Cigarette Smoking and Liver Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence among Japanese

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Background: Emerging epidemiologic data suggest that cigarette smoking may increase the risk of primary liver cancer. We evaluated this association based on a systematic review of epidemiologic evidence among Japanese populations.

Methods: Original data were obtained from MEDLINE searches using PubMed, complemented with manual searches. The evaluation was performed in terms of the magnitude of association ('strong', 'moderate', 'weak' or 'no association') in each study and the strength of evidence ('convincing', 'probable', 'possible' or 'insufficient'), together with biological plausibility as previously done by the International Agency for Research on Cancer.

Results: A total of 12 cohort studies and 11 case–control studies were identified. Nine cohort studies (two with adjustment for hepatitis B and C virus infections and seven without it) reported weak to strong positive associations between smoking and liver cancer, with dose–response relationships shown in three studies. Five case–controls studies (three with the virus adjustment and two without it) demonstrated such positive associations, with a dose–response relationship shown in only one study, while in six case–control studies, the observed associations were judged to be of the lowest magnitude or inverse due to the lack of any dose–response relationship.

Conclusion: We conclude that cigarette smoking ‘probably’ increases the risk of primary liver cancer among the Japanese. Potential confounding by hepatitis virus infection and virus–smoking interactions need to be addressed in future studies.

Key words: systematic review – epidemiology – smoking – liver cancer – Japanese

INTRODUCTION

Primary liver cancer is one of the most common cancers in Japan (1). Its primary prevention remains to be a major concern for both clinicians and epidemiologists, since patients with this tumor still present poor prognosis (1,2). More than 90% of primary liver cancers in Japan are known to be hepatocellular carcinomas (2), which are mostly attributable to chronic infection with hepatitis C virus (HCV) and hepatitis B virus (HBV) (2,3). However, emerging evidence suggests that hepatocarcinogenesis is a multistage process, in which environmental factors other than hepatitis viruses may play additional roles (4). One of such candidates is cigarette smoking, which has not yet attracted much attention of clinicians or the public. Recently, the International Agency for Research on Cancer listed liver cancer as a tobacco-related malignancy (5). In this context, the objective of the present study was to review and summarize epidemiological findings on cigarette smoking and liver cancer among Japanese populations. This work was...
CONDUCTED AS PART OF A PROJECT OF SYSTEMATIC EVALUATION OF THE EPIDEMIOLOGICAL EVIDENCE REGARDING LIFESTYLES AND CANCERS IN JAPAN (6).

METHODS

The details of the evaluation method have been described elsewhere (6). In brief, original data for this review were identified by MEDLINE searches using PubMed, complemented by manual searches of references from relevant articles where necessary. All epidemiologic studies on the association between cigarette smoking and liver cancer incidence or mortality from the Japanese from 1963 to 2005, including papers in press if available, were identified using the search terms ‘smoking’, ‘liver’, ‘hepatocellular’, ‘cohort’, ‘follow-up’, ‘case–control’, ‘Japan’ and ‘Japanese’ as keywords. Papers written in either English or Japanese were reviewed, and only studies on Japanese populations living in Japan were included. The individual results were summarized in the tables separately by a study design as cohort or case–control studies.

The evaluation was made based on the magnitude of association and the strength of evidence. First, the former was assessed by classifying relative risk (RR) in each study into the following four categories, while considering statistical significance (SS) or no statistical significance (NS): (i) ‘strong’ (symbol \[ \text{\textup{\textdagger\textdagger\textdagger}} \] or \[ \text{\textup{\textdagger\textdagger}} \] or \[ \text{\textup{\textdagger}} \] or \[ \text{\textup{\textdagger}} \] when RR < 0.5 (SS) or RR > 2.0 (SS); (ii) ‘moderate’ (symbol \[ \text{\textup{\textdagger\textdagger}} \] or \[ \text{\textup{\textdagger}} \] or \[ \text{\textup{\textdagger}} \] or \[ \text{\textup{\textdagger}} \] when RR < 0.5 (NS), 0.5 \leq RR < 0.67 (SS), 1.5 \leq RR \leq 2.0 (SS) or RR > 2.0 (NS); (iii) ‘weak’ (symbol \[ \text{\textup{\textdagger\textdagger}} \] or \[ \text{\textup{\textdagger}} \] or \[ \text{\textup{\textdagger}} \] or \[ \text{\textup{\textdagger}} \] when 0.5 \leq RR < 0.67 (NS), 0.67 \leq RR \leq 1.5 (SS) or 1.5 \leq RR \leq 2.0 (NS) and (iv) ‘no association’ (symbol \[ \text{\textup{\textdagger\textdagger}} \] or \[ \text{\textup{\textdagger}} \] or \[ \text{\textup{\textdagger}} \] or \[ \text{\textup{\textdagger}} \] when 0.67 \leq RR \leq 1.5 (NS). When RRs for three or more exposure levels were reported, that for the highest level was employed for this classification. In the case of multiple publications of analyses of the same or overlapping datasets, only data from the largest or most updated results were included. After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (7), in which evidence was classified as ‘convincing’, ‘probable’, ‘possible’ and ‘insufficient’. We assumed that biological plausibility corresponded to the judgment of the most recent evaluation from the International Agency for Research on Cancer (5). Notwithstanding the use of this quantitative assessment rule, an arbitrary assessment cannot be avoided when considerable variation exists in the magnitude of association between the results of each study. The final judgment, therefore, was made based on a consensus of the research group members, and it was therefore not necessarily objective. When we reach a conclusion that there is ‘convincing’ or ‘probable’ evidence of an association, we conduct a meta-analysis to obtain summary estimates for the overall magnitude of association.

MAIN FEATURES AND COMMENTS

We identified a total of 12 cohort studies (8–19) (Table 1) and 11 case–control studies (20–30) (Table 2). Of the cohort studies, three presented results by sex (9,14,19), four for men only (8,10,11,18) and five only for men and women combined (12,13,15–17). The respective numbers for the case–control studies are one (29), five (20,24–27) and five (21–23,28,30). One cohort study showed results separately in two different areas (11), and two case–control studies reported results separately based on hospital controls and community controls (25,29).

Study populations in the cohort studies were classified as two different types: mostly healthy subjects (n = 7) such as local residents (9,11,17–19), physicians (8) and atomic bomb survivors (14) versus patients with chronic liver disease (10,12,13,15,16) (n = 9) (Table 1). Chronic infections with both HCV and HBV were taken into account in only three studies, all of which followed patients with chronic liver disease (13,15,16). In the case–control studies, a similar classification was possible based on the type of controls: hospital or community controls (21–25,27–30) (n = 9) versus HBV carriers (20) or patients with chronic liver disease without liver cancer (26) (n = 2) (Table 2). In only two case–control studies, both HCV and HBV infections were controlled for (26,28).

A summary of the magnitude of association for the cohort studies and case–control studies is shown in Tables 3 and 4, respectively. Among all 12 cohort studies, five (9,13–15,19) reported strong positive associations of cigarette smoking with liver cancer in either sex or for both sexes combined (Tables 1 and 3); of the five studies, three (9,13,15) demonstrated clear dose–response relationships. Moderate, but not strong, positive associations were found in three cohort studies (10,11,18), and a weak association in one cohort study (17), without any presentation of dose–response relation. In the remaining three (8,12,16), virtually no association was observed. Among the seven cohort studies in which mostly healthy subjects were followed, six (9,11,14,17–19) revealed at least weak positive associations, whereas three (10,13,15) out of the five follow-up studies of patients with chronic liver disease showed such positive associations.

Among all 11 case–control studies, five (20,26–29) reported weak to strong positive associations with cigarette smoking, with a dose–response relationship presented in only one study (20) (Tables 2 and 4). In the remaining six studies (21–25,30), the observed associations were judged to be null or inverse due to the lack of dose–response relationship, although around 2- to 4-fold risk excess in light to moderate exposure categories was observed in five of them (21–25). In the nine case–control studies employing hospital or community controls, three (27–29) demonstrated at least weak positive associations, whereas both case–control studies using controls of HBV carriers or patients with chronic liver disease (20,26) afforded such positive associations.

In the cohort studies, cigarette smoking was almost consistently associated with elevated liver cancer risk. Information and selection biases may not be serious issues in those studies. However, potential confounding by chronic HBV and HCV...
Table 1. Cohort studies on cigarette smoking and liver cancer among Japanese

| Reference         | Study period | Study population | Category          | Number of cases | Relative risk (95% CI or P) | P for trend | Confounding variables considered | Comments                                                                 |
|-------------------|--------------|------------------|-------------------|-----------------|----------------------------|-------------|---------------------------------|--------------------------------------------------------------------------|
| Kono et al. (8)   | 1965–1983    | 5130 men         | Male physicians in western Japan | Death 51 men (primary 9, unspecified 42) | Never/past 1.00  | 1.14 (0.59–2.20) | Age, drinking                  | HBsAg and anti-HCV were not tested                                      |
| Akiba and Hirayama (9) | 1966–1981    | 265 118 (122 261 men and 142 857 women) | 95% of the census population in 29 health-center-covered areas in 6 prefectures | Death 1050 (652 men and 398 women) | For men | | | |
| Inaba et al. (10) | 1973–1988    | 270 men          | Patients with liver cirrhosis at the Juntendo University Hospital | Death 46 men | Never 1.00 | 1.0 | 0.002 | Age, prefecture, occupation, observation period | HBsAg and anti-HCV were not tested. Adjustment for alcohol consumption only slightly changed the relative risks |
| Shibata et al. (11) | 1958–1986    | 639 men in a farming area and 677 men in a fishing area | Residents in a farming or a fishing area in Kyushu | Death 11 men (farming area) and 22 men (fishing area) | Farming area | Non-smoker 2 | 1.0 | >0.1 | Age | HBsAg and anti-HCV were not tested |
|                   |              |                  |                   |                 | Current smoker 8 | 1.1 (0.2–4.7) | | | |
|                   |              |                  |                   |                 | 1–9/day 1 | 0.6 (0.1–3.7) | | | |
|                   |              |                  |                   |                 | 10–19/day 7 | 1.2 (0.2–5.7) | | | |
|                   |              |                  |                   |                 | 20–29/day 0 | – | | | |
|                   |              |                  |                   |                 | >30/day 0 | – | | | |
|                   |              |                  |                   |                 | Fishing area | Non-smoker 1 | 1.0 | >0.1 | Age | |
|                   |              |                  |                   |                 | Ex-smoker 2 | 2.9 (0.3–9.0) | | | |

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| Reference         | Study period | Number of subjects for analysis | Source of subjects | Event followed | Event | Number of incident cases or deaths | Number among cases | Relative risk (95% CI or \( P \)) | \( P \) for trend | Confounding variables considered | Comments |
|-------------------|--------------|--------------------------------|------------------|---------------|-------|-----------------------------------|------------------|---------------------------------|-----------------|----------------------------------|----------|
| Kato et al. (12)  | 1987–1990    | 1784                           | Patients with decompensated liver cirrhosis or post-transfusion hepatitis | Incidence      | 122   | Current smoker                    | 19               | 3.6 (0.6–22.3)                  |                 |                                  |          |
|                   |              |                                |                   |               |       | 1–9/day                           | 7                | 11.9 (1.5–96.8)                 |                 |                                  |          |
|                   |              |                                |                   |               |       | 10–19/day                         | 3                | 1.1 (0.1–10.6)                  |                 |                                  |          |
|                   |              |                                |                   |               |       | 20–29/day                         | 7                | 2.7 (0.4–19.2)                  |                 |                                  |          |
|                   |              |                                |                   |               |       | \( \geq 30 \)/day                | 2                | 3.2 (0.4–23.7)                  |                 |                                  |          |
|                   |              |                                |                   |               |       | Fishing area                      |                  |                                 |                 |                                  |          |
|                   |              |                                |                   |               |       | Non/ex-smoker                     | 3                | 1.00                            |                 | Age, drinking                    |          |
|                   |              |                                |                   |               |       | 1–19/day                          | 10               | 2.10 (0.44–9.95)                |                 |                                  |          |
|                   |              |                                |                   |               |       | \( \geq 20 \)/day                 | 9                | 1.86 (0.37–9.40)                |                 |                                  |          |
| Tsukuma et al. (13)| 1987–1991    | 917 (548 men and 369 women)   | Patients with chronic hepatitis or compensated cirrhosis at the Center for Adult Diseases, Osaka | Incidence      | 54    | Never smoker                      | 39               | 1.00                            |                 | Sex, age                         | HBsAg and anti-HCV status was unknown |
|                   |              |                                |                   |               |       | Past smoker                       | 10               | 0.94 (0.44–2.02)                |                 |                                  |          |
|                   |              |                                |                   |               |       | Current smoker                    | 23               | 0.96 (0.53–1.75)                |                 |                                  |          |
|                   |              |                                |                   |               |       | Smoking index                     | 0                | 1.00                            | 0.82             | Age, sex, stage of disease, serum alpha-fetoprotein, HBsAg, anti-HBc, anti-HCV, drinking |
|                   |              |                                |                   |               |       | 1–599                             | 11               | 0.83 (0.40–1.74)                |                 |                                  |          |
|                   |              |                                |                   |               |       | \( \geq 600 \)                     | 14               | 0.94 (0.47–1.89)                |                 |                                  |          |
| Goodman et al. (14)| 1980–1989    | 36 133                         | Atomic bomb survivors | Incidence     | 242   | For men                           | 213              | 4.36 (1.93–9.36)                |                 | Sex, city, age at the time of bombing, radiation dose to the liver | HBsAg and anti-HCV was not tested |
|                   |              |                                |                   |               |       | Never-smoker                      | 6                | 1.00                            |                 |                                  |          |
|                   |              |                                |                   |               |       | Ever-smoker                       | 146              | 4.36 (1.93–9.36)                |                 |                                  |          |
|                   |              |                                |                   |               |       | Ex-smoker                         | 46               | 4.56 (1.95–10.7)                |                 |                                  |          |
|                   |              |                                |                   |               |       | Quit \( \geq 24 \) years ago      | 14               | 4.04 (1.54–10.6)                |                 |                                  |          |
|                   |              |                                |                   |               |       | Quit 14–23 years ago              | 14               | 4.11 (1.58–10.7)                |                 |                                  |          |
|                   |              |                                |                   |               |       | Quit <14 years ago                | 14               | 5.60 (2.15–14.6)                |                 |                                  |          |
|                   |              |                                |                   |               |       | Present smoker                    | 100              | 4.26 (1.87–9.72)                |                 |                                  |          |
|                   |              |                                |                   |               |       | 1–22 pack-years                   | 38               | 6.47 (2.74–15.3)                |                 |                                  |          |
| Study            | Year       | Convenience Sample Size | Study Type | Subjects | Incidence | Smoking Index | History of Cigarette Smoking | History of Cigarette Smoking | Study Summary |
|------------------|------------|--------------------------|------------|----------|-----------|---------------|-------------------------------|-------------------------------|----------------|
| Chiba et al. (15) | 1977–1993 | 412 (249 men and 163 women) | Patients with HCV-associated chronic hepatitis or compensated cirrhosis at the Tsukuba University Hospital | 63 (54 men and 9 women) | 23–40 pack-years 39 | >41 pack-years 41 | Never-smoker 61 | Ever-smoker 20 | For women |
|                  |            |                          |            |          |            |                | Ever-smoker 20 | Ex-smoker 7 | Quit ≥25 years ago 3 |
|                  |            |                          |            |          |            |                | Quit 10–24 years ago 2 | Quit <10 years ago 2 | Present smoker 13 |
|                  |            |                          |            |          |            |                | ≥16 pack-years 8 |                       |                       |
|                  |            |                          |            |          |            |                | Non-smoker 1.00 | Smoking index <400 1.67 (0.75–3.73) | Smoking index ≥400 2.46 (1.11–5.49) |                       |
| Tanaka et al. (16) | 1985–1995 | 96 (62 men and 34 women) | Patients with liver cirrhosis at the Kyushu University Hospital | 37 (27 men and 10 women) |                       | Never smoker 12 | Past smoker 12 | Current smoker <20 cigarettes/day 9 | ≥20 cigarettes/day 4 |
| Mori et al. (17)  | 1992–1997 | 3052 (974 men and 2078 women) | Residents in a town in Saga prefecture | 22 (14 men and 8 women) | History of cigarette smoking No 10 | 1.00 | 2.10 (0.61–7.23) | 3.26 (0.38–28.2) | Smoking index <200 |
| Mizoue et al. (18) | 1986–1996 | 4050 men | Residents in 4 municipalities in Fukuoka prefecture | Death 59 men | Yes 22 | Never-smoker 10 | 1.00 | 0.30 | Smoking index ≥200 11 | 1.97 (0.57–6.87) |
| Ogimoto et al. (19) | 1988–1999 | 65,528 (28,287 men and 37,241 women) | Residents in 45 areas throughout Japan | Death 186 (number by sex not described) | Men (40–59 years) Never smoker 1.00 | Ex-smoker 1.00 | Collaborating institutes HBsAg and anti-HCV were not tested |
|                  |            |                          |            |          |                  |                  | Age, study area, drinking | HBsAg and anti-HCV were not tested | HBsAg and anti-HCV status was available, but not adjusted for |

All subjects were anti-HCV-positive and HBsAg-negative. The relative risks were not described in the original paper, and were re-estimated by one of the authors (KT). HBsAg and anti-HCV status was adjusted for past smoking. HBsAg and anti-HCV status was not tested.
| Reference Study period | Study population | Category | Number among cases | Relative risk (95% CI or P) | P for trend | Confounding variables considered | Comments |
|------------------------|------------------|----------|------------------|-----------------------------|------------|---------------------------------|----------|
|                        |                  | Current smoker | 1.96 (0.75–5.14) | Men (60–79 years)           |            |                                 |          |
|                        |                  | Never smoker  | 1.00             |                             |            |                                 |          |
|                        |                  | Ex-smoker    | 2.72 (1.21–6.11) |                             |            |                                 |          |
|                        |                  | Current smoker | 2.62 (1.18–5.84) | Women (40–59 years)         |            |                                 |          |
|                        |                  | Never smoker  | 1.00             |                             |            |                                 |          |
|                        |                  | Ex-smoker    | –                |                             |            |                                 |          |
|                        |                  | Current smoker | 2.82 (0.61–13.09)| Women (60–79 years)         |            |                                 |          |
|                        |                  | Never smoker  | 1.00             |                             |            |                                 |          |
|                        |                  | Ex-smoker    | 1.18 (0.16–8.67) |                             |            |                                 |          |
|                        |                  | Current smoker | 1.49 (0.46–4.87) |                             |            |                                 |          |

CI, confidence interval; HBsAg, hepatitis B surface antigen; anti-HCV, antibody to hepatitis C virus; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; LC, liver cirrhosis; AST, aspartate aminotransferase.
| Reference      | Study period | Study subjects                                      | Type and source                  | Definition                                                                 | Number of cases | Number of controls | Category       | Relative risk (95%CI or P) | P for trend | Confounding variables considered                                                                 | Comments |
|----------------|--------------|----------------------------------------------------|----------------------------------|----------------------------------------------------------------------------|----------------|-------------------|----------------|----------------------------|-------------|------------------------------------------------------------------------------------|----------|
| Oshima et al.  | 1972–1980    | Nested case–control (HBsAg-positive blood donors at the Osaka Red Cross Blood Center) | Cases: confirmed by record linkage with the Osaka Cancer Registry; Controls: healthy HBV carriers | 19 men 38 men | None or <10/day 1.0 < 10/day 1.2 ≥30/day 6.3 | 0.10 Matched (1:2) for birth year Adjusted for drinking | All subjects were HBsAg-positive. Anti-HCV was not tested |          |
| Tsukuma et al. | 1983–1987    | Hospital-based (Center for Adult Diseases, Osaka) | Cases: histologically confirmed as HCC; Controls: inpatients with gastrointestinal disease, or examinees for health checkups or gastroendoscopy; no liver disease, cancer, or smoking/alcohol-related disease | 229 (192 men and 37 women) 266 (192 men and 74 women) | Never 1.0 Ex-smoker 0.7 (0.3–1.9) Current smoker 2.5 (1.4–4.5) 1–19/day 4.2 20–39/day 2.2 ≥40/day 1.1 | Frequency matched for sex and age Adjusted for sex, age, HBsAg, history of blood transfusion, drinking, and family history of liver cancer | Anti-HCV was not tested |          |
| Tanaka et al.  | 1985–1989    | Hospital-based (Kyushu University Hospital)        | Cases: 40% were histologically confirmed as HCC; Controls: health examinees at a public health center | 204 (168 men and 36 women) 410 (291 men and 119 women) | Non-smoker 1.0 Ex-smoker 1.5 (0.8–2.8) Current smoker 1.5 (0.8–2.7) | Frequency matched for sex and age Adjusted for sex, age, HBsAg, history of transfusion, drinking, and family history of liver disease | Anti-HCV status was available for part of the subjects, but not adjusted for |          |
| Fukuda et al.  | 1986–1992    | Hospital-based (Kurume University Hospital)        | Cases: 77% were histologically confirmed as HCC; Controls: inpatients without chronic hepatitis or cirrhosis in two general hospitals in Kurume | 368 (287 men and 81 women) 485 (287 men and 198 women) | Never 1.0 Ex-smoker 1.3 (0.8–2.2) Current smoker 1.8 (1.1–3.1) | Matched (1:1 for men and 1:4 for women) for sex, age (≥55 years), residence, and time of hospitalization. Adjusted for sex | The odds ratios (and 95% CIs) and P value for trend were not described in the original paper, and were estimated by one of the authors (KT), based on the Mantel–Haenszel and Mantel Extension methods |          |

Table 2. Case–control studies on cigarette smoking and liver cancer among Japanese
Table 2. Continued

| Reference          | Study period   | Type and source | Study subjects                                                                 | Category | Relative risk (95%CI or P) | P for trend | Confounding variables considered | Comments                        |
|--------------------|----------------|-----------------|--------------------------------------------------------------------------------|----------|-----------------------------|-------------|---------------------------------|---------------------------------|
| Murata et al. (24) | 1984–1993      | Nested case-control (male participants in a gastric mass screening by the Chiba Cancer Association) | Cases: confirmed by record linkage with the Chiba Cancer Registry; Controls: participants in the screening without liver cancer | Cigarettes/day Matched (1:2) for sex, birth year (±2 years), and the first digit of the address code. | Anti-HCV and HBsAg were not tested |
| Shibata et al. (25) | 1992–1995      | Hospital-based (Kurume University Hospital) | Cases: confirmed as HCC by histological, angiographical, and/or other findings; Hospital controls (HCs): inpatients without chronic hepatitis or cirrhosis in 2 general hospitals in Kurume; Community controls (CCs): randomly sampled citizens of Kurume | Cigarette index Matched (1:1) for sex, age (±5 years for HCs and ±3 years for CCs), residence (for HCs) and time of hospitalization (for HCs). Anti-HCV and HBsAg status was available, but not adjusted for. | Adjusted for matching factors |
| Mukaiya et al. (26) | 1991–1993      | Hospital-based (Sapporo Medical University Hospital) | Cases: histologically and/or clinically confirmed as HCC; Controls: chronic liver disease (hepatitis or cirrhosis) without HCC | Non-smoker Matched (1:1) for age (±3 years). | Additional adjustment for drinking and HBV and HCV infections did not materially alter the results |
| Takeshita et al. (27) | 1993–1996 | Hospital-based (20 major hospitals in the southern part of Hyogo prefecture) | Cases: 64% were histologically confirmed as HCC; Controls: outpatients or inpatients with various diseases, but without liver disease positive for HBsAg and/or anti-HCV | Men Frequency matched for hospital, sex, age, and living area Adjusted for age and drinking | All the controls were HBsAg-negative and anti-HCV-negative by definition |
| Koide et al. (28) | 1994 | Hospital-based (Nagoya City University Hospital) | Cases: clinically and/or histologically confirmed as HCC; community controls: selected from the same resident community as cases, with no signs of hepatic diseases or HCC | 84 (64 men and 20 women) | 84 (64 men and 20 women) | Never 1.00 | Matched (1:1) for sex and age (±2 years) | Adjusted for sex, age, history of blood transfusion, anti-HBc, anti-HCV, and CYP2E1 |
|------------------|------|-----------------------------------------------|------------------|----------------|----------------|--------------|----------------|-----------------|
| Matsuo et al. (29) | 1995–2000 | Hospital-based (Kurume University Hospital) | Cases: confirmed as HCC by histological, angiographical, and/or other findings; hospital controls (HCs): inpatients without chronic hepatitis or cirrhosis in 2 general hospitals in Kurume; Community controls (CCs): randomly sampled citizens of Kurume | 222 (177 men and 45 women) | 326 HCs (177 men and 149 women) and 222 CCs (177 men and 45 women) | Men based on HCs | Non-smoker 1.00 | Matched for sex (1:4 for female HCs and 1:1 for other controls), age (±5 years for HCs and ±3 years for CCs), residence (for HCs), and time of hospitalization (for HCs) | Adjusted for matching factors |
|                 |      |                                              |                  |                |                 | Current + former | 5.41 (1.10–26.70) |                  |                  |
| Munaka et al. (30) | 1997–1998 | Hospital-based (University of Occupational and Environmental Health Hospital) | Cases: no detailed description; controls: no evidence of cancer in any organ | 78 (61 men and 17 women) | 139 (94 men and 44 women) | Cigarette index | Never 1.00 | Anti-HCV and HBsAg status was available except for CCs, but not adjusted for |
|                 |      |                                              |                  |                |                 |                  | 1 = 400 1.14 (0.58–2.25) |                  |
|                 |      |                                              |                  |                |                 |                  | 400 < 800 1.09 (0.56–2.14) |                  |
|                 |      |                                              |                  |                |                 |                  | ≥800 1.09 (0.56–2.15) |                  |

CI, confidence interval; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; anti-HCV, antibody to hepatitis C virus; HCC, hepatocellular carcinoma; HCs, hospital controls; CCs, community controls; HCV, hepatitis C virus; anti-HBc, antibody to hepatitis B core antigen; CYP2E1, cytochrome P450 2E1.
## Table 3. Summary of cohort studies on cigarette smoking and liver cancer among Japanese

| Reference          | Study period | Study population                                      | Magnitude of association |
|--------------------|--------------|-------------------------------------------------------|--------------------------|
| Kono et al. (8)    | 1965–1983    | Men 5130, Not specified                                | Death 51, –              |
| Akiba and Hirayama (9) | 1966–1981   | Men 122 261, ≥40                                     | Death 652, ↑↑            |
| Inaba et al. (10)  | 1973–1988    | Men 270 (liver cirrhosis), Not specified              | Death 46, ↑↑             |
| Shibata et al. (11)| 1958–1986    | Men 639 (farming area), 40–69                        | Death 11, –              |
|                    |              | Women 677 (fishing area), 40–69                       | Death 22, ↑↑             |
| Kato et al. (12)   | 1987–1990    | Men and women 1784 (cirrhosis and post-transfusion hepatitis), ≥16 | Incidence 122, –         |
| Tsukuma et al. (13)| 1987–1991    | Men and women 917 (chronic liver disease), 40–69      | Incidence 54, ↑↑↑        |
| Goodman et al. (14)| 1980–1989    | Men 36 133 (men and women), Not specified             | Incidence 156, ↑↑↑       |
|                    |              | Women, Not specified                                  | Incidence 86, ↑↑         |
| Chiba et al. (15)  | 1977–1993    | Men and women 412 (HCV-associated chronic liver disease), 40–72 | Incidence 63, ↑↑↑        |
| Tanaka et al. (16) | 1985–1995    | Men and women 96 (liver cirrhosis), 40–69             | Incidence 37, –          |
| Mori et al. (17)   | 1992–1997    | Men and women 3052, ≥30                               | Incidence 22, ↑↑         |
| Mizoue et al. (18) | 1986–1996    | Men 4050, 40–75                                       | Death 59, ↑↑             |
| Ogimoto et al. (19)| 1988–1999    | Men 28 287, 40–79                                     | Death 186 (number by sex not described), ↑↑↑ |
|                    |              | Women 37 241, 40–79                                   | Death, ↑↑                |

HCV, hepatitis C virus; ↑↑↑, strongly positive; ↑↑, moderately positive; ↑, weakly positive; –, no association.

## Table 4. Summary of case–control studies on cigarette smoking and liver cancer among Japanese

| Reference          | Study period | Study subjects                                      | Magnitude of association |
|--------------------|--------------|-----------------------------------------------------|--------------------------|
| Oshima et al. (20)| 1972–1980    | Men, Not specified 19                                | 38, ↑↑                   |
| Tsukuma et al. (21)| 1983–1987    | Men and women, ≤74, 229                              | 266, –                   |
| Tanaka et al. (22)| 1985–1989    | Men and women, 40–69, 204                            | 410, –                   |
| Fukuda et al. (23)| 1986–1992    | Men and women, 40–69, 368                            | 485, ↑↑                  |
| Murata et al. (24)| 1984–1993    | Men, Not specified 66                                | 132, ↑↑↑                 |
| Shibata et al. (25)| 1992–1995    | Men, 40–69, 115                                     | 115 hospital controls, – |
|                    |              |                                                     | 115 community controls, –|
| Mukaiya et al. (26)| 1991–1993    | Men, Not specified 104                               | 104 (chronic liver disease), ↑↑↑ |
| Takeshita et al. (27)| 1993–1996    | Men, Not specified 85                               | 101, ↑↑↑                 |
| Koide et al. (28)  | 1994         | Men and women, 46–79, 84                             | 84, ↑↑↑                  |
| Matsuo et al. (29) | 1995–2000    | Men, 40–75, 177                                     | 177 hospital controls, – |
|                    |              |                                                     | 177 community controls, ↑↑↑ |
|                    |              |                                                     | 149 hospital controls, – |
|                    |              |                                                     | 149 community controls, ↑↑ |
| Munaka et al. (30) | 1997–1998    | Men and women, 34–92, 78                             | 138, –                   |

↑↑↑, strongly positive; ↑↑, moderately positive; ↑, weakly positive; –, no association; ↑↑, weakly inverse; ↑↑↑, moderately inverse.
infections was not addressed in most studies. Since, in Japan, individuals with either or both infections may have more than 100 times higher risk than those without either (3,31), only a slight change in smoking habit among such infected individuals could result in a substantial distortion of associated RRs. Alcohol consumption, another potential confounder, was not adequately controlled in some studies. In addition, the lack of dose–response relationship in three-quarters of the cohort studies has made our conclusion more conservative.

As for the case–control studies, the data have been controversial. In some studies, the recruitment of hospital controls, which possibly included those with smoking-related diseases, may have biased the RRs towards unity. Confounding issues by hepatitis virus infection and alcohol drinking were the same as those in the cohort studies. The absence of dose–response relation in majority of the case–control studies appears very perplexing. Among cases, symptoms resulting from pre-existing liver disease or physicians’ advice on their health can lead to lifestyle changes including a reduction in number of cigarettes smoked per day. This might be responsible for elevated risks among light to moderate smokers observed in most case–control studies. However, the situation was similar in the cohort studies where smoking habit many years before the development of liver cancer was evaluated. Some unknown biological implications might exist in these non-linear relations.

An interaction issue between hepatitis viruses and cigarette smoking (i.e. possible difference in risk increase due to smoking according to hepatitis virus infection) should also be considered. Since the great majority of patients with hepatocellular carcinoma in Japan is known to be chronically infected with HBV or HCV (2,3), the following question naturally arises: ‘Does smoking increase the risk of hepatocellular carcinoma among people without either HBV or HCV infection?’ This question has not fully been addressed, probably due to the difficulty in conducting epidemiologic studies on this subject and its low practical implication in the prevention of liver cancer. It seems biologically implausible that cigarette smoking, without any hepatitis virus infection or heavy alcohol consumption, causes chronic liver disease, thereby playing a major role in hepatocarcinogenesis. On the other hand, the evaluation of the risk for smoking among people infected with HBV or HCV will be easier to be performed and will provide more practical information. It is noteworthy that, based on such evaluations, a limited number of cohort or case–control studies demonstrated clear dose–response relationships between smoking and liver cancer risk (13,15,20).

Finally, the authors consider that it will be problematic to perform a meta-analysis to obtain a summary estimate for the overall magnitude of association, since such an estimate may not be applicable to general populations of the Japanese due to the above interaction issue. Therefore, the planned meta-analysis was not conducted in this particular evaluation. In addition, the authors cannot exclude the possibility of publication bias and missing relevant epidemiologic studies, although they have long been knowledgeable about the situation of such studies in Japan.

EVALUATION OF THE EVIDENCE ON CIGARETTE SMOKING AND LIVER CANCER RISK AMONG JAPANESE

From these results and based on assumed biological plausibility as previously done by the International Agency for Research on Cancer (5), we conclude that cigarette smoking ‘probably’ increases the risk of primary liver cancer among the Japanese. Potential confounding by hepatitis virus infection and virus–smoking interactions need to be addressed in future studies.

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