.[25] Second, the YLL estimate is affected not only by the survival of the HCC cohort but also by the life expectancy of the reference cohort. Therefore, since the life expectancy of the reference population is influenced by the cancer itself, the YLL may have been underestimated. However, it is likely that this unavoidable bias was minimal, because a single cancer has a relatively small effect on the life tables of the general population which include all causes of death. Two ancillary methodological limitations rely on the impossibility, through present estimates, to: (i) assess the competing role of each prognostic factor in determining survival and YLL (i.e. multivariate analysis); (ii) calculate robust disability-adjusted life years saved. We attempted to overcome the first problem performing subanalyses after several patient stratifications but, for a comprehensive investigation of inter-relationships between variables, a new analytic (multivariable) approach would be required that, to the best of our knowledge, is currently not available. Second, the calculation of the quality-adjusted life expectancy in HCC cohorts would be of interest, but it relies on the availability of data regarding quality of life (utilities). Population-based statistics report disability-adjusted YLL, based on rough estimates of utilities.[27] However, for HCC patients, the quality of life changes not only according to the stage of underlying liver disease (pre-cirrhotic dis-

ease, compensated and decompensated cirrhosis) but also with the treatment adopted.[28, 29] These health states cannot be considered as a unique utility and the possible solution to obtain a comprehensive disability-adjusted YLL estimation is to build a dedicated multistage Markov model.

In conclusion, the present results offer a novel measurement of health care communication in the field of HCC, that is primary and secondary prevention of this tumour could have saved, on average, 12 years of life for each case prevented in the last decades. The increasing use of surveillance of patients at risk of HCC, and the advancement in and the management of this cancer has currently reduced this loss to 7.4 years. Moreover, it can be estimated that today a diagnosis of HCC at an early stage can guarantee the patient an entire lifespan (i.e. from birth) close to that of the general population.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Logit transformation of the survival ratio W (t) between the survival function of the 5346 patients forming the study population and that of the age-, year-of-onset- and gender-matched reference population. The logit transformation slope of the survival ratio between the study population and the matched referent cohort was estimable, providing evidence for the constant excess hazard assumption. The vertical dotted lines mark the time period when the data were used for extrapolation (10–12 years after diagnosis) while the horizontal dotted line is the slope of the logit survival ratio. The process was repeated for each subgroup analysed; when estimates resulted in too large standard errors, the subgroups were collapsed together.

Data S1. Temporal recruitment of participating centres and treatment modalities adopted & Survival and years of life lost in relationship with Barcelona-Clinic Liver Cancer classification.

AUTHORSHIP

Guarantor of the article: None.

Author contributions: A. Cucchetti contributed towards study concept and design, analysis and interpretation of data, drafting of the manuscript; F. Trevisani contributed towards interpretation of data and drafting of the manuscript L. Bucci contributed towards data-manager, data extrapolation and analysis of data; M. Ravaioli contributed towards drafting of the manuscript. A.D. Pinna contributed towards critical revision of the manuscript for important intellectual contents. All the other authors listed participated in this multicentric prospective database collection.

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APPENDIX 1

Other members of the ITA.LI.CA group

Dipartimento di Scienze Mediche e Chirurgiche, Alma Mater Studiorum - Università di Bologna: Luigi Bolondi, Maurizio Biselli, Paolo Caraceni, Alessandro Cucchetti, Marco Domenicali, Annagiulia Gramenzi, Donatella Magalotti, Anna Pecorelli, Carla Serra, Laura Venerandi; *Dipartimento di Scienze Chirurgiche e Gastroenterologiche, Università di Padova*: Alessia Gazzola, Francesca Murer, Caterina Pozzan, Veronica Vanin; *Unità Operativa di Chirurgia, Policlinico S. Marco, Zingonia*: Paolo Del Poggio, Stefano Olmi; *Unità Operativa di Medicina, Azienda Ospedaliera Bolognini, Seriate, Italia*: Claudia Balsamo, Elena Vavassori; *Dipartimento di Medicina Clinica e Sperimentale, Università di Padova*: Luisa Benvegnù; *Dipartimento di Malattie Apparato Digerente e Medicina Interna, Azienda ospedaliero-universitaria di Bologna, Unità Operativa di Radiologia*: Alberta Cappelli, Rita Golfieri, Cristina Mosconi, Matteo Renzulli; *Unità di Medicina Interna e Gastroenterologia, Complesso Integrato Columbus, Università Cattolica di Roma, Roma*: Giulia Bosco; *Unità Operativa di Gastroenterologia, Ospedale Belcolle, Viterbo*: Paola Roselli; *Unità Operativa di Medicina Protetta, Ospedale Belcolle, Viterbo*: Serena Dell'Isola, Anna Maria Lalungo, Elena Rastrelli; *Dipartimento di Medicina Interna, Unità di Gastroenterologia, IRCCS-Azienda Ospedaliera Universitaria San Martino-IST, Università di Genova*: Alessandro Moscatelli, Gaia Pellegatta, Antonino Picciotto, Vincenzo Savarino; *Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Gastroenterologia, Università di Palermo:* Maria Rosa Barcellona, Calogero Cammà, Giuseppe Cabibbo, Andrea Costantino; *Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Medicina Interna 2, Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Palermo*: Roberto Virdone; *Ospedale Regionale di Bolzano, Unità di Gastroenterologia, Bolzano*: Andrea Mega; *Unità di Medicina Interna e Gastroenterologia, Policlinico Gemelli, Università Cattolica di Roma, Roma*: Emanuele Rinninella; *Unità Operativa Gastroenterologia e Malattie del Ricambio, Azienda Ospedaliero-Universitaria Pisana, Pisa*: Valeria Mismas; *Dipartimento di Medicina Interna; Ospedale per gli Infermi di Faenza, Faenza*: Anna Chiara Dall'Aglio, Valentina Feletti, Arianna Lanzi, Federica Mirici Cappa, Elga Neri, Giuseppe Francesco Stefanini, Stefano Tamberi; *Unità di Malattie Infettive ed Epatologia, Azienda Ospedaliero-Universitaria di Parma:* Elisabetta Biasini, Emanuela Porro; *Dipartimento di Medicina Clinica e Chirurgia, Unità di Gastroenterologia, Università di Napoli "Federico II", Napoli:* Maria Guarino; *Clinica di Gastroenterologia, Università Politecnica delle Marche, Ancona*: Gianluca Svegliati Baroni, Laura Schiadà; *Unità di Gastroenterologia, Ospedale Sacro Cuore Don Calabria, Negrar*: Maria Chiaramonte, Fabiana Marchetti, Matteo Valerio.