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## Incidence of primary liver cancer in Italy between 1988 and 2002: An age–period–cohort analysis

Luigino Dal Maso<sup>a,\*</sup>, Mauro Lise<sup>a</sup>, Paola Zambon<sup>b</sup>, Emanuele Crocetti<sup>c</sup>, Diego Serraino<sup>a,d</sup>, Fulvio Ricceri<sup>e</sup>, Marina Vercelli<sup>f</sup>, Vincenzo De Lisi<sup>g</sup>, Giovanna Tagliabue<sup>h</sup>, Massimo Federico<sup>i</sup>, Fabio Falcini<sup>j</sup>, Tiziana Cassetti<sup>k</sup>, Andrea Donato<sup>l</sup>, Mario Fusco<sup>m</sup>, Mario Budroni<sup>n</sup>, Stefano Ferretti<sup>o</sup>, Rosario Tumino<sup>p</sup>, Silvano Piffer<sup>q</sup>, Francesco Bellù<sup>r</sup>, Lucia Mangone<sup>s</sup>, Adriano Giacomini<sup>t</sup>, Susanna Vitarelli<sup>u</sup>, Silvia Franceschi<sup>v</sup>

<sup>a</sup>Epidemiology and Biostatistics Unit, Aviano Cancer Center, IRCCS, Via Franco Gallini 2, 33081 Aviano (PN), Italy

<sup>b</sup>Registro Tumori del Veneto, Istituto Oncologico Veneto IRCCS, Padua, Italy

<sup>c</sup>Registro Tumori Toscana, Centro per lo Studio e la Prevenzione Oncologica, Firenze, Italy

<sup>d</sup>Registro Tumori Friuli Venezia Giulia, Agenzia Regionale Sanità, Udine, Italy

<sup>e</sup>Registro Tumori del Piemonte, Ospedale S. Giovanni Battista, CPO, Torino, Italy

<sup>f</sup>Registro Tumori Regione Liguria, IST/Università di Genova, Genova, Italy

<sup>g</sup>Registro Tumori della Provincia di Parma, Ospedale di Parma, Parma, Italy

<sup>h</sup>Registro Tumori Lombardia, Provincia di Varese, Istituto Nazionale Tumori, Milano, Italy

<sup>i</sup>Registro Tumori della Provincia di Modena, Policlinico, Modena, Italy

<sup>j</sup>Registro Tumori della Romagna, Ospedale G.B. Morgagni-L. Pierantoni, Forlì, Italy

<sup>k</sup>Registro Tumori Umbro di Popolazione, Università di Perugia, Perugia, Italy

<sup>l</sup>Registro Tumori della Provincia di Salerno, Salerno, Italy

<sup>m</sup>Registro Tumori della Campania, ASL Napoli 4, Naples, Italy

<sup>n</sup>Registro Tumori della Provincia di Sassari, Sassari, Italy

<sup>o</sup>Registro Tumori della Provincia di Ferrara, Università di Ferrara, Ferrara, Italy

<sup>p</sup>Registro Tumori di Ragusa, Ospedale Civile 'M.P. Arezzo', Ragusa, Italy

<sup>q</sup>Registro Tumori della Provincia di Trento, Osservatorio Epidemiologico, Trento, Italy

<sup>r</sup>Registro Tumori dell'Alto Adige, Bolzano, Italy

<sup>s</sup>Registro Tumori della Provincia di Reggio Emilia, Italy

<sup>t</sup>Registro Tumori Piemonte, Provincia di Biella, CPO, Biella, Italy

<sup>u</sup>Registro Tumori di Macerata, Università di Camerino, Camerino, Italy

<sup>v</sup>International Agency for Research on Cancer, Lyon, France

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### ABSTRACT

We conducted in Italy a study to evaluate trends of primary liver cancer (PLC) and to disentangle the period from birth-cohort effects on PLC incidence. Cases aged <80 years and diagnosed between 1988 and 2002 in 20 areas covered by population-based Cancer Registries were included. Age-standardised incidence rates and age-period-cohort effects were estimated. In 1998–2002, incidence rates of PLC were 21.1/100,000 men and 6.0/100,000 women. In both genders, incidence rates increased slightly between 1988–1992 and 1993–1997 but did not rise thereafter. Amongst men, PLC risk increased in every cohort born after 1913 and the rise became steeper for cohorts born in 1948. In women, an upward trend

\* Corresponding author. Tel.: +39 0434 659354; fax: +39 0434 659231.

E-mail address: [epidemiology@cro.it](mailto:epidemiology@cro.it) (L. Dal Maso).

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appeared only in the cohorts born after 1953. Incidence of PLC over the last two decades in Italy did not substantially change but huge geographical variability emerged, mainly due to different times and modalities of spread of hepatitis C virus.

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## 1. Introduction

Primary liver cancer (PLC) shows huge variations worldwide<sup>1,2</sup> with rising incidence or mortality rates reported in most European countries,<sup>3–5</sup> the United States<sup>6</sup> and Japan.<sup>7</sup>

The etiology of PLC is largely established with major risk factors for PLC – namely, hepatitis B (HB) and C viruses (HCV) and alcohol abuse – accounting for approximately 90% of cases.<sup>8–10</sup> The relative contribution of these three risk factors varies worldwide.<sup>11</sup> In Italy, two-third of PLC cases are attributable to HCV infection.<sup>9</sup> All-age HCV prevalence in Italy varies between 2% and 7%<sup>12</sup> but prevalence higher than 15% was reported in middle-age individuals in the South.<sup>12,13</sup>

Since the median latent period between hepatitis infection and hepatocellular carcinoma has been estimated between 3 and 4 decades,<sup>14,15</sup> variations of HCV (and HBV) carcinogenic consequences are expected to be fully seen many decades after changes in hepatitis virus prevalence.

The present study was designed to update recent trends of PLC incidence considering that HCV spread started to decrease only in the 1990s, whilst HBV prevalence had already started decreasing in Italy, as well as in other developed countries, in the early 1980s, after the introduction of screening of blood donations and blood products followed, 10 years later, by HBV vaccination campaigns.<sup>16</sup>

## 2. Materials and methods

As of May 2006, in Italy, 20 Cancer Registries (CRs), covering a population of 14 million inhabitants, 25% of the total population, are active and have published PLC incidence rates until at least the end of the 1990s (Table 1). Regions of Friuli Venezia Giulia, Romagna, Umbria, and part of Veneto, the provinces of Alto Adige, Biella, Ferrara, Florence and Prato, Genoa, Macerata, Modena, Parma, Ragusa, Reggio Emilia, Salerno, Sassari, Trento and Varese, part of Naples province and the municipality of Turin were included. Only 10 CRs reported at least 12 registration years and contributed to trend estimates (Table 1). CRs vary in size, ranging from approximately 190,000 to 1.9 million populations, and in a number of registration years available, from 6 to 25 years. Four CRs were in southern Italy (i.e. Naples, Ragusa, Salerno and Sassari), eight in central Italy (i.e. Ferrara, Florence and Prato, Macerata, Modena, Parma, Romagna, Reggio Emilia, and Umbria) and the remaining eight in northern Italy.<sup>1,17,18</sup>

A total of 28,963 incident cases of malignant neoplasms of the liver (ICD10 = C22) that had been diagnosed during 1988–2002 in areas covered by Italian CRs were extracted from CRs anonymous database including all cancers reported after 1986.<sup>18</sup>

To reduce the possibility of misclassification of PLC with other rarer neoplasms of the liver whose etiology is different from hepatocellular carcinoma, the following cases were excluded: (1) those occurring in patients aged 80 years or older ( $n = 5227$ ); (2) specified morphological subtypes different from hepatocellular carcinoma ( $n = 1854$ ) and (3) C22.1–C22.4 (i.e. cancer of intrahepatic bile ducts, hepatoblastoma and sarcomas;  $n = 1570$ ). Exclusion criteria overlapped for some cases leaving 22,096 PLC in the 20 CR for the overall period 1988–2002. Unspecified morphologies (800–802) or ICD10 sites (C22.7, C22.9) and PLC reported as second primary tumours ( $n = 1447$ , 6.5%) were included.

Age-standardised incidence rates (IRs) were computed by gender, place of residence and overall using the direct method<sup>19</sup> and, as standard, we used the 1991 Italian population. Age-standardised rates based on the world standard population were also calculated. Since no appreciable change in trends or geographical comparisons emerged, only the estimates based on Italian population were shown. Ninety-five percent confidence intervals (CI) of IRs were computed according to the Poisson distribution.<sup>19</sup> The annual percent change was then computed from a log-linear regression model.

To perform age-period-cohort (APC) analysis, cases were grouped by gender into 5-year age groups at diagnosis, between the limits of 30 and 79 years (42 cases below age 30 were excluded). The periods 1988–1992,<sup>17</sup> 1993–1997,<sup>1</sup> and 1998–2002<sup>18</sup> were considered, and a set of 10-year approximate birth cohorts was estimated by subtracting the midpoint of the 5-year age group from the corresponding 5-year period. For example, the earliest possible cohort (central year 1913) related to individuals aged 75–79 diagnosed with cancer in 1988–1992: they could have been born in any of the ten years from 1908 to 1917.

A formal statistical examination was then conducted by fitting the age-period-cohort model<sup>20</sup> to establish whether trends were better described by period effects (secular changes in risk), by changes in birth-cohort effects (subsequent generations), or both.

A sequence of models was fitted starting with the one-factor age model, proceeding with the two-factor age-drift, age-period and age-cohort models, and finally to the full three-factor APC model, testing the statistical significance of the term added at each step. The best-fitting model was defined as the one minimising the Akaike Information Criterion.<sup>21</sup>

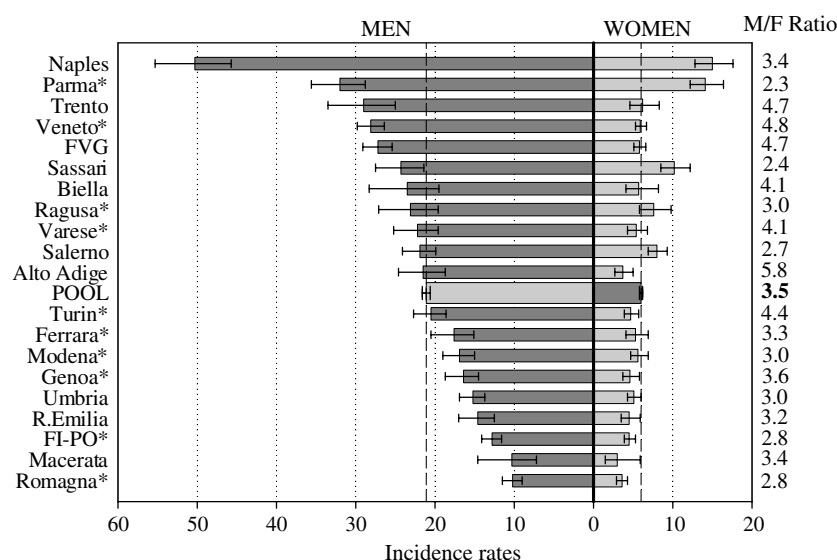
Since there is a controversy on different APC models,<sup>22</sup> we use the simplest model in which, to avoid the non-identifiability problem, the effect for cohorts centred in 1928 and 1933, showing similar pattern, was set equal.

**Table 1 – Observed cases and standardised incidence rates of primary liver cancer by sex and period in 20 Italian Cancer Registries (CRs), 1988–2002**

Cancer Registry	Complete period	Population (all ages × 1000)	Men				Women			
			Cases	Incidence rates			Cases	Incidence rates		
				1988–1992	1993–1997	1998–2002		1988–1992	1993–1997	1998–2002
Alto Adige	1995–2002	460	357	–	25.7	21.5	75	–	4.2	3.7
Biella	1995–2002	189	183	–	18.7	23.5	67	–	5.7	5.7
Ferrara <sup>b</sup>	1991–2002	353	381	12.4	14.1	17.6	171	3.7	5.5	5.3
Florence-Prato <sup>b</sup>	1988–2002	1161	1289	14.0	15.3	12.8	556	4.8	4.8	4.5
Friuli Venezia Giulia	1995–2002	1188	1388	–	28.2	27.2	386	–	5.2	5.8
Genoa <sup>b</sup>	1988–2000	834	1053	17.0	18.0	16.4	418	4.9	5.4	4.6
Macerata	1991–1999	293	172	11.2	12.9	10.3	69	5.2	4.0	3.0
Modena <sup>b</sup>	1988–2002	615	766	15.7	15.6	16.9	322	4.7	5.8	5.6
Naples	1996–2002	541	609	–	48.7	50.3	218	–	14.4	15.0
Parma <sup>b</sup>	1988–2002	395	940	20.5	33.2	32.0	436	7.3	9.9	14.1
Ragusa <sup>b</sup>	1988–2002	292	370	14.4	19.2	23.1	129	4.5	4.4	7.6
Reggio Emilia	1996–2002	450	241	–	13.9	14.6	96	–	5.0	4.5
Romagna <sup>b</sup>	1988–2002	853	733	9.9	11.5	10.2	278	2.6	3.5	3.6
Salerno	1996–2001	1088	631	–	22.1	21.9	274	–	7.7	8.0
Sassari	1992–2002	469	508	19.9	23.5	24.3	246	13.2	8.0	10.2
Turin <sup>b</sup>	1988–2001	942	1143	13.3	18.4	20.5	389	3.5	5.1	4.7
Trento	1995–2000	460	369	–	29.2	29.0	100	–	5.9	6.2
Umbria	1994–2002	831	677	–	16.8	15.2	271	–	5.0	5.1
Varese <sup>b</sup>	1988–2000	803	986	20.6	23.5	22.2	273	4.6	4.1	5.4
Veneto <sup>b</sup>	1988–2001	1912	3431	27.2	28.6	28.1	1095	6.2	7.5	5.9
Pool (All CRs)		14,129	16,227	17.7	20.8	21.1	5869	4.9	5.7	6.0
Pool (CRs with 12 year)		8160	11,092	17.8	20.0	19.3	4067	4.9	5.6	5.6

a Truncated (0–79 years) and age-standardised on Italian population 1991, per 100,000.

b Cancer Registries with at least 12 registration years.



**Fig. 1** – Incidence rates age-standardised on Italian Population 1991, per 100,000) and male-to-female (M/F) ratio of primary liver cancer in 20 Italian Cancer Registries (CR). Ages 0–79 years, 1998–2002 (bars represent 95% confidence intervals, dashed lines represent pooled IRs). \*Cancer Registries with at least 12 registration years. FVG = Friuli Venezia Giulia; FI-PO = Florence-Prato.

### 3. Results

Between 1988 and 2002, 16,227 male cases and 5869 female cases of PLC were reported in Italy below the age of 80 years. The age distribution of PLC was similar for men and women, only 1940 cases (8.8%) occurred in people below age 55 years and the median age at diagnosis was 67 years in men and 71 years in women.

Table 1 shows a number of cases reported in the complete period and IR by sex and period in 20 CRs. The 10 CRs that had provided data (15,159 PLC) for at least 12 years showed no clear trend in PLC incidence. PLC IRs in men slightly increased between 1988–1992 period (IR = 17.8/100,000) and 1993–1997 (20.0/100,000) but did not substantially change thereafter (19.3/100,000 in 1998–2002). In women, the same pattern emerged with IRs between 4.9 and 5.6/100,000 throughout the considered period. Considering annual IRs, the annual change between 1988 and 2002 was 0.8% in men (95% CI: –0.5% to 2.1%) and 1.1% in women (95% CI: 0.2–2.1%).

Fig. 1 shows PLC IR for all 20 CRs in the more recent 5-year period (i.e. 1998–2002). Pooled IRs were 21.1/100,000 men and 6.0/100,000 women but IRs ranged in men between 10.2/100,000 men in Romagna and 50.3/100,000 in Naples. In women, IRs varied between 3.0 in Macerata and 15.0 in Naples. Male-to-female ratio was 3.5 overall as in most of the CRs but it was higher (>4) in northern Italian CRs (i.e. Alto Adige, Biella, Friuli Venezia Giulia, Trento, Turin, Varese and Veneto).

Fig. 2 shows the geographical distribution of CRs and the corresponding IRs in men and women. In men, IRs statistically higher than pooled estimates emerged in Northeastern and southern CR, whilst lower IRs emerged in central Italy. In women, IRs were higher in southern but lower in central Italy.

The relative contribution of age, cohort of birth and period to IRs of PLC is shown in Table 2. A statistically significant

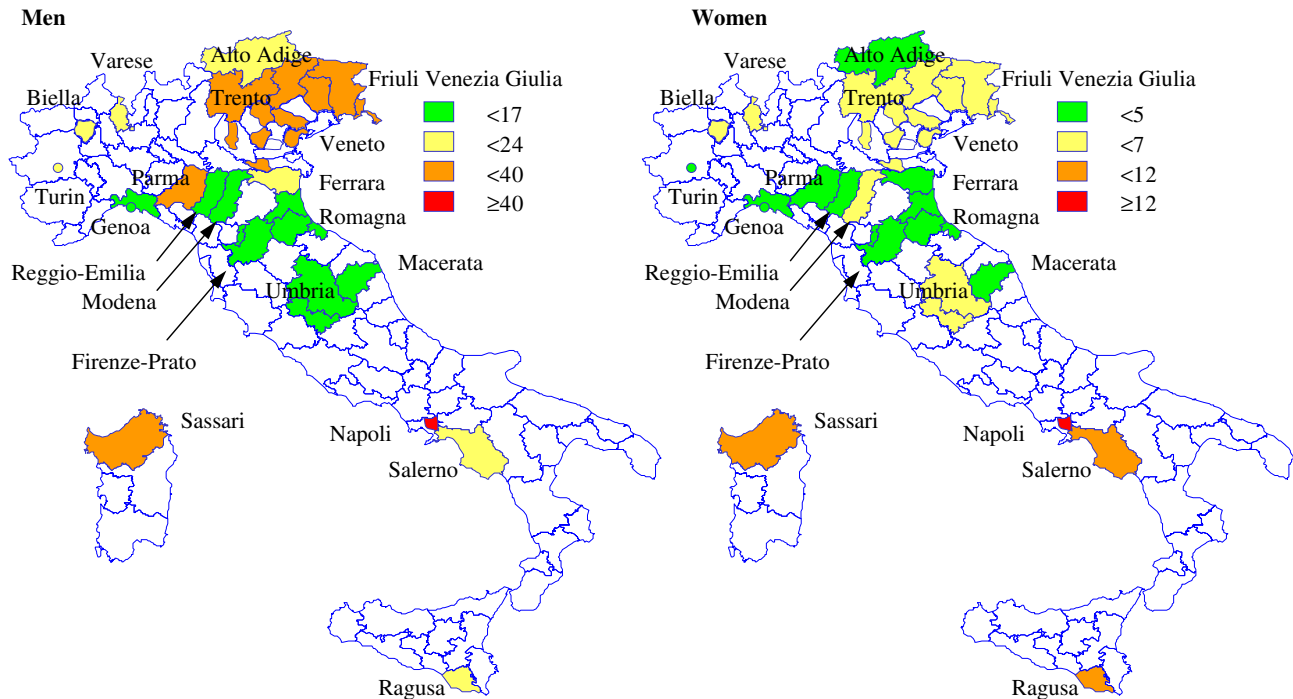
‘improvement’ emerged, both in men and women, using a full-term APC model, compared to age-cohort or age-period models. These results suggest an independent effect of the three terms on IRs, in the Italian population.

Age-specific IR of PLC was similar throughout the periods of diagnosis (Fig. 3). Conversely, cohort analyses suggested upward trends in men born after 1943. The pattern in women is similar but difficult to interpret because of random variation (e.g. estimates for the last two age-groups were based on less than 20 cases in 1988–2002).

The estimates of relative contribution of age-, birth-cohort- and period-effect by the full-term APC model are shown in Fig. 4. Amongst males, cohort effects were slightly upwards starting with the first generation considered (born around 1913). A steeper increase was seen for the cohorts born between 1948 and 1963; a plateau emerged thereafter. Amongst women, no appreciable cohort effect was seen until the cohort born in 1953, when an upward effect was noticed. Period-effect suggested a small decline between 1993–1997 and 1998–2002 in both genders (Fig. 4).

### 4. Discussion

Our study shows (1) the most up-to-date picture of PLC incidence in 20 CRs in Italy; (2) an assessment of PLC incidence trends from the 10 oldest CRs in the country using APC analysis. Several CRs in Italy had some of the highest incidence rates of all Europe.<sup>1</sup> In Naples, the IRs for PLC (age 0–79, world standardised 29.5 and 8.3/100,000 in men and women, respectively) approached those found in highest risk areas of Asia.<sup>1</sup> More than 2-fold differences in PLC incidence were seen in both genders between nearby areas such as Naples and Salerno in southern Italy or Parma and Reggio Emilia in central Italy. The reasons of such huge variations in PLC IRs at a local level in Italy are only partially understood



**Fig. 2 – Geographical distribution of age-standardised incidence rates age-standardised on Italian Population 1991, per 100,000 of primary liver cancer in 20 Italian Cancer Registries (CR) by sex. Age 0–79 years, 1998–2002 (categories were chosen as follows: the first (in green) represents IRs statistically below the pooled estimates; the second (in yellow), IRs not statistically different from the pooled estimates; the third (in orange), IR statistically higher than the pooled IRs but less than 2-fold higher; finally, the last categories (in red) represent IRs more than 2-fold higher compared to the pooled estimates).**

**Table 2 – Comparison of age–period–cohort models of primary liver cancer incidence in Italian Cancer Registries<sup>a</sup> by sex, 1988–2002**

Sex	Terms in model	Degrees of freedom	Deviance	AIC <sup>b</sup>	Models to compare	Deviance difference	Degrees of freedom	P value <sup>c</sup>
Men	Age (A)	20	56.5	–118,903				
	Age–drift (Ad)	19	45.4	–118,912	Ad versus A	11.1	1	<0.001
	Age–period (AP)	18	30.8	–118,925	AP versus A	25.7	2	<0.001
	Age–cohort (AC)	9	18.5	–118,919	AC versus A	38.0	11	<0.001
	Age–period–cohort (APC)	8	6.4	–118,929	APC versus AP	24.4	10	0.007
					APC versus AC	12.1	1	<0.001
Women	Age (A)	20	43.1	–36,840				
	Age–drift (Ad)	19	29.8	–36,851	Ad versus A	13.3	1	<0.001
	Age–period (AP)	18	23.0	–36,856	AP versus A	20.1	2	<0.001
	Age–cohort (AC)	9	9.1	–36,852	AC versus A	34.0	11	<0.001
	Age–period–cohort (APC)	8	3.6	–36,855	APC versus AP	19.4	10	0.035
					APC versus AC	5.5	1	0.019

a Cancer Registries with at least 12 registration years.

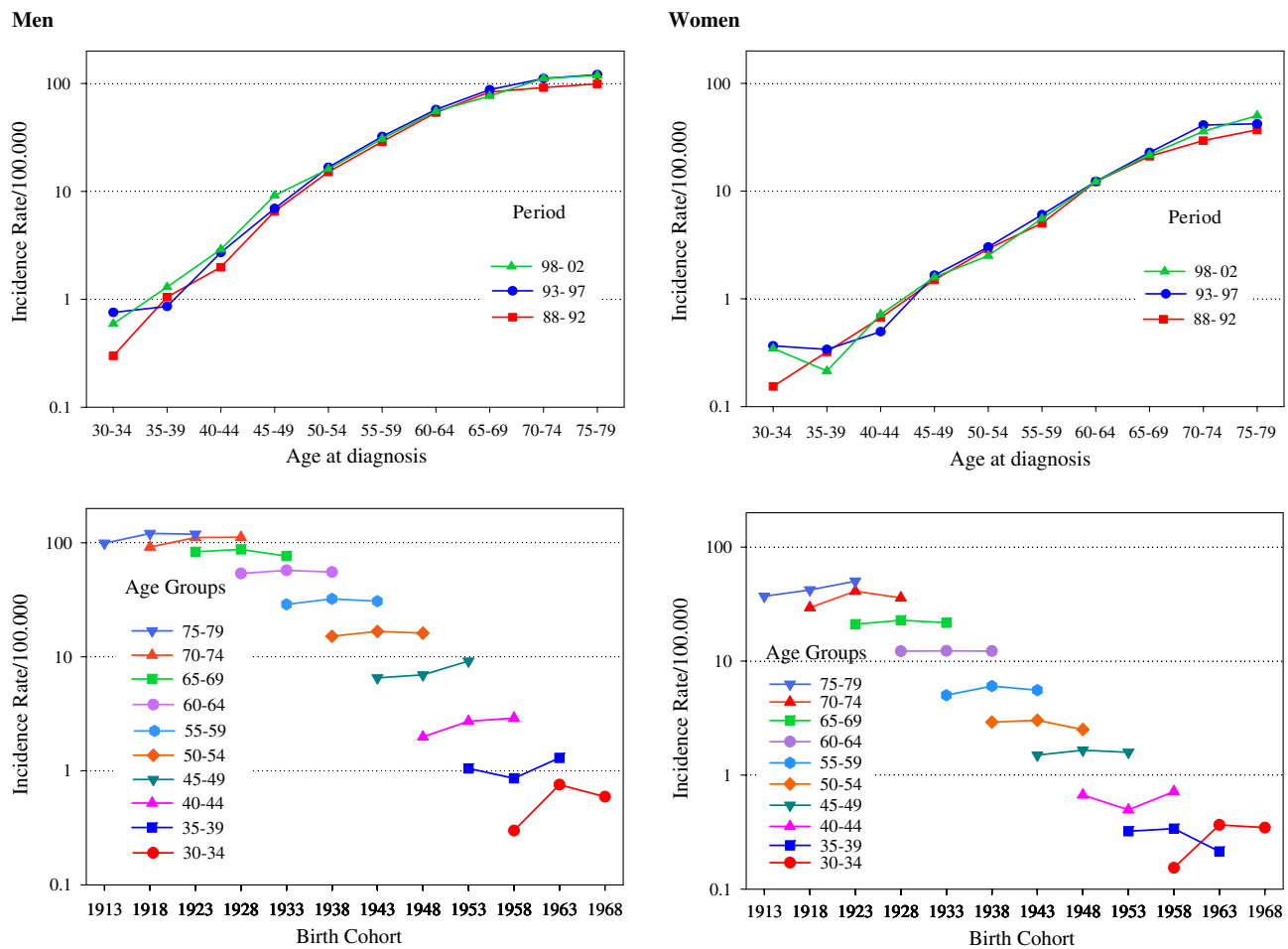
b AIC, Akaike Information Criterion was used as a qualitative measure of model goodness-of-fit that accommodates for differences in model complexity, with lower values indicating better fit.

c P-values based on  $\chi^2$  test refer to comparison between two models.

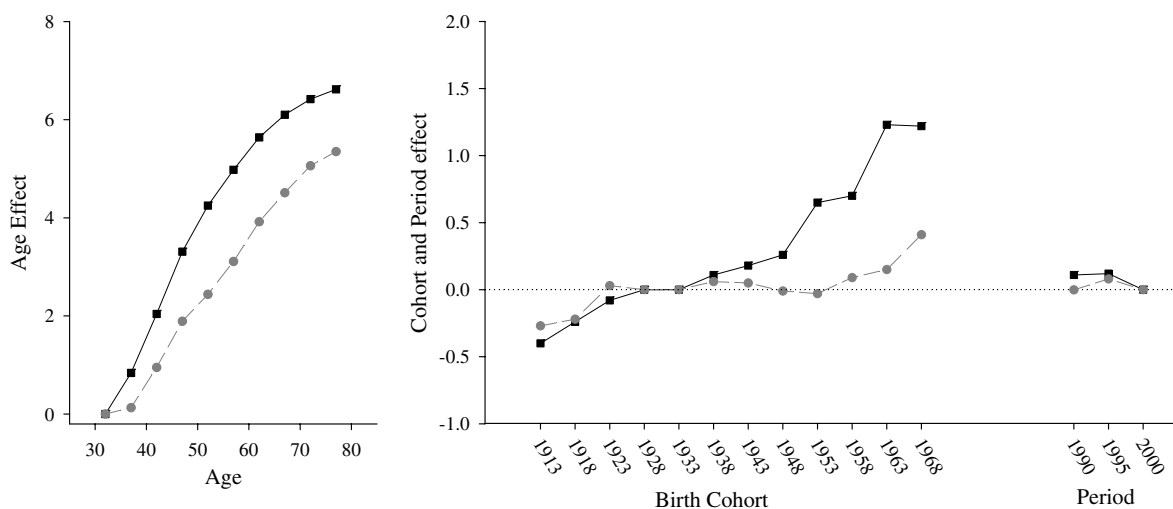
but are consistent with comparisons of mortality rates of PLC in Italy.<sup>23</sup>

Over two-third of PLC in Italy are attributable to HCV<sup>9,11</sup> and therefore, the incidence of this tumour chiefly reflects the prevalence of HCV infection three or four decades earlier. Population representative surveys of HCV in Italy are rare and mostly based on small groups.<sup>24–26</sup> However, a large nation-

wide hospital-based survey<sup>12</sup> has showed that in 1996–1997, HCV seroprevalence ranged from 1.6% in the North to 7.3% in the South, with central Italian regions showing intermediate values (6.1%). Most interestingly, the age-specific curve of HCV seroprevalence (Fig. 5)<sup>12</sup> shows that in the North, HCV prevalence did not vary greatly by age, and the highest value is found amongst adults aged 35–40 years. By contrast, in the



**Fig. 3** – Age-specific and cohort-specific incidence rates of primary liver cancer in Italian Cancer Registries (Cancer Registries with at least 12 registration years) by sex, period of diagnosis and age groups.

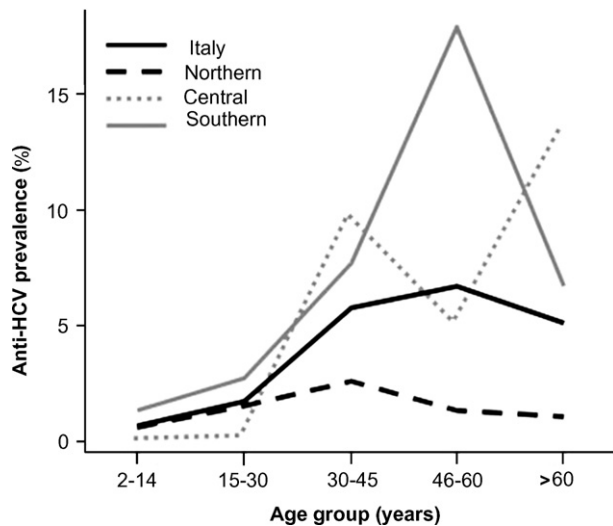


**Fig. 4** – Age, period and cohort (APC) effects on primary liver cancer incidence in Italian Cancer Registries (Cancer Registries with at least 12 registration years) estimated by an APC model (cohort effect in 1928 was set equal to the cohort effect in 1933 (men ■–■; women ●–●)).

South, HCV seroprevalence steeply rose with age, outgrowing 15% in the age group 46–60 years. These findings point to the

two periods of intense HCV transmission in Italy. The first was attributable to iatrogenic transmission before the intro-





**Fig. 5 – Anti-hepatitis C virus (HCV) prevalence in northern, central and southern Italy according to the age group (Wiley-Liss, 2005 – Reprinted with permission of Wiley-Liss, a subsidiary of John Wiley & Sons, Inc.<sup>12</sup>).**

duction of disposable syringes (1975) and routine screening for HCV infection in blood products and blood transfusions (1988).<sup>12</sup> Iatrogenic transmission, especially in the 1940s and 1950s, involved the South of Italy much more than the North. Intravenous drug use in the 1970s and 1980s was at the heart of the second period of HCV spread,<sup>12</sup> and was more frequent amongst men than women, and in the North than in the South of Italy, as was also shown by the pattern of the HIV epidemic.<sup>27</sup>

The current picture of PLC incidence is dominated by cancer cases diagnosed in middle-aged or older individuals. Therefore, it chiefly reflects the different impact of the iatrogenic spread of HCV infection in various parts of the country many decades ago. Conversely, incidence trends are nearly exclusively based on North Italian areas, where HCV transmission through intravenous drug use predominated, and it was mainly responsible for the upsurge of PLC incidence in male cohorts born after the late 1940s.

Altogether, the PLC incidence pattern herein described suggests that in Italy, such cancer will continue to increase in the next two or three decades in the cohorts born between 1948 and 1963. Conversely, the North-South gradient should be attenuated by the gradual depletion of the large pool of old individuals iatrogenically infected with HCV in the South.

The beneficial effect of the vaccine against HBV, whose seroprevalence showed a North-South gradient similar to HCV,<sup>16</sup> of children born as from 1978 are still to be seen. Finally, the reduction in alcohol consumption that has been taking place in Italy since the 1970s has already reduced mortality from cirrhosis<sup>28</sup> and should also have a beneficial effect on PLC incidence.

Lack of information on cancer incidence from large parts of southern Italy represents the main limitation of the present study. The misclassification of secondary liver cancer as PLC is a major problem in studies of cancer mortality<sup>3</sup> while

it should be a less severe drawback in studies of cancer incidence. Histological confirmation in Italian Cancer Registries is reported in only 58% of PLC, but imaging techniques (e.g. ultrasound, multiphasic computed tomography scan, magnetic resonance imaging or angiography) and measurement of serum tumour  $\alpha$ -fetoprotein is consistently performed.<sup>29</sup> To further reduce misclassification, we excluded individuals aged 80 years or older from our present report.

Age-period-cohort models provide a good framework for understanding future cancer trends<sup>30</sup> but caution in their interpretation is required, particularly for findings in the younger age cohorts, where the number of cancers observed is typically small.

In conclusion, our findings from Italy suggest a slight increase of IRs of PLC between 1988 and 1997 followed by a flattening, but southern Italy contributed little to the evaluation of trends. Major steps in the prevention of new HBV and HCV infections have been taken in developed countries and should be extended to increasingly numerous immigrants from countries highly endemic for the two viruses. The same holds true for the prevention of heavy alcohol drinking. As part of secondary prevention, HCV-infected individuals should be counselled to minimise their risk of transmitting HCV and referred for medical evaluation and antiretroviral considerations.<sup>31</sup>

### Conflict of interest statement

None declared.

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