

Meta-analysis of epidemiologic studies on cigarette smoking and liver cancer

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Background Whereas the International Agency for Research on Cancer (IARC) Monograph concluded that the evidence for the relationship between cigarette smoking and liver cancer is sufficient, the US Surgeon General's report summarized the data as suggestive but not sufficient.

Methods A meta-analysis of previous epidemiologic studies may help to clarify the potential association. We identified 38 cohort studies and 58 case-control studies in a systematic literature search for studies on liver cancer and cigarette smoking. The meta-relative risk (mRR) of liver cancer and dose-response trends were calculated. Tests for heterogeneity, publication bias assessment and influence analyses were performed.

Results Compared with never smokers, the adjusted mRR was 1.51 [95% confidence interval (CI) 1.37–1.67] for current smokers and 1.12 (95% CI 0.78–1.60) for former smokers. The increased liver cancer risk among current smokers appeared to be consistent in strata of different regions, study designs, study sample sizes and publication periods.

Conclusion The results of our meta-analysis show that tobacco smoking is associated with liver cancer development, which supports the conclusion by the IARC Monograph. This conclusion has an important public health message for areas with high smoking prevalence and high liver cancer incidence such as China.

Keywords Cigarette smoking, liver cancer, meta-analysis

Introduction

The incidence of liver cancer varies greatly by geographic region and by sex. The age standardized rates (ASRs) for men are 5.3 per 100 000 in North America, 6.2 per 100 000 in Western Europe and 36.9 per 100 000 in East Asia;¹ the corresponding ASRs for women are 1.9 per 100 000, 1.7 per 100 000 and 13.3 per 100 000.¹ Chronic infection with

hepatitis B virus (HBV) and hepatitis C virus (HCV) and aflatoxin exposure is responsible for the variation in risk by region and for a large proportion of the burden of liver cancer.^{2,3} Consumption of alcoholic beverages may explain part of the sex difference in liver cancer rates.⁴ Other risk factors of liver cancer have been identified, such as combined oral contraceptives,⁵ vinyl chloride⁶ and radionuclides such as Thorotrast.⁷ Cirrhosis of various aetiology, such as

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alcoholic cirrhosis, other and unspecified cirrhosis and primary biliary cirrhosis, predisposes to liver cancer.^{8,9} Liver flukes, particularly *Opisthorchis viverrini*,¹⁰ have been identified as risk factors for cholangiocarcinoma, a carcinoma of the intrahepatic bile duct. In certain regions of Thailand where *O. viverrini* is endemic, the number of cholangiocarcinoma cases, which are usually quite rare, may outnumber those of hepatocellular carcinoma (HCC).

Several constituents of tobacco smoke are known liver carcinogens in humans and experimental animals. *N*-Nitrosodimethylamine is carcinogenic in many species including mice, rats and monkeys, and is known to lead to the development of liver tumours.¹¹ 4-Aminobiphenyl also produces liver tumours in mice.^{12,13} An association between 4-aminobiphenyl–DNA adduct levels in the liver, which were found to be higher in the blood of smokers than of non-smokers, and HCC in Taiwanese patients has been reported.¹⁴ Arsenic in drinking water and liver cancer mortality was associated in a dose-dependent manner in both ecological and case–control studies in Taiwan. Increased risks of liver cancer due to arsenic in drinking water were also reported in small cohort studies in Taiwan and Japan.¹⁵ Finally, another tobacco smoke constituent, vinyl chloride, has been classified as carcinogenic to humans with sufficient evidence for causing angiosarcoma of the liver and HCC.¹⁶

The association of liver cancer with tobacco smoking has been controversial. Early-on cohort studies from the USA,¹⁷ the Philippines,¹⁸ Japan¹⁹ and China²⁰ reported increased risks of liver cancer among smokers and some evidence of a dose–response relationship,^{19,20} albeit in some studies this was observed only in HBV carriers.²⁰ However, in many of the earlier studies it was difficult to rule out residual confounding by other strong risk factors such as alcohol consumption, HBV and HCV infections.²¹ Based on the consistency of increased risks in cohort and large case–control studies, evidence for increasing risks with increasing duration or intensity of smoking and careful control or stratification for potential confounders, the recent IARC Monograph on tobacco smoke²² concluded that there is now sufficient evidence that tobacco smoking causes liver cancer. At about the same time, however, the US Surgeon General's report on the health consequences of smoking (2004)²³ concluded that the evidence is suggestive but not sufficient to infer a causal relationship between smoking and liver cancer, mainly because exposures to other risk factors that may act as confounders complicated the evaluation.

We performed a comprehensive meta-analysis of published epidemiologic studies to investigate the potential association between cigarette smoking and liver cancer risk. In particular, we assessed the association considering potential confounding factors such as HBV infection, HCV infection and alcohol consumption.

Methods

Search strategy and selection criteria

We conducted a systematic literature search for epidemiologic studies (1966 to April 2009) on liver cancer and cigarette smoking in the MEDLINE database. We also checked the reference lists of articles retrieved from the MEDLINE search. The keywords used for the search in MEDLINE were: liver neoplasms [Mesh] AND (tobacco [Mesh] OR smoking [Mesh]). No language restriction was applied. The data extraction was made by two blinded reviewers independently. The controversies were resolved through discussion and consensus of all authors.

Studies to be included were required to provide enough information to estimate the relative risk (RR) and 95% confidence interval (CI) for tobacco smoking variables. The crude and best adjusted odds ratios (ORs) from the 96 selected publications were recorded. When several publications were available from the same study, either the most recent publication or the publication with the best adjusted OR was included in order to avoid duplicate observations. The corresponding authors were contacted when the publications contained relevant information but did not have the appropriate risk estimates or the necessary information to calculate them or to clarify potential overlap between published studies. Essential characteristics of the cohort studies are shown in Table 1 and those of the case–control studies are shown in Table 2.

Statistical analysis

Meta-relative risks (mRRs) were calculated with random effect models to combine study-specific risk estimates. Proc Mixed procedure of SAS (SAS Institute Inc., Cary, NC), weighted regression using inverse variance has been performed to compute the summary measures of association. Since liver cancer is considered a rare outcome, risk ratio and OR estimates were not differentiated. Subgroup analyses were performed by sex (men and women), region (America, Europe and Asia), study design (case–control and cohort), number of cases (≤ 200 and >200), control type in case–control studies (hospital and population), year of publication (1966–90 and 1991–2008) and specific adjustment (adjustment at least for alcohol consumption or HBV/HCV infections) in the analysis.

In order to reduce the risk of biased results of the meta-analysis, we performed a subgroup analysis restricted to high-quality studies, which considered major potential confounders and had appropriate control selections. Since not all studies were adjusted for all the major potential confounders at the same time, the following criteria for adjustment were used for selection: (i) alcohol consumption and HCV infection in Western countries, but not in Mediterranean countries, and in Japan; (ii) alcohol consumption and HBV

Table 1 Summary characteristics of 38 cohort studies on cigarette smoking and liver cancer included in the meta-analysis

Author (year)	Region	Country	Period	Study population	Cohort size	Years of follow-up	No. of cases	Potential confounders considered in study design or analysis ^a
Lund (1981) ²⁷	Europe	Norway	1966–77	Women	26 000	12	25	
Carstensen (1987) ²⁸	Europe	Sweden	1964–79	Men	25 000	16	54	A, O
Nordlund (1997) ²⁹	Europe	Sweden	1963–89	Women	28 089	26	41	A, O
Hammond (1966) ¹⁷	America	USA	1959–63	Men	440 558	4	96	
McLaughlin (1995) ³⁰	America	USA	1954–80	Men	248 046	26	363	A, O
Basa (1977) ¹⁸	Asia	Philippines	1968–73	Men and women	16 492	6	754	
Oshima (1984) ³¹	Asia	Japan	1972–80	Men, HBsAg+	9646	6.2	20	A
Tu (1985) ²⁰	Asia	China	1980–82	Men	12 222	3	70	
Kono (1987) ³²	Asia	Japan	1965–83	Men	5130	19	51	A, D
Hirayama (1989) ¹⁹	Asia	Japan	1965–82	Men	265 118	17	123	A
Akiba (1990) ³³	Asia	Japan	1966–81	Men and women	265 118	16	1050	A, O, S
Shibata (1990) ³⁴	Asia	Japan	1960–86	Men	1316	28	33	A
Kato (1992) ³⁵	Asia	Japan	1987–90	Men and women, cirrhosis	1441	3	122	A, S
Tsukuma (1993) ³⁶	Asia	Japan	1987–91	Men and women, chronic liver disease	917	3	54	A, S, B, C, D, O
Goodman (1995) ³⁷	Asia	Japan	1980–89	Men and women	36 133	9	242	A, S, O
Chiba (1996) ³⁸	Asia	Japan	1977–93	Men and women, HCV+ and HBV–	412	4.9	63	A, S, B, C, D, O
Chen (1996) ^{39b}	Asia	Taiwan	1991–93	Men and women	6487	–	33	A, S, O
Murata (1996) ^{40b}	Asia	Japan	1984–93	Men	17 200	9	66	
Chen (1997) ⁴¹	Asia	China	1972–93	Men	9351	16	66	A, D, O
Lam (1997) ⁴²	Asia	China	1976–96	Men	1696	20	16	A, O
Yu (1997) ⁴³	Asia	Taiwan	1980–94	Men, HBsAg+	1506	7.1	16	A, B, D, O
Liaw (1998) ⁴⁴	Asia	Taiwan	1982–93	Men and women	14 397	8	128	A, S, D, B
Tanaka (1998) ⁴⁵	Asia	Japan	1985–95	Men and women, liver cirrhosis	96	8	37	A, S, B, C, D
Sun (1999) ⁴⁶	Asia	China	1987–98	Men, HBsAg+	145	10	22	
Yu (1999) ^{47b}	Asia	Taiwan	1988–92	Men	7342	10	84	A, O
Mizoue (2000) ⁴⁸	Asia	Japan	1986–96	Men	13 270	8.8	59	A, D
Mori (2000) ⁴⁹	Asia	Japan	1992–97	Men and women	3052	4.6	22	A, S
Evans (2002) ⁵⁰	Asia	China	1992–2000	Men and women	83 794	8	977	A
Wang (2003) ⁵¹	Asia	Taiwan	1991–2000	Men	11 837	10	115	A, B, C, O
Jee (2004) ⁵²	Asia	Korea	1993–2002	Men and women	1 283 112	10	3807	A, D, O
Ogimoto (2004) ⁵³	Asia	Japan	1988–99	Men and women	65 528	12	186	

(continued)

Table 1 Continued

Author (year)	Region	Country	Period	Study population	Cohort size	Years of follow-up	No. of cases	Potential confounders considered in study design or analysis ^a
Wen (2004) ⁵⁴	Asia	Taiwan	1982–2000	Men and women	86 580	8	245	A
Wang (2004) ⁵⁵	Asia	China	1986–2002	Men	18 244	12.9	202	A, D, O
Yun (2005) ⁵⁶	Asia	Korea	1996–2000	Men	733 134	4	1434	A, D, O
Fujita (2006) ^{57b}	Asia	Japan	1988–99	Men and women	110 792	10	58	A, S, D, O
Chen (2006) ⁵⁸	Asia	Taiwan	1991–92	Men and women	3653	11	164	A, B, D, S, O
Ikeda (2007) ⁵⁹	Asia	Japan	1995	Men and women	846	5	237	A, D, S, O
Ohishi (2008) ^{60b}	Asia	Japan	1970–2002	Men and women	20 000	12–44	224	A, B, C, D, S, O

^aA = age; B = HBV; C = = = alcohol consumption; S = sex; D = other.^bNested case-control studies.

infection in China and Taiwan; and (iii) alcohol consumption, HBV infection and HCV infection in Mediterranean countries.

Heterogeneity of the estimates across studies was tested, using the DerSimonian and Laird non-iterative weighted method.²⁴ Begg's plots and Egger's tests were utilized to assess publication bias. Sensitivity analyses were performed by removing one study at a time to assess whether the meta-estimates were strongly influenced by any particular study.

Dose-response trends were calculated, taking into account the trend between liver cancer risk and cigarette smoking within each study.²⁵ In order to evaluate the relationship more carefully, we focussed on studies with adjusted estimates. The studies had used different cutoffs for the categories of smoking intensity and pack-years, as well as different reference categories. Thus, a linear model within each study was fitted to estimate the increase of the RR for each cigarette per day or pack-year increase. We assigned the midpoint of each category as the number of cigarettes per day or the pack-years for each category. When the highest category was open-ended, we assigned the lower end value of the category multiplied by 1.5.

Results

A total of 284 publications were retrieved from the MEDLINE search. After careful filtering and checking of the reference lists, 38 cohort studies (including five nested case-control studies) and 58 case-control studies met our criteria of presenting RRs or enough data to calculate RRs and CIs. Most of the estimates retrieved were specific for cigarette smoking, though some studies specified 'tobacco smoking' generally and thus the estimates may presumably reflect smoking of several tobacco products such as cigars and pipes in addition to cigarettes. The remaining publications did not meet our criteria because they were either case series or the main effect of cigarette smoking was not estimated. Each study was included in the meta-estimates where possible, but not all studies presented the estimates for main effects overall, stratified estimates or smoking intensity estimates. Therefore, the number of studies included in each summary estimate varied.

Overall, relative to never smokers, ever cigarette smoking and current cigarette smoking were associated with an increased risk of liver cancer (Table 3). We observed a consistent increased risk of liver cancer with current smoking status when the results were stratified by sex (men and women), study design (case-control and cohort), number of cases (≤ 200 and >200), year of publication (1966–90 and 1991–2008) and specific adjustment by alcohol consumption, HBV or HCV infection. The mRR estimates for current smokers in different regions were similar although the estimates for the America and

Table 2 Summary characteristics of 58 case-control studies on cigarette smoking and liver cancer included in the meta-analysis

Author (year)	Region	Country	Period	Study population	No. of cases	Type of controls	Potential confounders considered in study design or analysis ^a
Kew (1985) ⁶¹	Africa	South Africa	1985	Men and women	240	Hospital	
Kew (1990) ⁶²	Africa	South Africa	1990	Women	46	Hospital	A, S, O
Olubuyide (1990) ⁶³	Africa	Nigeria	1987-88	Men and women	100	Hospital	A, S
Mohamed (1992) ⁶⁴	Africa	South Africa	1992	Men and women	101	Hospital	A, S, B, D, O
Ryder (1992) ⁶⁵	Africa	The Gambia	1981-82	Men and women	70	Population	
Stemhagen (1983) ⁶⁶	America	USA	1975-80	Men and women	265	Population/hospital	A, S, O
Austin (1986) ⁶⁷	America	USA and Cuba	1986	Men and women	86	Hospital	A, S, D, O
Yu (1987) ⁶⁸	America	USA	1975-79	Men and women	70	Population	A, S, O
Yu (1988) ⁶⁹	America	USA	1969-85	Men and women	165	Hospital	
Hsing (1992) ⁷⁰	America	USA	1986	Women	76	Population	
Siemiatycki (1995) ⁷¹	America	Canada	1979-86	Men	48	Population	A, O
Hassan (2002) ⁷²	America	USA	1994-95	Men and women	115	Hospital	A, S, B, C, D, O
Yuan (2004) ⁷³	America	USA	1984-2001	Men and women	295	Population	A, B, C, S, D, O
Marrero (2005) ⁷⁴	America	USA	2002-03	Men and women	70	Hospital	A, S, D, O
Zhu (2007) ⁷⁵	America	USA	1984-88	Men	168	Population	A, D, O
Hassan (2008) ⁷⁶	America	USA	2000-06	Men and women			
Farker (2003) ⁷⁷	Europe	Germany	2003	Men and women	70	Hospital	
Hardell (1984) ⁷⁸	Europe	Sweden	1974-81	Men	83	Population	A, S, O
Tzonou (1991) ⁷⁹	Europe	Greece	1976-84	Men and women	185	Hospital	B, C
Filippazzo (1985) ⁸⁰	Europe	Italy	1980-83	Men and women	120	Hospital	
Trichopoulos (1987) ⁸¹	Europe	Greece	1976-84	Men and women	194	Hospital	
La Vecchia (1988) ⁸²	Europe	Italy	1984-87	Men and women	151	Hospital	A, S, D, O
Vall Mayans (1990) ⁸³	Europe	Spain	1986-88	Men and women	96	Hospital	
Peters (1994) ⁸⁴	Europe	Germany	1986-93	Men and women, liver cirrhosis	86	Hospital	
Gorisas (1995) ⁸⁵	Europe	Greece	1989-92	Men and women	51	Hospital	A, S, B, C, D
Hadziyannis (1995) ⁸⁶	Europe	Greece	1991-92	Men and women	65	Hospital	
MILTS (1997) ⁸⁷	Europe	Europe	1994-96	Women	317	Population	
Kuper (2000) ⁸⁸	Europe	Greece	1995-98	Men and women	330	Hospital	A, B, C, S, O
Gelatti (2005) ⁸⁹	Europe	Italy	1999-2002	Men and women	200	Hospital	A, S, B, C, D, O
Franceschi (2006) ⁹⁰	Europe	Italy	1999-2002	Men and women	229	Hospital	A, S, B, C, O

(continued)

Table 2 Continued

Author (year)	Region	Country	Period	Study population	No. of cases	Type of controls	Potential confounders considered in study design or analysis ^a
Yu (1987) ⁶⁸	Asia	Hong Kong	1977–80	Men and women, HBsAg–	19	Hospital	
Lu (1988) ⁹¹	Asia	Taiwan	1985	Men and women	131	Hospital	
Hiyama (1990) ⁹²	Asia	Japan	1984–87	Men and women	229	Hospital	A, B, D, O
Tsukuma (1990) ⁹³	Asia	Japan	1983–87	Men and women	229	Hospital	A, S
Chen (1991) ⁹⁴	Asia	Taiwan	1985–87	Men	200	Population	A, S, O
Choi (1991) ⁹⁵	Asia	Korea	1986–90	Men	216	Hospital	A, S, B, D, O
Lin (1991) ⁹⁶	Asia	China	1984–86	Men, HBsAg–	200	Hospital	A, S, O
Lin (1991) ⁹⁷	Asia	China	1986–87	Men and women	122	Hospital	A, S, D, O
Srivatanakul (1991) ⁹⁸	Asia	Thailand	1987–88	Men and women	65	Hospital	A, S, O
Yu (1991) ⁹⁹	Asia	Taiwan	1986–87	Men and women	127	Population	A, S, D, B, C, O
Tanaka (1992) ¹⁰⁰	Asia	Japan	1985–89	Men and women	204	Hospital	A, S
Fukuda (1993) ¹⁰¹	Asia	Japan	1986–92	Men and women	368	Hospital	A, S, O
Yamaguchi (1993) ¹⁰²	Asia	Japan	1976–85	Men and women	466	Hospital	
Pyong (1994) ¹⁰³	Asia	Japan	1989–92	Men	68	Hospital	A, S, B, C, D, O
Tanaka (1995) ¹⁰⁴	Asia	Japan	1983–89	Men and women	646	Hospital	A, B, D, O
Shin (1996) ¹⁰⁵	Asia	Korea	1990–93	Men and women	203	Population/hospital	A, S, O, B, C, D
Shibata (1998) ¹⁰⁶	Asia	Japan	1992–95	Men	115	Population	A, S
Mukaiya (1998) ¹⁰⁷	Asia	Japan	1991–93	Men, chronic liver disease	104	Hospital	A
Koide (2000) ¹⁰⁸	Asia	Japan	1994	Men and women	84	Population	A, S, B, C
Takeshita (2000) ¹⁰⁹	Asia	Japan	1993–96	Men	85	Hospital	A, D, S, O
Yu (2002) ¹¹⁰	Asia	China	1995–97	Men and women	248	Population	A, S, B
Lam (2001) ¹¹¹	Asia	Hong Kong	1997–99	Men and women	750	Population	A, O
Shimada (2003) ¹¹²	Asia	Japan	2001	Men and women, liver cirrhosis, HBsAg–/HVC+	53	Hospital	S, D
Gao (2003) ¹¹³	Asia	China	2003	Men and women	78	Population	
Chen (2003) ¹¹⁴	Asia	China	1986–88	Men and women	35 936	Population	A, O
Matsuo (2003) ¹¹⁵	Asia	Japan	1995–2000	Men and women	222	Population	
Munaka (2003) ¹¹⁶	Asia	Japan	1997–98	Men and women	78	Hospital	A, S
Hara (2008) ¹¹⁷	Asia	Japan	2001–04	Men and women	209	Hospital	A, S, B, C, D

^a A = age; B = HBV; C = HCV; D = alcohol consumption; S = sex; O = other.

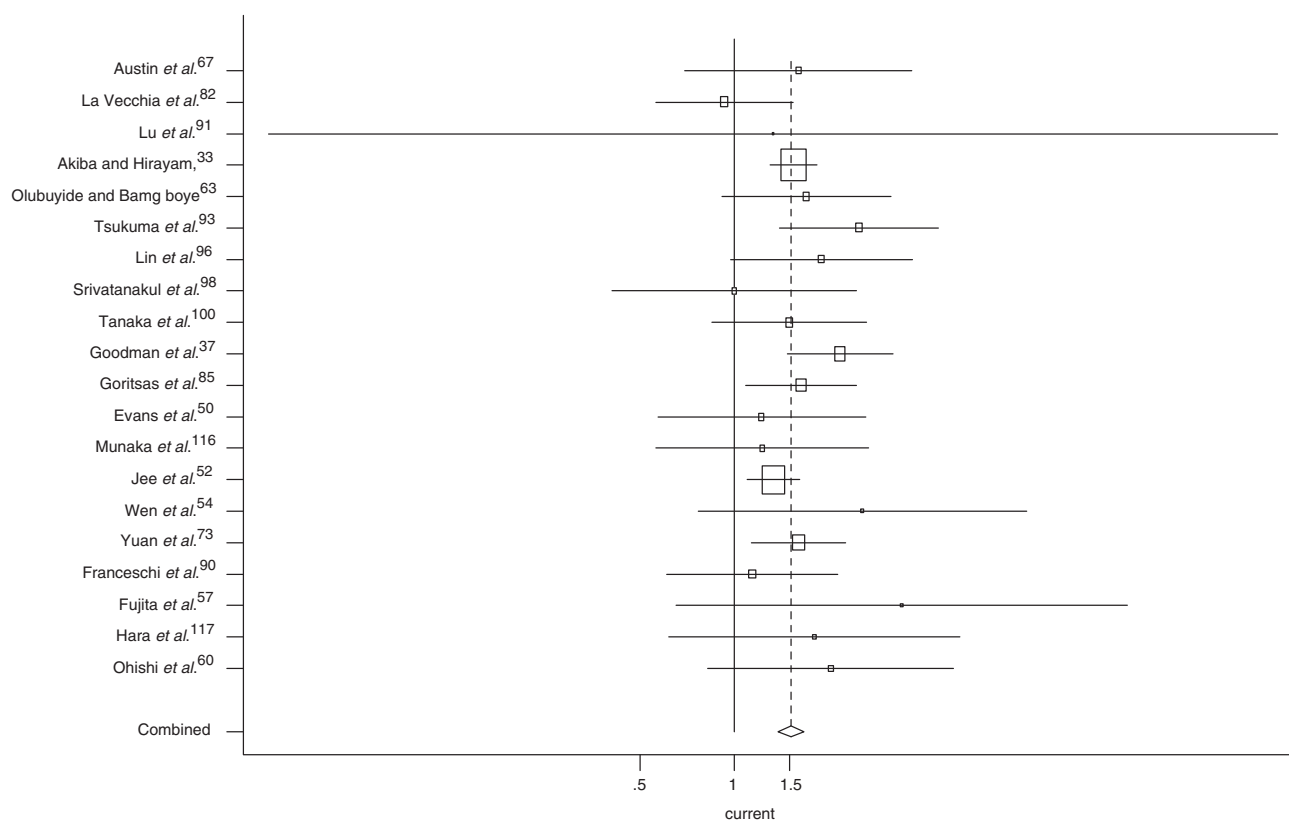


Figure 1 Association between current smoking status and HCC risk by publication

Europe were not statistically significant. For HBV-subjects, the mRR estimate appeared to be higher than for HBV+ subjects, but the difference was not statistically significant and the estimates were based on few studies. Heterogeneity was not detected for the majority of the strata of current smoking except when stratified by sex. The point estimates from the studies were fairly consistent with the summary measure (Figure 1). Moreover, publication bias was not suggested according to Begg's test (Figure 2) and Egger's test (figure not shown). Influence analysis confirmed that the summary estimates were not driven by any particular study (see Supplementary data available at *IJE* online).

For ever smokers, the results were not as consistent across strata, and there was evidence of heterogeneity ($P=0.006$). However, a positive association was observed in strata with five or more studies. For former smokers, overall a small increase in risk was suggested, and there was evidence of heterogeneity ($P=0.015$). Most of the mRRs were between the respective mRR for current smoker and unity; however, associations were detected only in select strata: among men, for studies in Asia, for larger studies and for more recent studies.

The mRRs for adjusted estimates were similar to those for crude estimates (data not shown for

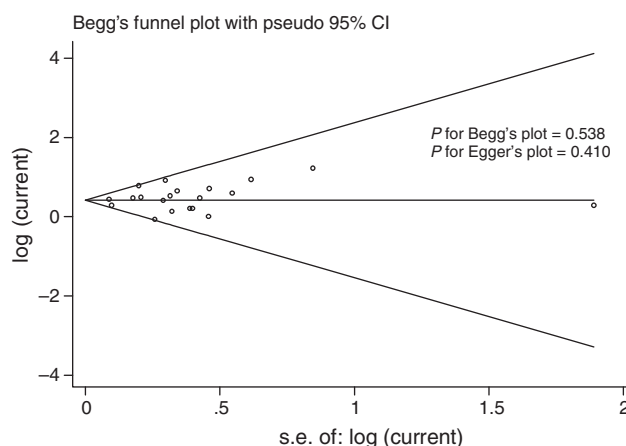


Figure 2 Begg's plot for current smoking and liver cancer s.e. = standard error.

the crude). When we restricted the studies to those adjusting at least for alcohol consumption, HBV or HCV infection, the magnitude of the association between current smoking and liver cancer risk changed only slightly, compared with the overall mRR (Table 3). Table 4 shows the analysis using the subset of high-quality studies as described in the Methods section. There is less heterogeneity than in

Table 3 Stratified mRR and 95% CI of smoking status and liver cancer risk

	Ever smoker				Current smoker				Former smoker			
	Studies (n)	mRR	95% CI	Test for heterogeneity	Studies (n)	mRR	95% CI	Test for heterogeneity	Studies (n)	mRR	95% CI	Test for heterogeneity
Overall	11	1.27	(1.02–1.58)	0.006	21	1.51	(1.37–1.67)	0.659	10	1.12	(0.78–1.60)	0.015
Sex												
Men	10	1.37	(1.30–1.45)	0.005	21	1.61	(1.38–1.89)	<0.001	13	1.47	(1.19–1.82)	0.002
Women	5	1.21	(1.06–1.37)	0.173	12	1.86	(1.33–2.60)	0.013	4	1.45	(0.80–2.65)	0.921
Region												
America	4	1.09	(0.68–1.77)	0.110	2	1.60	(0.20–12.73)	1.000	1	–	–	–
Europe	0	–	–	–	3	1.26	(0.65–2.46)	0.221	2	0.71	(0.07–7.46)	0.546
Asia	7	1.37	(1.04–1.81)	0.014	14	1.56	(1.36–1.79)	0.536	8	1.42	(1.04–1.93)	0.072
Study design												
Case-control	8	1.24	(1.10–1.41)	0.064	13	1.51	(1.26–1.81)	0.686	6	0.89	(0.58–1.37)	0.269
Cohort	3	1.55	(0.52–4.60)	0.007	7	1.52	(1.31–1.78)	0.276	4	1.51	(0.80–2.85)	0.040
Control type												
Hospital	3	1.33	(0.71–2.50)	0.529	12	1.48	(1.20–1.83)	0.616	5	0.88	(0.54–1.43)	0.179
Population	4	1.29	(1.07–1.57)	0.151	1	–	–	–	1	–	–	–
Case number												
≤200 cases	7	1.27	(1.10–1.45)	0.358	9	1.43	(1.10–1.86)	0.640	3	0.70	(0.27–1.78)	0.685
>200 cases	4	1.25	(0.61–2.59)	<0.001	11	1.54	(1.36–1.74)	0.412	7	1.24	(1.08–1.41)	0.041
Year of publication												
1966–90	2	0.85	(0.12–5.81)	0.581	6	1.53	(1.26–1.87)	0.254	3	0.69	(0.29–1.62)	0.754
1991–2008	9	1.37	(1.13–1.65)	0.036	14	1.52	(1.31–1.76)	0.686	7	1.25	(1.09–1.43)	0.070
HBV status												
HBV+	1	–	–	–	2	1.50	(0.63–3.57)	0.840	–	–	–	–
HBV–	1	–	–	–	3	2.61	(0.78–8.74)	0.408	–	–	–	–
Adjustment by HBV												
Yes	5	1.21	(0.85–1.71)	0.114	6 ^a	1.38	(1.01–1.88)	0.499	5	0.92	(0.54–1.54)	0.190
No	6	1.30	(0.92–1.85)	0.005	14	1.55	(1.37–1.75)	0.561	5	1.25	(1.07–1.46)	0.043
Adjustment by HCV												
Yes	3	1.51	(0.76–3.00)	0.237	5 ^b	1.55	(1.00–2.38)	0.845	3	0.84	(0.29–2.47)	0.925
No	8	1.21	(0.92–1.60)	0.004	15	1.51	(1.35–1.69)	0.358	7	1.28	(1.07–1.39)	0.006
Adjustment by alcohol consumption												
Yes	4	1.19	(0.83–1.70)	0.419	9 ^c	1.43	(1.21–1.68)	0.570	5	1.16	(0.99–1.35)	0.128
No	7	1.34	(0.92–1.94)	0.002	11	1.60	(1.38–1.86)	0.569	5	1.31	(0.70–2.44)	0.030

Dash represents fewer than two study estimates available.

^aFour of the six studies also adjusted for HCV, four of the six studies also adjusted for alcohol consumption and all of the six studies also adjusted for sex.^bFour of the five studies also adjusted for HBV, three of the five studies also adjusted for alcohol consumption and all of the five studies also adjusted for sex.^cFour of the nine studies also adjusted for HBV, three of the nine studies also adjusted for HCV and six of the nine studies also adjusted for sex.

Table 4 Stratified mRR and 95% CI of smoking status and liver cancer risk (high-quality studies^a)

	Ever smoker				Current smoker				Former smoker			
	Studies (n)	mRR	95% CI	Test for heterogeneity	Studies (n)	mRR	95% CI	Test for heterogeneity	Studies (n)	mRR	95% CI	Test for heterogeneity
Overall	4	1.24	(0.84–1.84)	0.354	6	1.41	(1.15–1.73)	0.668	5	1.18	(1.01–1.39)	0.715
Region												
America	2	1.43	(0.18–11.40)	0.576	1	–	–	–	0	–	–	–
Europe	0	–	–	–	1	–	–	–	1	–	–	–
Asia	2	1.06	(0.12–9.18)	0.257	4	1.38	(1.03–1.86)	0.528	4	1.20	(0.99–1.45)	0.888
Study design												
Case-control	2	1.43	(0.18–11.40)	0.576	3	1.50	(0.79–2.85)	0.614	2	0.81	(0.03–23.45)	0.967
Cohort	2	1.06	(0.12–9.18)	0.257	3	1.37	(0.91–2.06)	0.372	3	1.21	(0.93–1.56)	0.990
Control type												
Hospital	2	1.43	(0.18–11.40)	0.576	2	1.28	(0.04–43.27)	0.471	2	0.81	(0.03–23.45)	0.967
Population	0	–	–	–	1	–	–	–	0	–	–	–
Case number												
≤200 cases	3	1.08	(0.56–2.09)	0.499	1	–	–	–	1	–	–	–
>200 cases	1	–	–	–	5	1.40	(1.12–1.75)	0.717	4	1.18	(0.98–1.42)	0.552
Year of publication												
1966–90	0	–	–	–	0	–	–	–	0	–	–	–
1991–2008	4	1.24	(0.84–1.84)	0.354	6	1.41	(1.15–1.73)	0.668	5	1.18	(1.01–1.39)	0.715
Adjustment by alcohol consumption												
Yes	3	1.21	(0.71–2.08)	0.283	5	1.43	(1.14–1.80)	0.601	4	1.20	(0.99–1.45)	0.888
No	1	–	–	–	1	–	–	–	1	–	–	–
Adjustment by HBV												
Yes	3	1.21	(0.71–2.08)	0.283	3	1.45	(0.52–4.02)	0.535	3	0.84	(0.29–2.47)	0.925
No	1	–	–	–	3	1.40	(0.97–2.02)	0.379	2	1.21	(0.57–2.57)	0.916
Adjustment by HCV												
Yes	2	1.43	(0.18–11.40)	0.576	3	1.45	(0.52–4.02)	0.535	3	0.84	(0.29–2.47)	0.925
No	2	1.06	(0.12–9.18)	0.257	3	1.40	(0.97–2.02)	0.379	2	1.21	(0.57–2.57)	0.916

^aSee Methods section for details.

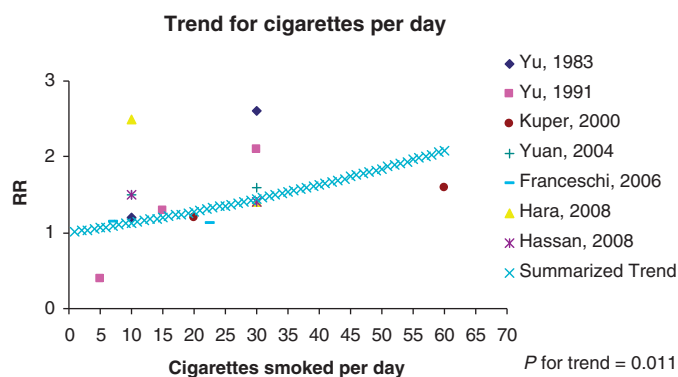


Figure 3 The dose-response relationship between number of cigarettes per day and HCC

the comprehensive meta-analysis; generally the associations are stronger for current smokers than for former smokers; the summary estimates for current and former smoking are highly consistent between the overall and the cohort results and these results are also consistent with the summary estimates from the comprehensive meta-analysis.

Dose-response trends were assessed with a subset of studies that provided estimates in the publications (Figure 3). A positive dose-response relationship with the number of cigarettes smoked was observed, but heterogeneity in these findings was also evident. After examining the possible sources of heterogeneity, type of controls in case-control studies might have contributed to the heterogeneity observed. The dose-response relationship was less evident among studies having hospital controls compared with those having population controls (see Supplementary data available at *IJE* online).

Discussion

Most of the studies included in this meta-analysis consist of HCC only or primary liver cancer (mainly HCC), except for five studies with cholangiocarcinoma ranging from 10 to 42% of all cases in each study (Hardell⁷⁸ 15%; Hsing⁷⁰ 22%; Murata⁴⁰ 42%; Shin¹⁰⁵ 16.7%; Stemhagen⁶⁶ 10%). It is true that the aetiology of cholangiocarcinoma might be different from that of HCC. However, the studies with higher percentage of cholangiocarcinoma only had crude estimates available; thus, studies including cholangiocarcinoma in their case definition did not have much impact on the adjusted meta-estimates.

Our meta-analysis supports the association between cigarette smoking and liver cancer risk. The risk appears to be moderate, with an ~1.5-fold increase for current smoking. Major differences in liver cancer risk due to cigarette smoking were not suggested by sex, study design, number of cases or time period of publication. Some large cohort studies, particularly in low-incidence countries, did not report

an increased HCC risk among ever smokers compared with non-smokers. Nonetheless, the results of the meta-analyses of high-quality studies are generally consistent with the comprehensive meta-analyses, particularly for cohort studies and 'former' smokers.

For former smokers, the less consistent point estimates may be due to the smaller number of studies included. The estimates for former smokers with a larger number of studies were consistent with the expected association. In addition, former smokers may have included people who had quit for a long time and their risk would be expected to be much lower or may reach that of never smokers. Furthermore, the definitions of former smokers varied by study. For example, the minimum period of time since quitting was not defined and left to the judgement of the interviewed subject in some studies. In other studies, if the subject had quit for ≥ 1 year prior to interview, he/she was defined as a former smoker. In addition, there might be temporal ambiguity due to the nature of case-control studies. The early signs and symptoms of liver cancer may result in the patient quitting smoking.

A positive dose-response trend was observed for the number of cigarettes smoked per day, which further supports a causal association between cigarette smoking and liver cancer risk. However, there was substantial heterogeneity for the overall dose-response relationship. The evidence of heterogeneity disappeared when the dose-response relationship was examined by type of control population. The dose-response relationship for studies with hospital controls was either null or negative, whereas that for studies with population controls was positive. Thus, type of controls in case-control studies is one likely source of heterogeneity. Additionally, different adjustment variables, including alcohol consumption, HBV or HCV status, might be another source of heterogeneity. However, most of the studies included in the dose-response analysis were those considered to have relatively high-quality adjustment.

The associations observed support a role of tobacco smoking in the aetiology of HCC. Biological plausibility further corroborates such a relationship as several chemicals in tobacco smoke can be metabolized and then activated to be carcinogenic in the liver. A strong relationship has been reported between DNA-adducts of 4-aminobiphenyl and polycyclic aromatic hydrocarbons and the risk of HCC.^{14,26} As mentioned in the introduction, these two components of tobacco smoke are human carcinogens and have been shown to cause liver tumours in experimental animals.

Important liver cancer risk factors, such as HBV infection, HCV infection and alcohol consumption, were considered carefully as potential confounders in assessing the association between cigarette smoking and liver cancer risk in our analysis. The summary point estimates were similar with or without adjustment by HBV or HCV status. The similar risk estimates with and without additional alcohol adjustment further support the effect of smoking, independent of alcohol, on liver cancer development. Due to limited information available on the effect modification between smoking and these important liver cancer risk factors, we were not able to assess any potential effect modification.

A limitation of concern in our meta-analysis was the difference in adjustment factors across studies. We attempted to take the best adjusted estimate, i.e. the estimate that adjusted for as many of the potential confounders as possible. We also calculated a combined estimate for the studies that minimally adjusted on alcohol consumption, HBV or HCV infection. Unfortunately, there were not enough studies that adjusted on all three potential confounders to have a meaningful combined estimate. Another limitation of concern in a meta-analysis is publication bias. Although our statistical assessment of publication

bias suggested that this bias was limited, the bias cannot be ruled out. A pooled analysis would be a possible solution to address some of these limitations in future studies.

In conclusion, our meta-analysis supports the hypothesis that there is a moderate association between liver cancer risk and cigarette smoking. The results of our meta-analysis support the conclusion in the IARC Monograph. Further studies that allow the investigation of the dose-response relationship between tobacco smoking and HCC, stratified by lifetime alcohol habits and HCV status in Western countries or lifetime alcohol habits and HBV status in China, as well as the careful investigation of potential effect modification with these factors in large and well-conducted studies are still desirable. This conclusion has an important public health message for areas with high smoking prevalence and high liver cancer incidence such as China.

Supplementary data

Supplementary data are available at *IJE* online.

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KEY MESSAGES

- Tobacco smoking is associated with a modest increase in liver cancer in current smokers and to a lesser degree in former smokers.
- The increase in risk is consistent across different populations by gender, region and adjustment for potential confounders.
- The public health impact particularly in high-risk areas for liver cancer may be substantial, but better understanding of effect modification by hepatitis B and C and alcohol consumption is desirable.

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