

SMOKING AND LIVER CANCER IN CHINA: CASE-CONTROL COMPARISON OF 36,000 LIVER CANCER DEATHS vs. 17,000 CIRRHOSIS DEATHS

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Liver cancer and liver cirrhosis are common causes of death in China, where chronic lifelong hepatitis B infection is a major cause of both diseases. To help determine whether smoking is a cofactor for the development of liver cancer, we ascertained retrospectively the smoking habits of 36,000 adults who had died from liver cancer (cases) and 17,000 who had died from cirrhosis (controls) in 24 Chinese cities and 74 rural counties. Calculations of the smoker vs. nonsmoker risk ratios (RR) for liver cancer mortality were standardised for age and locality. Among adult men (aged 35+) there was a 36% excess risk of death from liver cancer among smokers (smoker vs. nonsmoker standardised risk ratio [RR] = 1.36, with 95% confidence interval [CI] 1.29–1.43, $2p < 0.00001$; attributable fraction 18%). In the general male population this indicates absolute risks of death from liver cancer before age 70 of about 4% in smokers and 3% in nonsmokers (in the absence of other causes). Most liver cancer, however, occurs among the 10–12% of men with haematological evidence of chronic hepatitis B infection, so among them the corresponding risks would be about 33% in smokers and 25% in nonsmokers. The RR was approximately independent of age, was similar in urban and rural areas, was not significantly related to the age when smoking started but was significantly ($p < 0.001$) greater for cigarette smokers than for smokers of other forms of tobacco. Among men who smoked only cigarettes, the RR was significantly ($p < 0.001$ for trend) related to daily consumption, with a greater hazard among those who smoked 20/day (RR 1.50, 95% CI 1.39–1.62) than among those who smoked fewer (mean 10/day: RR = 1.32, 95% CI 1.23–1.41). Smoking was also associated with a significant excess of liver cancer death in women (RR 1.17, 95% CI 1.06–1.29, $2p = 0.003$; attributable fraction 3%), but fewer women (17%) than men (62%) were smokers, and their cigarette consumption per smoker was lower. Among women who smoked only cigarettes, there was a significantly greater hazard among those who smoked at least 20/day (mean 22/day: RR = 1.45, 95% CI 1.18–1.79) than among those who smoked fewer (mean 8/day: RR = 1.09, 95% CI 0.94–1.25). These associations indicate that tobacco is currently responsible for about 50,000 liver cancer deaths each year in China, chiefly among men with chronic HBV infection.

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Liver cancer is one of the most important types of cancer in China, causing some 250,000 male and 100,000 female deaths annually, mostly among middle-aged men.^{1–3} About 10–12% of Chinese adults are lifelong “antigenaemic carriers” of the hepatitis B virus (HBV), with persistent haematological evidence of chronic infection (*i.e.*, with the viral surface protein generally detectable in their blood).³ Most of these chronic carriers were infected by maternal-infant transmission in the perinatal period or by infection in early childhood. Once an individual becomes an antigenaemic carrier, chronic HBV replication in the liver generally continues indefinitely, causing, by middle age, a substantial risk of cirrhosis and, especially if there has also been prolonged exposure to certain chemical carcinogens, an even more substantial risk of liver cancer.^{4–6} The absolute risks vary widely from one part of China to another but at current nationwide death rates, more than a quarter of all male HBV carriers will die in middle age from liver cancer. The most important hepatic chemical carcinogen in China is probably dietary aflatoxin (or some other toxin from fungal contami-

nation of poorly stored foodstuffs).^{5,6} However, cigarette smoke is also a major source of carcinogens, some of which, after absorption into the bloodstream, will remain chemically inert until “metabolically activated” into a short-lived DNA-damaging form by partial oxidation in hepatocytes. Hence, cigarette smoking might increase still further the risk that an HBV carrier will develop liver cancer, and even a moderate increase in such a large absolute risk would be important.

Studies in “Western” populations in which liver cancer causes far fewer deaths than cirrhosis does have generally found smokers to have a moderate excess risk of both diseases.^{7–11} When, however, the International Agency for Research on Cancer¹² first reviewed the evidence on smoking and liver cancer, it was unable to decide whether the association was causal, since smoking is commonly associated with consumption of alcohol, and in those populations alcohol is a major correlate of cirrhotic liver damage that might appreciably increase the relative risk of liver cancer.^{8–13}

In China, the position is somewhat different since liver cancer causes far more deaths than cirrhosis does, and while smoking is common (at least among men) and is associated with alcohol consumption, cirrhotic liver damage is chiefly caused not by alcohol but by persistent lifelong HBV infection. In early adult life, such infection generally remains asymptomatic and is therefore unlikely to affect the initiation of tobacco use.^{14–18} Hence, it may be possible to assess any real effects of smoking on liver cancer particularly reliably in China. We report here the findings of a large retrospective study of smoking and death from liver cancer in many parts of urban and rural China, in which, to avoid any possibility of positive confounding by causes of cirrhosis, deaths from cirrhosis in the same localities were used as controls.

METHODS

Cases and controls

Details of the study design, field survey methods and participants have been described elsewhere.¹⁹ Briefly, 24 major cities and 74 rural counties were chosen for a large national study of smoking and mortality in China, involving retrospective ascertainment of the smoking habits and the causes of death of about 1,000,000 individuals who had died in 1986–1988. The cities were selected nonrandomly to include a wide geographical spread, whereas the

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counties were chosen by stratified random sampling to represent the full range of county-specific mortality rates for the 7 most prevalent cancers (including liver cancer) in the 2,000-odd counties of rural China.¹ (There is great variation between different parts of China in the standardised mortality rates from liver cancer, perhaps chiefly due to geographic variation in previous levels of exposure to dietary carcinogens.³) In each area, all those who died during 1986–1988 were to be identified from local administrative record, and medical causes were to be assigned to those deaths (see below). Information on the smoking habits of each adult who had died was sought by a trained research team through interviewing the surviving spouse or another family member (or sometimes, in rural areas, other local informants), using a short structured questionnaire. The information sought on smoking habits included types of tobacco (cigarette or other), amount smoked, age at starting smoking and age at stopping. This was used to determine whether people had ever smoked by 1980, that is, before there was much chance of their smoking habits being changed by the disease that eventually caused death during 1986–1988. Information was also sought from informants about their own smoking habits. Smokers were defined as those who, by 1980, had smoked on most days for at least 6 months. The main analyses are of those aged 35 years or more when they died, and hence at least in their late twenties in 1980; among Chinese men older than this, about 3/4 of all persistent smokers had started by age 25.¹⁹

Causes of death were sought chiefly from official death certificates, supplemented, if necessary, by review of medical records, or by discussion (a few years after the death) with local health workers, family members or both. The underlying cause of each death was coded centrally by trained nosologists at 5 designated centres using the World Health Organization International Classification of Diseases, 9th revision (ICD-9). Among the dead whose smoking habits were ascertained retrospectively, a total of 26,294 males and 9,642 females had died of liver cancer (ICD-9 155) at ages 35 or more, accounting for 20% of the total cancer deaths at these ages in males and 12% in females, and a further 11,321 men and 5,619 women had died of liver cirrhosis (ICD-9 571) in the same age range.

In the present study, individuals of the same sex and age who died of liver cirrhosis during the same period in the same county or city district were used as controls for assessment of the effects of smoking on liver cancer. The strengths and limitations of such comparisons have been described previously:¹⁹ one particular strength is that any bias affecting assessment of smoking habits in the cases should similarly affect assessment of smoking habits in the control group. Hence, differences between the recorded proportions of smokers in cases and in controls can be used to calculate the odds ratio (smoker *vs.* nonsmoker), comparing liver cancer deaths *vs.* cirrhosis deaths (and hence against the general HBV-infected Chinese population: see below). The excess of liver cancer deaths among smokers is then inferred from the excess prevalence of smoking among those who died of liver cancer (compared to the prevalence among the controls). No information was collected in the study about alcohol consumption, but the use of liver cirrhosis deaths as a control group would have the advantage of limiting or avoiding any potential confounding with the

effects not only of HBV but also of any lesser causes of chronic liver disease in this population.

Validation of the control group

As the comparison is of liver cancer deaths *vs.* cirrhosis deaths, the risk ratio that is calculated actually compares the risk ratio (smoker *vs.* nonsmoker) for liver cancer *vs.* the risk ratio (smoker *vs.* nonsmoker) for cirrhosis in this population.¹⁹ This comparison assumes that individuals in the control group had in 1980 had smoking habits that were at least approximately similar to those of the general population. Some direct confirmation of this is provided by the self-described smoking habits of the 220,000 informants who had been married to those who had died (of any cause) in 1986–1988. In our study, informants were asked to describe their own smoking habits as well as those of the dead person. The prevalences of smoking before 1980 among the 70,000 male and 150,000 female informants who were aged 35–69 when their spouses died (standardised to the age and urban/rural proportions of the liver cirrhosis control group) were 61.5% and 14.8% respectively, which were similar to those of 62.3% and 14.9% among men and women aged 35–69 in that control group. Although this comparison is of the self-described habits of the informants and the proxy-described habits of those who died of cirrhosis, it does provide some reassurance that in this population smoking is at most only weakly related to cirrhosis, and hence helps validate the main case-control comparison of liver cancer deaths *vs.* cirrhosis deaths.

Statistical methods

Standard analytical methods for an unmatched case-control study were used to calculate the Observed minus Expected number of smokers among the cases ($O - E$), its variance V , the risk ratio ($\exp[(O - E)/V]$) and its 95% confidence intervals $\{\exp[(O - E)/V \pm 1.96/\sqrt{V}]\}$, as well as for the appropriate graphical presentation of the results.^{20–22} The analyses were performed separately for males and females and were stratified by 5-year age group and by locality (*i.e.*, by county or city district of residence). Since the study sought to cover the whole population in a specific locality for a period of up to 3 years, the absolute liver cancer death rates for nonsmokers and smokers in a particular population can be calculated from the liver cancer death rate for the whole of that population (M , calculated with appropriate adjustment for incompleteness of coverage¹⁹), the smoker:nonsmoker death rate ratio (RR) and the prevalence of smoking in the control group, giving death rates of $M/(1 + (RR - 1) \times \text{prevalence})$ for nonsmokers and of RR times this for smokers. Two-sided p values were used for all main analyses except for the trend test of the effects by types and amount of tobacco smoked, in which 1-sided P values were used.

RESULTS

Table I shows the number of smokers and nonsmokers among liver cancer cases and among controls, and the smoker *vs.* nonsmoker liver cancer death rate ratio (RR). The proportion of people who had ever smoked was greater in cases than in controls both for men and for women, indicating an increased risk of liver cancer

TABLE I – SMOKING AND LIVER CANCER DEATH IN CHINA, 1986–1988, AT AGES 35 AND OVER: NUMBER OF CASES AND OF CONTROLS WHO HAD, BY 1980, EVER SMOKED OR NEVER SMOKED, AND STANDARDIZED LIVER CANCER DEATH RATE RATIO (SMOKER *VS.* NONSMOKER)

Sex	Liver cancer deaths (cases)		Liver cirrhosis deaths (controls)		Liver cancer death rate ratio (95% CI)	Percent liver cancer attributed to smoking ¹
	Ever	Never	Ever	Never		
Male	17847	8447	6969	4352	1.36 (1.29–1.43)	18%
	(68%)	(32%)	(62%)	(38%)		
Female	1766	7876	937	4682	1.17 (1.06–1.29)	3%
	(18%)	(82%)	(17%)	(83%)		

¹These attributable percentages relate to the cases in this study, of which 63% were urban. The attributable percentages for all China, in which only 30% of population is urban, would be 19% for men and 2% for women.

death among smokers. Overall there was a highly significant excess risk of mortality from liver cancer among males (RR 1.36; 95% CI 1.29–1.43; $2p < 0.00001$) and a significant excess among females (RR 1.17; 95% CI 1.06–1.29; $2p = 0.003$). Among males, the RR for smokers was highly significant both in urban areas (1.35, 95% CI 1.27–1.44) and in rural areas (1.39, 95% CI 1.27–1.52; Table II). Among females, the smoker vs. nonsmoker RR was statistically significant only in urban areas. However, the heterogeneity between the RR for urban females (1.24, 95% CI 1.10–1.40) and that for rural females (1.00, 95% CI 0.83–1.21) was not conventionally significant ($2p > 0.1$), so the lack of apparent hazard among rural females may be due partly to the play of chance (the upper 95% confidence limit for the rural RR is 1.21) and partly to the relatively low cigarette consumption per smoker among women in rural areas.

Effects among men by categories of diagnostic criteria for liver cancer

In Table II the smoker vs. nonsmoker liver cancer death rate ratio is shown for 3 broad categories of diagnostic criteria for liver cancer among men aged 35–69. Only 1/4 of the cases were confirmed by pathology (26% urban, 15% rural), and almost all of the other cases were diagnosed by ultrasound, by X-ray or by alpha-fetoprotein (AFP) assay. If, however, no other primary cancer was detected, most of these diagnoses are likely to have been correct despite the lack of pathological confirmation, as liver cancer accounts for such a large proportion (about 1/4, in middle aged men) of all cancer deaths in China.¹⁹ Perhaps because of this, the apparent effects of smoking on liver cancer mortality were of comparable magnitude for those whose liver cancer was diagnosed pathologically and for those whose liver cancer was diagnosed in other ways (Table II). The RRs in Table II involve comparison of each particular diagnostic category of liver cancer with the same group of controls (*i.e.*, with all deaths ascribed to cirrhosis). Exclusion from the controls of that minority in whom the attribution of death to cirrhosis did not involve any instrumental or laboratory tests left the RR values in Table II almost unchanged.

Among females, the overall standard of diagnosis for liver cancer was similar to that among males in both urban and rural areas, and again no apparent differences in the smoker vs. nonsmoker death rate ratios at ages 35–69 were seen between the 3 different categories of diagnostic criteria (data not shown).

Absolute rates in male smokers and nonsmokers

The age standardised death rate at ages 35–69 from liver cancer for the whole population of each geographical area (irrespective of whether the smoking habits were ascertained, which, in most cases, they were) is estimated by assuming that, at these ages, some 90% of liver cancer deaths would have been registered as such.¹⁹ This local liver cancer death rate, combined with the local prevalence of smoking (in the control group) and the local smoker vs. nonsmoker liver cancer death rate ratio, can be used to calculate the local age-standardised liver cancer death rates for smokers and for nonsmokers separately. These are plotted against each other in Figure 1 for men aged 35–69 years. For statistical stability, cities with fewer than 500 liver cancer deaths during the study period are grouped together as “other urban”. Rural counties each involve

even smaller numbers of such deaths (typically only about 100–200 per county), so they were combined into 2 groups: low risk rural and high risk rural. The high risk rural counties were, by definition, those with a cumulative death rate at ages 0–59 from liver cancer and cirrhosis combined of at least 40 per 1,000 (*i.e.*, with at least a 4% risk of death from liver disease before age 60, in the absence of other causes of death). These high-risk rural counties were mainly in the southern or eastern coastal provinces. Among nonsmokers there is a 4-fold variation in the male liver cancer death rates per 1,000 at ages 35–69 between these major study areas, from 0.3/1,000 (corresponding to a 1% risk of death from liver cancer at ages 35–69) in Beijing to 1.2/1,000 (corresponding to a 4% risk) in Fuzhou and in the group of high-risk rural counties. In each study area in Figure 1, however, the liver cancer rate was higher in smokers than in nonsmokers. For nonsmokers and smokers, respectively, the male liver cancer mortality rates per 1,000 at ages 35–69 were 0.68 and 0.91 in urban areas, 0.68 and 0.88 in low-risk rural areas and 1.20 and 1.77 in high-risk rural areas. For all China, with 30:70 mixture of urban and rural adults,¹⁹ the mortality rates per 1,000 for nonsmokers and smokers were 0.90 and 1.22, respectively, at ages 35–69, corresponding to risks of death from liver cancer at these ages of 3% for nonsmokers and 4% for smokers. If this excess is causal, then at 1986–1988 death rates, about 1/4 of liver cancer deaths among smokers could be attributed to the habit, and about 1% of all male smokers would die before age 70 from tobacco-induced liver cancer. In most parts of China, however, liver cancer is largely restricted to the 10–12% of adults who are chronically infected with the hepatitis B virus, among whom the risks of death from liver cancer before age 70 must therefore be about 25% for nonsmokers and 33% for smokers (or about 33% vs. 50% in the high-risk areas); see Discussion.

Effects among men by age at risk and age began smoking

Overall, there were 26,294 male deaths from liver cancer at ages 35+. Figure 2 shows the relative risk of liver cancer for all men aged 35 and over in various categories. When the results are examined separately for each 10-year group of age at death, smokers have, throughout middle and old age, a significant and consistent excess of about 1/3 in their risk of death from liver cancer. Even at ages 35–44 (where liver cancer accounts for about 1/2 of all male cancer mortality in China), there was a highly significantly elevated risk of liver cancer death associated with smoking, indicating that some risk appears relatively soon after starting to smoke. A further 1,382 men died of liver cancer at ages 25–34 in 1986–1988 (data not shown), but these early deaths were not significantly related to the 1980 smoking habits (RR 1.02, 95% CI 0.80–1.30). This might be a false negative result, due chiefly to the play of chance (as the upper 95% confidence limit for the risk ratio is 1.3), or it could be that nearly all the liver cancer deaths around age 30 are little affected by exposure to tobacco (which, in general, begins around age 20–24 in this population). No information on smoking had been sought for those who died before age 25.

In Figure 2, the relative risk for liver cancer death is also plotted against the age when the individual reportedly began smoking. It includes all smokers, irrespective of the type or amount of tobacco smoked. The relative risk for liver cancer showed no tendency for

TABLE II – MALE LIVER CANCER DEATH RATE RATIO (SMOKER VS. NONSMOKER) ACCORDING TO CATEGORIES OF DIAGNOSTIC CRITERIA FOR LIVER CANCER AT AGES 35–69 IN URBAN AND RURAL CHINA

Diagnostic criteria	Urban (16,803 cases)		Rural (9,491 cases)	
	% of cases	Risk ratio (95% CI)	% of cases	Risk ratio (95% CI)
Pathology	26	1.26 (1.15–1.39)	15	1.33 (1.15–1.54)
Ultrasound, X-ray or AFP	69	1.38 (1.29–1.48)	75	1.41 (1.28–1.55)
Other	5	1.34 (1.12–1.61)	10	1.40 (1.18–1.66)
All	100	1.35 (1.27–1.44)	100	1.39 (1.27–1.52)
Percent liver cancer attributed to smoking ¹		17%		20%

¹19% for all men in China: see Table I footnote.

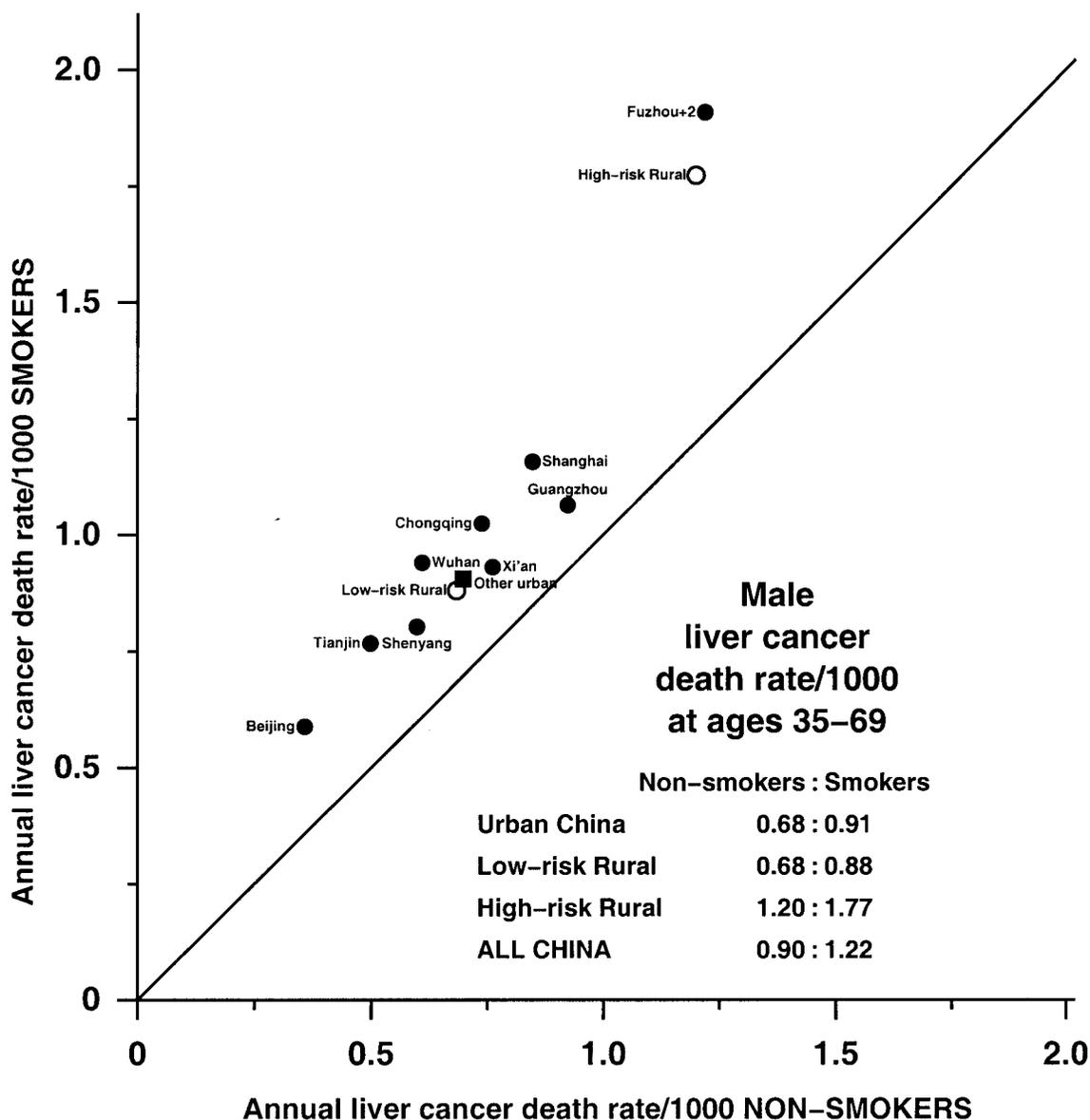


FIGURE 1 – Male death rates from liver cancer at ages 35–69 in smokers vs. nonsmokers, 1986–1988, in various parts of China. Rural counties were grouped into high- and low-risk areas and cities contributing fewer than 500 liver cancer deaths were not shown separately but were combined together as “Other urban”. A rate of 1.5 per 1,000 per year at ages 35–69 corresponds to a 35-year probability of 5% of dying from liver cancer at these ages (as the rate at ages 35–69 is the mean of the rates in the 7 component 5-year age ranges, 35–39, . . . , 65–69), and the rates of 0.9 and 1.2 for ALL CHINA correspond to probabilities of 3% and 4% respectively.

those individuals who began smoking at younger ages to be at greater risk than those who began later. This lack of apparent trend may be due, in part, to inaccurate reporting of age at starting smoking, as it concerns habits several decades earlier, possibly before the informant even knew the dead person. Moreover, the great fluctuations in Chinese social circumstances during the decades before 1980, with large changes in cigarette sales per adult, mean that middle-aged cigarette smokers who died in 1986–1988 are unlikely to have had consistent tobacco consumption since early adult life.

Effects among men by type and amount of tobacco consumption

For men aged 35 and over, the smoker vs. nonsmoker liver cancer death rate ratio appeared to be greater for those whose most recent habit was reported to have involved only cigarettes than for those who partly, or only, smoked other forms of tobacco (chiefly

long Chinese pipes) (Fig. 2). The risk ratio for cigarette smokers was 1.41 (standard error 0.03), while for mixed smokers and smokers of other tobacco only the risk ratios were 1.25 (0.05) and 1.18 (0.06), respectively (trend test: $1p < 0.001$). Among those who smoked cigarettes only, there was also a significantly positive dose-response relationship with daily cigarette consumption, with risk ratios of 1.32 (0.04), 1.50 (0.05) and 1.63 (0.10), respectively, for those reported to have smoked about 10, 20 or 30 cigarettes per day (trend test: $1p < 0.001$).

Effects among women by type and amount of tobacco consumption

Among females (data not shown), there was no significant heterogeneity of smoking hazard with respect to locality (urban/rural), age at death, age began smoking or type of tobacco. But, few smoked substantial numbers of cigarettes: of female controls

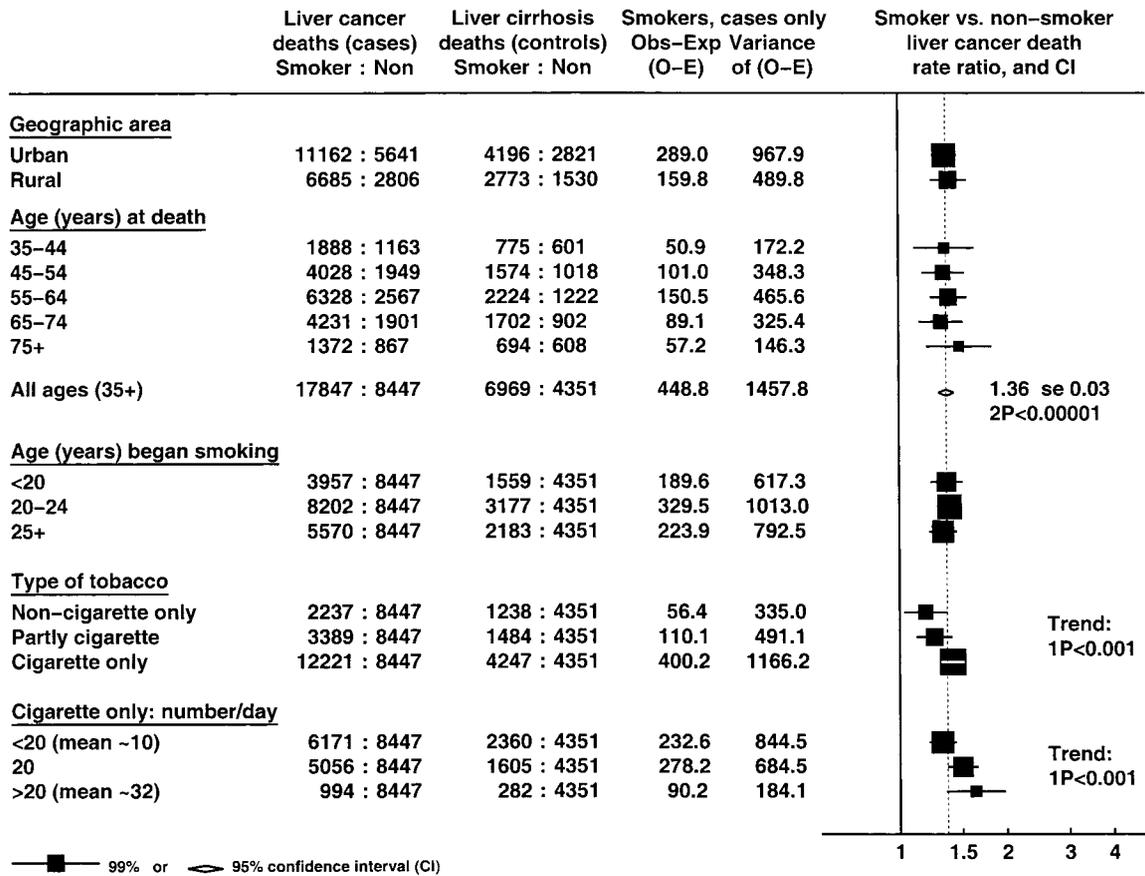


FIGURE 2 – Smoker vs. nonsmoker liver cancer death rate ratios in various subgroups. Males aged 35 or over, 1986–1988. For each particular subgroup, the observed minus the expected (O–E) number of smokers among cases, its variance and the RR (closed square, with area proportional to the total number of deaths) are given. In each subgroup there is a significant excess of liver cancer among smokers, as the entire 99% CI (horizontal line) is to the right of the solid vertical line. The dotted vertical line indicates the overall RR, and open diamond indicates the overall RR and its 95% CI.

aged 35+, 11% smoked cigarettes only (3% consuming at least 20/day and 8% consuming less). Among women who smoked cigarettes only, the few who consumed at least 20/day (mean 22/day) had RR 1.45 (0.13), which is significantly greater than the RR of 1.09 (0.06) among those who smoked fewer (mean 8/day).

DISCUSSION

Validity and plausibility of the evidence of hazard

Our study involves many more cases than any previous study of smoking and liver cancer. For men, it shows tobacco smoking to be associated with a moderate, but highly significant, proportional increase in the risk of death from liver cancer throughout middle and old age (i.e., from about age 35 onwards). Among adult men the excess risk of death associated with smoking appeared to be greater for cigarette smokers than for smokers of other forms of tobacco and was associated positively with the number of cigarettes smoked daily, with a relative risk of 1.50 for men smoking 20 cigarettes a day. Although far fewer women than men consumed substantial numbers of cigarettes, smoking was also associated with an increased female risk of death from liver cancer, with a relative risk of 1.45 among women who smoked at least 20 cigarettes a day.

The analyses were standardised for age and area of residence, and the observed excess risk of liver cancer associated with smoking is unlikely to have been inflated by any systematic bias or confounding, since the use of cirrhosis deaths as controls not only allows for any extent to which cirrhosis itself (or any causes of

cirrhosis, such as chronic HBV infection) can predispose to liver cancer in this population but also ensures that any bias in the retrospective assessment of smoking affects both cases and controls similarly. Smoking information for both cases and controls was provided by family members, and it is unlikely that the informants for the cases who had died of liver cancer would have been more likely to exaggerate the smoking habits than were the informants for the controls who had died of liver cirrhosis, for at the time of the study few people in China were much aware of the effects of smoking even on lung cancer,²³ and most would have been still less aware of the possible effects on other types of cancer. Moreover, the original survey did not focus on the effects of smoking on any particular disease, so there is no good reason to expect any material bias between the dead cases and the dead controls in the accuracy of the retrospectively obtained information about smoking. The prevalence of smoking reported for the live informants was almost the same as that reported for the cirrhosis deaths (see Methods). Separate analyses that used the live informants as controls found that in this particular population there is little association between smoking and cirrhosis.¹⁹

The liver is a possible site for metastasis from other types of cancer that can be caused by smoking, but at the time of our study the smoker vs. nonsmoker risk ratio for overall cancer mortality in middle age was only about 1.5.¹⁹ Hence, even if a moderate proportion of the deaths ascribed to primary liver cancer were in fact due to misdiagnosed metastasis from other types of cancer, the risk ratios in the present case-control comparisons would not be

materially distorted. Also, as primary liver cancer is common in China, it is unlikely, particularly for men in early middle age (among whom about 1/2 of all cancer deaths are attributed to primary liver cancer), that a substantial proportion of the deaths attributed to this cause were actually due to metastasis from other smoking-related cancers. Moreover, about 1/4 of the male cases involved pathologically confirmed liver cancer, and restriction of the analysis to these cases still yielded a highly significant excess risk among smokers. The present study involves uniquely large numbers of cases, so its findings are statistically stable and provide strong evidence of an independent association between smoking (particularly of cigarettes) and liver cancer.

The results of this retrospective study are largely compatible with those from other case-control¹⁴⁻¹⁶ and prospective studies²⁴⁻²⁷ in Chinese populations, although none of these other studies was nationally representative, and none involved large numbers of cases. In 2 prospective studies in Shanghai,^{24,25} each involving just under 100 liver cancer deaths, cigarette smoking was associated (independently of alcohol consumption) with about a 2-fold relative risk of liver cancer. In 2 prospective studies in Taiwan,^{26,27} each involving just over 100 liver cancer deaths, smoking was also associated (independently of alcohol drinking and chronic HBV carrier status) with about a 2-fold relative risk of liver cancer.

An association between liver cancer and smoking has also been reported in non-Chinese populations^{7-10,28-31} but has been difficult to interpret as most of those studies involved only small numbers of liver cancer cases, or involved populations where cirrhosis is largely due to alcohol, and is therefore also correlated with smoking. In Britain, for example (where cirrhosis mortality is about 1/3 of that in China, and liver cancer mortality is about 1/40 that in China³), a prospective study¹⁰ found both diseases to be positively associated with smoking. The relationship between smoking and cirrhosis was, however, attributed almost entirely to the confounding effects of alcohol drinking.^{10,13} As cirrhosis can make liver cancer more probable, it is difficult in such populations to determine reliably whether the association between smoking and liver cancer is largely or wholly due to confounding by alcohol, or whether there is also an independent effect of tobacco.³²⁻³⁴

As cirrhosis and liver cancer in the present population are determined chiefly by chronic HBV infection,³⁵⁻³⁸ not by alcohol, there is little reason to expect much confounding with smoking. (Chronic HBV infection in China, although usually acquired in early childhood, is largely asymptomatic in early adult life and should not materially affect the uptake of smoking.) Although no information was available in the present study on alcohol drinking or on chronic HBV infection, the use of those who had died of cirrhosis as controls should ensure that any possible confounding effects from these factors (or any other causes of liver disease) are likely to be minimal. Further evidence to support this is also provided by the elevated risk observed in women, among whom substantial alcohol drinking is rare.³

Cigarette smoke contains chemicals that are directly-acting causes of liver cancer in experimental animals (*e.g.*, methylnitrosourea) and is also a major source of other carcinogens that, after absorption into the bloodstream, can be metabolised and thereby activated as carcinogens by oxidation in the hepatocytes,^{39,40} and there is some evidence of an increased incidence of hepatocellular carcinoma in animals exposed to tobacco smoke constituents.⁴¹ It is, however, not known whether these experiments reflect the chief mechanisms by which smoking increases the incidence of liver cancer in humans.

Future changes in the relative risk

The 50% excess risk of liver cancer among men in the present study who smoked 20 cigarettes a day is somewhat smaller than the corresponding excess risks in some other studies. This disparity may be due partly to the lack of positive confounding in the present study and partly to differences in patterns of previous

tobacco consumption. Both in urban and, particularly, in rural areas, most of those who, in our study, smoked only cigarettes in 1980 would have been born before 1930, and few of them were likely to have smoked cigarettes persistently from early adulthood, given the great fluctuations in Chinese social circumstances (and cigarette consumption) during the decades before 1980. It is, therefore, likely that the observed smoker *vs.* nonsmoker relative risk of liver cancer under-estimates the relative risk that will eventually be seen in China with prolonged cigarette smoking. Recently there has been a large increase in cigarette consumption in China, involving chiefly an increase in cigarette consumption per smoker rather than an increase in the proportion of smokers.^{23,42} As cigarettes continue to replace other forms of tobacco, the relative risk of liver cancer for persistent smokers in China may well become somewhat greater than that in the present study.

Absolute risks: possible interaction with HBV infection

Although, at least at present, the relative risk is modest, the absolute risk is substantial because Chinese men are already at such high risk of the disease, particularly if they are "antigenaemic" carriers of HBV (*i.e.*, they usually have detectable levels of the HBV surface protein in their bloodstream, indicating chronic infection). In a special study of 181 consecutive cases of liver cancer, mostly from Jiangsu province, 94% were found to be antigenaemic and of the 6% who were not, all were found to have part of the HBV genome integrated into the DNA of their cancer cells, but not of their normal liver cells, indicating that the cancer arose from a single cell that had, earlier in the life of host, had its genome mutated by HBV infection.^{6,38} Thus, in parts of China, and perhaps in almost all of China, hepatitis B (or perhaps, in a few cases, hepatitis C) virus infection is a cause of virtually all cases of liver cancer. As only 10-12% of adults are chronic antigenaemic carriers of HBV, and they probably account for the large majority of all cases of liver cancer in China, the absolute risk among them must be substantial, and the chief absolute effect of smoking must be to increase it.

At the male death rates seen in the study, the probability of death from liver cancer at ages 35-69 (in the absence of other causes of death), comparing smokers *vs.* nonsmokers, would be 4% *vs.* 3% in China as a whole, and 6% *vs.* 4% in the high-risk counties or in the high-risk cities (such as Fuzhou). In most parts of China almost all of this mortality would be concentrated in the 10-12% of adults who are chronic antigenaemic HBV carriers, for whom the corresponding risks might be about 33% *vs.* 25% in China as a whole, or about 50% *vs.* 33% in certain high-risk counties or cities.

Based on the present study, it is estimated that smoking, chiefly by aggravating the hazards of chronic HBV (or, less commonly, HCV) infection, is a cause of almost 1/5 of the male liver cancer deaths in China. (For discussion of the meaning of causality in this context, see Reference 19.) There are about 0.25 million male liver cancer deaths each year in China, and if the observed associations were largely or wholly causal, then (assuming a mix of 30% in urban and 70% rural), the present results indicate that smoking is a cause of about 19% of these deaths, and of a small percentage of the 0.1 million female liver cancer deaths each year. This would mean that smoking is currently responsible for about 50,000 liver cancer deaths a year in China (plus, of course, more than 10 times as many deaths from various other diseases¹⁹). Eventually, as a result of the current policy of nationwide HBV vaccination of all Chinese infants (and perhaps substantial decreases in fungal contamination of stored foodstuffs), the other causes of liver cancer will decrease and the disease will become substantially less common. Until then, however, as the relative risks associated with smoking rise and the population in middle and old age grows larger, the absolute number of deaths from tobacco-induced liver cancer may well rise substantially, both in China and worldwide.

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