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Declining rates of hepatocellular carcinoma in urban Shanghai: incidence trends in 1976–2005

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Abstract In China, hepatocellular carcinoma (HCC) incidence rates in several registry catchment populations are amongst the highest worldwide. The incidence rates in urban Shanghai were analyzed between 1976 and 2005 to describe and interpret the time trends. Age-specific and age-standardized rates were calculated and graphically presented. An age-period-cohort model was fitted to assess the effects of age at diagnosis, calendar period, and birth cohort on the changing HCC incidence rates. In total, 35,241 and 13,931 men and women were diagnosed with HCC during 1976–2005 in urban Shanghai. The age-standardized incidence rates in urban Shanghai were 33.9 per 10^5 among men and 11.4 per 10^5 among women in 1976–1980, but decreased in both sexes to 25.8 per 10^5 and 8.5 per 10^5, respectively by 2001–2005. Accelerating rates in birth cohorts born in the early-1930s and decelerating rates circa 1945 were observed in both sexes, with further accelerations noted in the late-1950s (in women) and early-1960s (in men). Given the parameterization, increases in risk of HCC were seen in successive male and female generations between 1900 and 1935, followed by a further increase among successive cohorts born around 1960, with a reduction in risk in the most recent generations. The incidence rates of HCC in urban Shanghai from 1976 to 2005 have declined in both sexes, with the complex but similar patterns observed in successive generations suggestive of a shared changing prevalence in risk factors in men and women, with a role possibly for HBV interventions reducing risk of HCC in cohorts born after 1960.

Keywords Hepatocellular carcinoma · Incidence · Time Trend · Age-period-cohort analysis · Shanghai

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Background

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer mortality and is ranked seventh as a cause of cancer incidence worldwide, and age-standardized rates are elevated in Eastern Asia, South-Eastern Asia and Middle Africa [1]. In China, along with Japan and Korea, incidence rates in several registry catchment populations are amongst the highest worldwide [2, 3]. In urban Shanghai in 2007, HCC ranked as the third and seventh most common cause of cancer occurrence in men and women respectively [4].

Time trends of hepatocellular carcinoma incidence rates may in theory be attributed to ageing, characterized by changes in cumulative exposure to carcinogens over time (an age effect), changes occurring during specific calendar

periods irrespective of age (a period effect), or changes affecting persons born in specific or successive generations irrespective of age (a cohort effect). An age-period-cohort (APC) model was fitted to better understand the effects of the three factors on disease rates [5, 6]. Such models have been used to describe hepatocellular carcinoma mortality in Taiwan where the relative risk of dying from HCC in the period 2001–2005 was estimated to be approximately 40% higher compared to earlier periods in both sexes, and a strong birth cohort was implicated [7]. In Italy, an analysis of HCC incidence between 1988 and 2002 showed that a steep increase was seen for male cohorts born successively between 1948 and 1963 [8].

To interpret the incidence trends of HCC in urban Shanghai and provide possible insight into the etiology of HCC and the changing prevalence and distribution of risk factors in the population, we conducted an APC analysis of secular trends of incidence rates over the time period 1976–2005. We aimed to assess the contributions of age, period and cohort effects on the observed trends in the Shanghai population, and interpret the results on the basis of putative local explanatory factors.

Materials and methods

Introduction of cancer registration in Shanghai

Details of the Shanghai Cancer Registry have been reported elsewhere [2, 3, 11]. Briefly, Shanghai is situated at the outlet of the Yangtze River, covering a total area of 6,340.5 km^2 of which the urban area is about 289.4 km^2. It is administratively divided into 18 districts and one county, including nine urban districts. In 2009, the total population of the Shanghai Municipality was 19.2 million, with 14.0 million living in urban areas. The Shanghai Cancer Registry is one of largest population-based Cancer Registries in China. The cancer registration in Shanghai officially started in 1963 at the Shanghai Tumor Hospital which was affiliated to the Shanghai First Medical University. The Registry transferred to the Shanghai Center for Disease Control and Prevention in 2002, and predominantly has collected information on new cancer cases within the nine urban districts. As an associate member of the IACR, there are standard procedures at the Registry, with respect to data collection, processing and reporting. The data has been published in the last six volumes of *Cancer Incidence in Five Continents* (http://ci5.iarc.fr).

Population at risk

The registration area for this study covered the ten original urban districts of Shanghai, namely Huang Pu, Nan Shi, Lu Wan, Xu Hui, Chang Ning, Jing An, Pu Tuo, Zha Bei, Hong Kou and Yang Pu. The total population of urban areas at the end of each year during the period of 1976–2005 was provided by the Shanghai Municipal Bureau of Public Security. The mid-year population by sex was estimated based on the populations at the ends of two consecutive years and used as the annual average population, and a surrogate for the person-years at risk.

During the period of 1976–2005, there were eight national or local city censuses and information on the population in urban and rural areas was obtained. Based on these censuses, the population was estimated via linear interpolation and extrapolation for the remaining years [9]. The periods were divided into 5-year periods, 1976–, 1981–, …, 2001–2005, 5-year age groups (0–4, 5–9, …, 80–84, 85 and over) and stratified by sex. For the age-period-cohort analysis, we tabulated the data using the "Lexis diagram" to compute the risk time (person-years) in triangular subsets as that suggested by Carstensen [10].

Incident cases

According to the regulation issued by the Shanghai Municipal Bureau of Public Health, all medical facilities in Shanghai are responsible for notifying all newly-diagnosed cancer cases as well as benign tumors of the central nervous system to the Registry. A standardized notification card, which includes information on name, date of birth, sex, address, occupation, primary site of tumor, date and basis of cancer diagnosis was used for reporting cancer cases.

All patients who resided outside the catchment area were excluded from the Cancer Registry file. Information on cancer notification cards was computerized, using specifically-designed software in which Chinese characters are read directly. To ensure quality of the information notification cards were independently coded and registered into the cancer database by two persons. Cancer death cards were periodically checked with the cancer notification cards. Deceased cancer cases without notification cards, on confirmation of diagnosis through home visit of relatives or information from hospitals where the cases were diagnosed and treated, were additionally filed in the Registry as new cancer cases. Otherwise, the cards were coded as the death certificate only (DCO) cases. Notification cards with similar contents in terms of name, sex, date of birth, address and primary site of tumor (or some of these items) were printed out, examined by the Registry staff manually, and then deleted if they were duplicates [9]. In order to ensure validity of the data, the database for the HCC cases registered during 1976–2005 was reexamined to ensure elimination of any remaining duplicates.

Incident cases diagnosed registry 1976–2005 were extracted from the Shanghai Cancer Registry. The calendar periods of 1976–2001 and 2002–2005 were respectively collected by the Shanghai Cancer Institute and the Shanghai Center for Disease Control and Prevention. The *International Classification of Diseases, the ninth version* (ICD-9) was used to classify the registered incident HCC cases (Code 155). Table 1 shows the distribution of basis of diagnosis and means of confirmation for incident cases. Based on the diagnosis evidences recommended by IARC, we calculated the proportions of histological verification, cytological deduction or/and biochemical or/and immune assays, surgery or medical imaging (B ultrasound, X ray, CT, endoscope, etc.), clinical deduction and death certificate only for each period during 1976–2005.

Statistical analyses

Age-adjusted and truncated (35–64 years and 25–79 years) rates alongside cumulative incidence (from birth to 64 and 74 years) were estimated. The standard world population was used to directly standardize the incidence rates over each 5-year calendar period in order to monitor the secular trends of HCC among different populations [11]. The estimated annual percentage change (EAPC) was used to quantify the trends [12]. A regression line was fitted to the natural logarithm of the rates, i.e. $y = \alpha + \beta x + \varepsilon$, where $y = \ln$ (rate) and $x =$ calendar year, and the EAPC calculated as $100 \times (e^{\beta} - 1)$.

We used a Poisson regression model to examine the effects of age, period and cohort [10, 13]. The general form of an age-period-cohort model for rates, (a, p) at age a in period p for persons in cohort $c = p - a$, is:

$$\log[\lambda(a,p)] = f(a) + g(p) + h(c)$$

where the a, p and c represent the mean age, period and cohort, respectively for the observational units.

We restricted the APC analysis to those aged 25–79 because of too few cases in the younger and older age groups, as well as concerns with respect to the accuracy and completeness of the information in the latter age group. In implementing APC modeling, each variable is a factor with a corresponding parameter per single-year for age, period and cohort. Because of the higher resolution of age, period and cohort beyond the traditional 5-year age and period tabulation, their effects were modeled with parametric smooth functions. In the APC model, we incorporated restricted B-splines (natural splines) with seven parameters for the age, period and cohort terms to reduce random variation. The relevant sub-models were arranged into a sequence that provides relevant comparisons of drift, and non-linear period and cohort effects in an analysis of deviance [5]. We compared the difference of the deviance between these different models using the Chi-square test to examine for the significance of effects between the sub-models. Statistical significance was attributed to two-sided P values <0.05.

For the sake of allowing reconstruction of the fitted rates from the reported values and overcoming the identifiability problem, we chose to apply a parameterization method proposed by Carstensen [10]. We had an a priori assumption that cohort-effects were the main drivers of the changing

Table 1 Proportion (%) of diagnosis type for hepatocellular carcinoma incident cases in urban Shanghai, China (1976–2005)

Sex	Period	Diagnosis evidences				
		Histological verification	Cytological or biochemical or immune deduction	Surgery or medical imaging*	Clinical deduction	Death certificate
Male	1976–1980	10.3	0.2	44.1	6.7	38.7
	1981–1985	7.8	1.0	43.4	4.9	42.9
	1986–1990	12.1	7.4	48.9	9.7	21.9
	1991–1995	13.7	14.5	64.3	7.3	0.2
	1996–2000	15.2	15.0	65.8	4.0	0.0
	2001–2005	20.0	22.3	49.5	3.2	5.0
	Total	13.3	10.3	52.7	6.0	17.7
Female	1976–1980	10.1	0.4	32.0	5.4	52.1
	1981–1985	8.1	0.7	34.2	5.1	51.9
	1986–1990	12.2	5.6	45.5	9.5	27.2
	1991–1995	12.1	11.9	67.6	8.2	0.2
	1996–2000	11.5	11.1	71.3	5.9	0.2
	2001–2005	17.9	18.4	52.4	3.5	7.8
	Total	12.1	8.2	51.1	6.3	22.3

* Including B ultrasound, X-ray, CT, etc

rates, given that the whole population would be equally exposed to environmental risk factors and in the presumed absence of period-related trends including changing registry practices or screening interventions [14, 15]. Models were fitted sequentially. First, an age-cohort model was fitted, using the first birth cohort (1901–1905) as the reference cohort. Then the log of the fitted values from this model was used as offset variable in a model with a period-effect. The period effects from this model were then used as the residual log rate ratios by period. The drift parameter, which represented the linear trend not exclusively identifiable as a period or cohort effect, was extracted using the weighted average of the marginal number of cases.

The age function represents the log of the age-specific rates for the reference cohort (i.e. longitudinal age-specific rates). The cohort function is interpretable as the log-rate ratios relative to the reference cohort, while the period function represents the log-rate ratios relative to the age-cohort prediction (residual log-rate ratios). With this method, minor fluctuations tend to be void of interpretation, and we focus only on the major changes in the trends. All data were analyzed using the R (version 2.11.1) statistical software and the Epi (version1.1.17) package [16, 17].

Results

Incidence

In total, 49,172 patients were newly diagnosed with HCC between 1976 and 2005 in urban Shanghai, of which 71.7% were men and 28.3% were women. The 30-year crude incidence rates are presented in Table 2, which shows a slight increase in rates in both men and women generally. The age-adjusted standardized incidence rates have however decreased from 33.9 per 10^5 males in 1976–1980 to 24.7 per 10^5 males in 1991–1995 and then increased to 25.8 per 10^5 in 2001–2005. The female age-standardized incidence rate declined from 11.4 per 10^5 women in the first period to 8.5 per 10^5 women in the last period. The EAPC were −1.6% (95%CI: −1.8% to −1.4%) and −1.8% (95%CI: −2.0% to −1.6%) among men and women respectively, which suggested a slight decrease per annum in HCC incidence from 1976 to 2005. The truncated incidence rates in ages 35–64 years and the cumulative rates indicate similar decreasing trends amongst men and women. In the last three periods (1991–2005), there appears to be stabilization in the trends of HCC incidence in both men and women.

If we look at the observed rates, aggregated into 5-year periods, cohorts and age classes to produce fairly stable rates. A general gradient of higher HCC incidence rates with increasing age is observed throughout the analyzed periods and cohorts. There is some interaction between age and period or cohort, as indicated by the intersection of the rates in both males and females. Following increases in successive birth cohorts from 1901, a period of lesser increase or stability emerges in cohorts born up to the 1930s. Thereafter, there are increases observed in generations born up before 1956, followed by further declines in cohorts born in subsequent years. These observations are apparent in both men and women.

Table 2 The incidence rates of hepatocellular carcinoma (1976–2005, Shanghai, China)

Sex	Period	Cases	Age-adjusted rate (per 10^5)	Truncated rate (per 10^5)		Cumulative rate (%)		EAPC (%) (95% CI)
				35–64 years	25–79 years	0–64 years	0–74 years	
Male	1976–1980	5,483	33.9	71.8	62.9	2.4	3.9	−3.4 (−12.5 to 6.6)
	1981–1985	5,645	30.1	59.8	55.7	2.0	3.6	0.1 (−1.5 to 1.7)
	1986–1990	6,358	29.1	54.7	53.3	1.9	3.5	−0.7 (−3.8 to 2.5)
	1991–1995	5,919	24.7	46.4	44.8	1.6	2.9	−0.7 (−4.4 to 3.2)
	1996–2000	5,853	25.0	47.8	45.1	1.6	2.9	2.7 (−2.7 to 8.4)
	2001–2005	5,983	25.8	50.5	45.9	1.7	2.9	−3.6 (−9.0 to 2.0)
	Total	35,241	28.0	54.6	50.8	1.9	3.2	−1.6 (−1.8 to −1.4)
Female	1976–1980	1,992	11.4	18.8	20.5	0.7	1.4	−5.1 (−17.2 to 8.9)
	1981–1985	2,263	10.8	17.7	19.4	0.6	1.3	−0.7 (−2.9 to 1.5)
	1986–1990	2,541	10.1	15.3	18.1	0.6	1.2	−0.9 (−3.7 to 2.0)
	1991–1995	2,418	8.7	12.4	15.2	0.5	1.0	−1.1 (−4.5 to 2.4)
	1996–2000	2,341	8.4	12.2	14.2	0.4	1.0	−1.2 (−4.9 to 2.7)
	2001–2005	2,376	8.5	12.8	14.0	0.5	0.9	−2.4 (−11.5 to 7.8)
	Total	13,931	9.6	14.8	16.7	0.5	1.1	−1.8 (−2.0 to −1.6)

Table 3 Fitting of the age-period-cohort models for the hepatocellular carcinoma incidence in urban Shanghai (age groups of 25–29 to 75–79 years, 1976–2005)

Sex	Terms in model	Deviance	*df*	ΔDeviance	Δ*df*	*P* value
Male	Age	3,049.0	124	–	–	–
	Age-drift	2,867.5	123	181.4	1	<0.001
	Age-cohort	884.6	117	1,893.0	6	<0.001
	Age-period-cohort	845.6	111	39.0	6	<0.001
	Age-period	2,837.5	117	−1,991.9	−6	<0.001
	Age-drift	2,867.5	123	−30.0	−6	<0.001
Female	Age	7,674.4	123	–	–	–
	Age-drift	7,652.9	122	21.6	1	<0.001
	Age-cohort	6,926.9	116	726.0	6	<0.001
	Age-period-cohort	5,028.3	110	1,898.6	6	<0.001
	Age-period	5,741.1	116	−712.8	−6	<0.001
	Age-drift	7,652.9	122	−1,911.8	−6	<0.001

df degree of freedom

Age-period-cohort models

Table 3 provides a table of deviance of the sequential models to assess the goodness-of-fit of the models and the contribution of each of the effects to improving the fit. The age-drift model improved the fit over the age-only model significantly ($P < 0.001$), while both non-linear period and non-linear cohorts effects improved the fit, both unadjusted and adjusted for cohort and period, respectively.

Figures 1 and 2 display the rate ratios (RRs) in males and females respectively. From the age-effect curve, we can find a steady increase in slope up to the 65–69 years age groups before leveling off for older ages in males. Common to both sexes, was the observation of accelerating rates in birth cohorts born in the early-1930s then decelerating rates circa 1945, with further accelerations noted in the late 1950s (in women) and early-1960s (in men). Given the parameterization, there are thus increases in risk of HCC incidence in both sexes in successive generations between 1900 and 1935, a reduction thereafter (until towards the end of WWII), and a further increase among cohorts born around 1960, with a further reduction in risk seem among cohorts born thereafter. The period rate ratios remained close to one, given the assumption of a zero period slope although in women the non-linear period-effect was of greater magnitude.

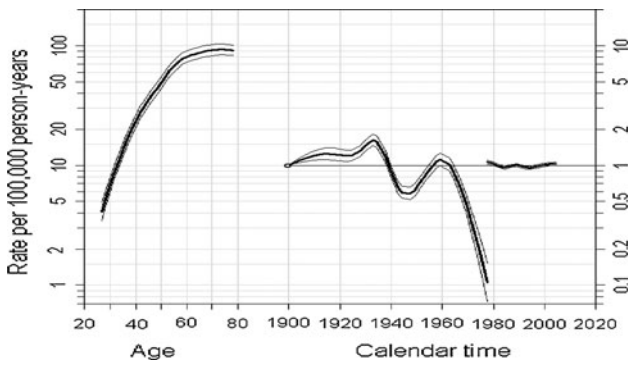

Fig. 1 Estimated effects from the age-period-cohort model in males (hepatocellular carcinoma, age group of 25–29 to 75–79 years, 1976–2005, Shanghai, China). The *left curve* shows the fitted age-specific rates for 10^5 person-years at risk during the reference cohort (1901–1905), the *middle curve* the rate ratios of cohorts relative to the reference cohort (1901–1905), and the *right curve* the rate ratios of period conditional on the estimated age and cohort effects. *Values* are plotted together with 95% confidence limits

Discussion

Studies of population-based trends of incidence and mortality rates for a particular disease can often provide us with hypotheses or clues regarding the underlying determinants. Our study suggested that the incidence of HCC in urban Shanghai have been decreasing for both men and women in past three decades, and this time trend could be predicted by both time period of diagnosis and birth cohort components. When we used different birth cohorts (i.e. first-, mid- and last-birth cohort) as references, the results remained consistent (data and results not shown). A similar trend of rates has been found in some other studies, e.g. in Italy. HCC incidence rates in men slightly increased between 1988–1992 and 1993–1997, but did not substantially change thereafter. In women, the same pattern emerged with rates between 4.9 and 5.6/100,000 throughout the considered period [8]. The incidence rates in Shanghai have remained higher than most European and American populations, as well as several Eastern Asian countries. The IARC *Cancer Incidence in Five Continents* Volume

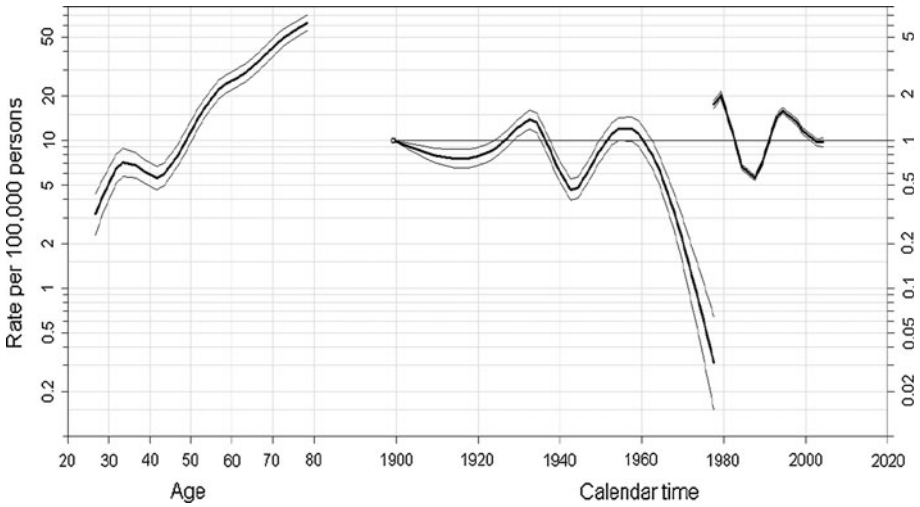

Fig. 2 Estimated effects from the age-period-cohort model in females (hepatocellular carcinoma, age group of 25–29 to 75–79 years, 1976–2005, Shanghai, China). The *left curve* shows the fitted age-specific rates for 10^5 person-years at risk during the reference cohort (1901–1905), the *middle curve* the rate ratios of cohorts relative to the reference cohort (1901–1905), and the *right curve* the rate ratios of period conditional on the estimated age and cohort effects. *Values* are plotted together with 95% confidence limits

IX reports that for most European countries, the rates of HCC during 1998–2002 were less than 5 per 10^5 and 2.5 per 10^5 in males and females respectively [2].

Our study found a decrease in risk of incidence in successive cohorts born from the 1950s to the 1980s. This might suggest that unknown exposures earlier in life may, in part, explain the birth cohort effect. Environmental risk factors of HCC include exposure to aflatoxin B1, alcohol consumption, smoking consumption, and unhealthy dietary intake, all of which may have partially contributed to the trends in HCC incidence observed in Shanghai [18, 19]. Another possible explanation for the decreased risk in later birth cohorts (after 1956–1960) may relate to public health efforts to stop HBV transmission. Measures to prevent HBV infection have focused on the avoidance of unsafe blood exposure. Serological screening of blood products began in the late 1970s and has quickly been applied by most blood centers in China. Routine strict serum HBsAg screening was introduced to all blood centers by the Chinese Ministry of Health in the early 1980's. The law for Donating Blood was issued in 1998 and enactment of Regulations for the Management of Blood in Clinical Facility enhanced safety of blood transfusion [20].

As is well-established many HCC cases are associated with either chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection [21]. Studies have showed that chronic carriers of hepatitis B surface antigen (HBsAg) were mostly infected during early childhood [22]. The rates of HBsAg carriers in the children of 0–5 years old have declined from 7.42% in 1980 to 1.10% in 1998 [23]. A large-scale HBV vaccination of newborns in Shanghai might bring a further drop of HBV infection in the future. In fact, 95% of the newborns in urban Shanghai had been inoculated with the HBV vaccine since the year of 1992 [24, 25]. In those persons infected with HBV or HCV whom develop hepatocellular carcinoma, there is a latency period of one to three decades [26]. Due to the aggressive vaccination program, we would expect to see decreased incidence in these children as they become adults about one to three decades later [7]. Thus, about 10–30 years of further follow-up are needed before this hypothesis can be directly tested. But based on a mathematical model of HBV transmission, suppose that all newborns can be vaccinated, the prevalence of HBV carriage will decline to 0.2% in 70 years [27]. This clues a long way to see the clear results of HCC prevention and control in China mainland.

As a whole, the period effect decreased during 1976–2005. Preventative measures have been implemented in Shanghai in recent decades from the period of 1970s in order to reduce the prevalence of key risk factors. These measures include attempts to reduce smoking consumption, and a focus on a balanced diet [24, 28]. In addition, government measures have been taken to ensure an improved water quality by purifying polluted water sources in the last 30 years. Other measures include screening for HCC cases in high-risk populations which began in 1981 [24, 28]. These programmers and measures are directed towards ensuring a better lifestyle, especially with regards to decreasing aflatoxin B1 exposure and detecting HCC at earlier stages. Wang et al. [29] reported the exposures of aflatoxin in dietary in rural residents was higher than urban residents. They also found that the results among urban residents was much lower than that in a study conducted at end of 1980s [30]. In addition, we found that the slopes of the female period-effect curve increased from the period of 1990s steadily. This may be attributable to the advancement on the HCC diagnostic standard (i.e. alpha-fetoprotein (AFP)) since the 1990s, which can increase the rates of HCC via early detection [31]. However, we found no obvious changes of period effect in males.

This study may fill a gap in long-term incidence analyses of HCC in China, providing a better understanding of

the effects of age, period and cohort. However, APC models do not test hypotheses about the effects of environmental or historical influences; instead, they organize data and provide useful mathematical formulae for summarizing disease rates over time [32]. APC analyses also have important limitations. First, the approach shares all the intrinsic limitations of standard descriptive analysis. Second, the identifiability problem limits the specificity of conclusions that can be derived from contrasts between the linear trends [33]. Given the much lower proportion of histological verification (about 13%) was really fewer than that in the study of other kinds of cancer (about 80%) in China [34]. The results from our analysis should be interpreted with caution although the combined proportion of "cytological deduction, biochemical and immune assays" and "surgery or/and medical imaging" was around 60% both in males and females during 1976–2005.

Although the trend of HCC incidence has been on the decline, the incidence rate in Shanghai remains one of the highest in global terms. As public health measures are taken to control HBV through vaccination, we may see a proportion of HCC cases due to HCV increase. Furthermore, as China develops and adopts a more western lifestyle we may see a greater role of noninfectious risk factors contributing to HCC incident patterns and trends. For instance, diabetes mellitus (DM), nonalcoholic steatohepatitis (NASH) and obesity need further investigation with more focus on examining the prospects for prevention of HCC in China, as well in those countries where rapidly-developing economies that has led to a lifestyle rapidly approaching those seen in many western countries [24, 35–39].

In summary, the decreasing trend of hepatocellular carcinoma incidence was observed for both men and women in urban Shanghai during the past 30 years, with the complex but similar patterns observed in successive generations perhaps indicating a changing prevalence in risk factors in both sexes, and a role for HBV interventions reducing risk of HCC in successive cohorts born after 1960. The high incidence (and poor prognosis) reiterates the importance of epidemiological studies in China to investigate and elucidate possible risk factors other than infection, alcohol consumption and cigarette smoking. The long-term impact of the implemented vaccination measures on rates of HCC incidence needs careful monitoring and evaluation.

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Conflict of interest None declared for all authors.

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