Alcohol Drinking and Liver Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence among the Japanese Population

Keitaro Tanaka1, Ichiro Tsuji2, Kenji Wakai3, Chisato Nagata4, Tetsuya Mizoue5, Manami Inoue6 and Shoichiro Tsugane6, for the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan†

1Department of Preventive Medicine, Faculty of Medicine, Saga University, Saga, 2Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, 3Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, Nagoya, 4Department of Epidemiology and Preventive Medicine, Gifu University School of Medicine, Gifu, 5Department of Epidemiology and International Health, Research Institute, International Medical Center of Japan, Tokyo and 6Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan

Received July 6, 2008; accepted September 15, 2008; published online October 22, 2008

Background: Although alcohol consumption has been recognized as a risk factor for primary liver cancer, it will be informative to summarize relevant epidemiologic data in the Japanese who have characteristic environmental determinants (e.g. hepatitis C virus infection) and genetic traits (e.g. presence of poor acetaldehyde metabolizers).

Methods: We systematically reviewed epidemiologic studies on alcohol drinking and liver cancer among Japanese populations. Original data were obtained through searches of the MEDLINE (PubMed) and Ichushi databases, 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 assessed by the International Agency for Research on Cancer.

Results: Among 22 cohort studies identified, 14 (64%) reported weak to strong positive associations between alcohol and liver cancer risk, 3 (14%) reported no association and five (23%) reported weak to moderate inverse associations; such inverse associations were found mostly in follow-up studies of patients with chronic liver disease (particularly, cirrhotic patients), yet recent studies on patients with chronic hepatitis C presented fairly consistent positive associations. Of 24 case–control studies identified, 19 (79%) showed weak to strong positive associations, whereas the remainder demonstrated no association (n = 4) or a moderate inverse association (n = 1).

Conclusion: We conclude that there is ‘convincing’ evidence that alcohol drinking increases the risk of primary liver cancer among the Japanese population.

Keywords: systematic review – epidemiology – alcohol – liver cancer – Japanese

INTRODUCTION

Alcohol has long been viewed as a hepatotoxic agent, and its heavy consumption is known to cause hepatocellular injury that can lead to enhanced fibrosis and eventually to liver cirrhosis through various mechanisms presumed (1). Alcohol drinking has also been implicated in the etiology of primary liver cancer that often develops from cirrhosis (2). In the most recent evaluation by the International Agency for Research on Cancer (IARC), the occurrence of liver cancer has been ‘causally’ related to the consumption...
of alcoholic beverages (3). In the second report published by the World Cancer Research Fund and the American Institute for Cancer Research, the Panel has judged that alcohol consumption is ‘probably’ a direct cause of liver cancer (4).

Primary liver cancer is one of the most common cancers in Japan (5). More than 90% of primary liver cancers in this country are hepatocellular carcinomas (HCCs) that are mostly attributable to chronic infections with hepatitis C virus (HCV) and hepatitis B virus (HBV) (6,7); HCV and HBV infections are estimated to account for 70 and 15%, respectively, of the recent occurrences of HCC in Japan (6). This tendency clearly contrasts with the situation in southeast Asia and sub-Saharan Africa where HBV represents a dominant risk factor of HCC, and with that in Western countries where HCV infection plays an increasingly important role (2,8). The role of alcohol in hepatocarcinogenesis might differ between Japan and such areas. Moreover, ~50% of the Japanese are poor metabolizers of acetaldehyde (9), the first metabolite of ethanol, which has been recognized as being possibly carcinogenic to humans (10). Such poor metabolizers have not been found in Africans or Caucasians (9), and thus the Japanese as Mongoloids might be more susceptible to alcohol than other ethnic groups.

The aim of the present study was to review and summarize epidemiologic findings on alcohol drinking and liver cancer among Japanese populations. This work was conducted as part of a project of systematic evaluation of the epidemiologic evidence regarding lifestyles and cancers in Japan (11).

PATIENTS AND METHOD

The details of the evaluation method have been described elsewhere (11). In brief, original data for this review were identified through searches of the MEDLINE (PubMed) and Ichushi (Japana Centra Revuo Medicina) databases, complemented by manual searches of references from relevant articles where necessary. All epidemiologic studies on the association between alcohol drinking and liver cancer incidence/mortality among the Japanese from 1950 (or 1983 for the Ichushi database) to June 2008, including papers in press if available, were identified using the following as keywords: alcohol, liver, hepatocellular, cohort, follow-up, case–control, Japan and Japanese. 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 as cohort or case–control studies.

The evaluation was made based on the magnitudes of association and the strength of evidence. First, the former was assessed by classifying the relative risk (RR) in each study into the following four categories, while considering statistical significance (SS) or no statistical significance (NS): (i) ‘strong’ (symbol ↓↓↓↓ or ↑↑↑↑) when RR < 0.5 (SS) or RR > 2.0 (SS); (ii) ‘moderate’ (symbol ↓↓ or ↑↑) when RR < 0.5 (NS), 0.5 ≤ RR < 0.67 (SS), 1.5 < RR ≤ 2.0 (SS) or RR > 2.0 (NS); (iii) ‘weak’ (symbol ↓↓ or ↑↑) when 0.5 ≤ RR < 0.67 (NS), 0.67 ≤ RR < 1.5 (SS) or 1.5 < RR ≤ 2.0 (NS) and (iv) ‘no association’ (symbol −) when 0.67 ≤ RR ≤ 1.5 (NS); the RR used in this paper denotes ratio measures of effect, including risk ratios, rate ratios, hazard ratios and odds ratios. 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 data sets, only data from the largest or most updated results were included. Studies that reported RRs for indefinite exposure levels, or did not provide RRs or data necessary for the present authors to calculate relevant RRs, were excluded.

After this process, the strength of evidence was evaluated in a manner similar to that used in the WHO/FAO Expert Consultation Report (12), 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 IARC (3). Despite the use of this quantitative assessment rule, an arbitrary assessment cannot be avoided when considerable variation exists in the magnitudes of association among 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 22 cohort (13–34) (Table 1) and 24 case–control studies (35–58) (Table 2). Of those cohort studies, two presented the results by sex (19,31), seven for men only (13–16,26,29,32) and 13 for men and women combined (17,18,20–25,27,28,30,33,34). The respective numbers for the case–control studies are two (45,54), nine (36–38,42,44,48–51) and 13 (35,39–41,43,46,47,52,53,55–58). Several studies showed the results separately according to study areas (16), different age categories (31), the severity of chronic liver disease (CLD) (33) or different control groups (49,54,56).

Study populations in the cohort studies, except for one study based on male alcoholics (26), were classified broadly into two categories: mostly healthy subjects (n = 7) such as local residents (14,16,25,31,32), physicians (13) and atomic bomb survivors (19) and patients with CLD (15,17,18,20–24,27–30,33,34) (n = 14) (Table 1). Chronic infections with both HCV and HBV were taken into account in 12 studies, all of which followed patients with CLD (18,20–24,27–30,33,34). In the case–control studies, excluding one study based on military men exposed to thorotrast (38), a
Table 1. Cohort studies on alcohol drinking and liver cancer among Japanese

| Reference          | Study period | Study population                      | Event followed | Category               | Number among cases | Relative risk (95% CI or P) | P for trend | Confounding variables considered | Comments                     |
|--------------------|--------------|---------------------------------------|----------------|------------------------|--------------------|---------------------------|-------------|----------------------------------|------------------------------|
| Kono et al. (13)   | 1965–83      | Male physicians in western Japan       | Death          | Never/past             | 51 men (primary 9, unspecified 42) | 1.00          | Age, smoking                      | HBsAg and anti-HCV were not tested. |
|                    |              |                                       |                | Occasional             |                    | 1.34 (0.61–2.98)         |             |                                  |                              |
|                    |              |                                       |                | <2 go/day              |                    | 1.80 (0.80–4.02)         |             |                                  |                              |
|                    |              |                                       |                | ≥2 go/day              |                    | 2.36 (1.04–5.35)         |             |                                  |                              |
| Hirayama (14)      | 1966–82      | 95% of the census population in 29 health-center-covered areas in six prefectures | Death          | For liver cancer       | 788 men (liver cancer) or 123 men (primary liver cancer) | 1.00          | Age                              | HBsAg and anti-HCV were not tested. |
|                    |              |                                       |                | Not daily              |                    | 1.00          |                                  |                              |
|                    |              |                                       |                | Daily                  |                    | 1.25 (P < 0.01)          |             |                                  |                              |
|                    |              |                                       |                | For primary liver cancer |                  |                           |             |                                  |                              |
|                    |              |                                       |                | Not daily              |                    | 1.00          | Age                              | HBsAg and anti-HCV were not tested. |
|                    |              |                                       |                | Daily                  |                    | 1.89 (P < 0.01)          |             |                                  |                              |
| Inaba et al. (15)  | 1973–88      | Patients with liver cirrhosis at Juntendo University Hospital | Death          | Never                  | 46 men              | 1.00          | Age, HBsAg, histories of blood transfusion, hepatitis and surgical operation, smoking | Anti-HCV was not tested            |
|                    |              |                                       |                | Current/past           |                    | 0.41 (0.08–2.20)         |             |                                  |                              |
| Shibata et al. (16)| 1958–86      | Residents in a farming area or a fishing area in Kyushu | Death          | Farming area           | 11 men (farming area) and 22 men (fishing area) | 1.0 >0.1 | Age                              | HBsAg and anti-HCV were not tested. |
|                    |              |                                       |                | Non-drinker            | 2                   | 1.0           |                                  |                              |
|                    |              |                                       |                | Sake <1 go/day         | 6                   | 1.1 (0.2–5.5)           |             |                                  |                              |
|                    |              |                                       |                | Sake 1–2 go/day        | 2                   | 1.6 (0.2–11.6)          |             |                                  |                              |
|                    |              |                                       |                | Sake ≥2 go/day         | 1                   | 1.1 (0.1–13.5)          |             |                                  |                              |
|                    |              |                                       |                | Fishing area           |                     |                           |             |                                  |                              |
|                    |              |                                       |                | Non-drinker            | 2                   | 1.0           | Age                              |                              |
|                    |              |                                       |                | Sake <1 go/day         | 0                   | –             |                                  |                              |
|                    |              |                                       |                | Sake 1–2 go/day        | 0                   | –             |                                  |                              |
|                    |              |                                       |                | Sake ≥2 go/day         | 1                   | 5.5 (0.6–51.1)          |             |                                  |                              |
| Study          | Year   | Patients | Incidence | Details |
|---------------|--------|----------|-----------|---------|
| Kato et al.   | 1987–90 | 1784     | 122       | Patients with decompensated liver cirrhosis or post-transfusion hepatitis |
|               |        |          |           | Fishing area |
|               |        |          |           | Shochu none: 4 |
|               |        |          |           | Shochu <2 go/day: 14 |
|               |        |          |           | Shochu ≥2 go/day: 4 |
|               |        |          |           | Never drinker: 46 |
|               |        |          |           | Past drinker: 19 |
|               |        |          |           | Occasional drinker: 4 |
|               |        |          |           | Current drinker: 5 |
|               |        | Total alcohol index |
|               |        | 0        | 46        | 1.00 |
|               |        | 1–1999   | 10        | 0.49 (0.23–1.02) |
|               |        | 2000+    | 13        | 0.53 (0.27–1.04) |
|               |        | Nondrinker: 1.00 |
|               |        | Occasional drinker: 0.77 (0.20–2.99) |
|               |        | Former drinker: |
|               |        | <80 g ethanol/day: 1.46 (0.56–3.79) |
|               |        | ≥80 g ethanol/day: 1.66 (0.69–3.96) |
|               |        | Current drinker: |
|               |        | <80 g ethanol/day: 1.10 (0.39–3.07) |
|               |        | ≥80 g ethanol/day: 1.15 (0.35–3.78) |
|               |        | Ex-drinker: 4 |
|               |        | Quit ≥16 years ago: 0.96 (0.33–2.77) |
| Tsukuma et al. | 1987–91 | 917 (548 men and 369 women) | 54 | Patients with chronic hepatitis or compensated cirrhosis at Center for Adult Diseases, Osaka |
|               |        | Nondrinker: 1.00 |
|               |        | Occasional drinker: 0.77 (0.20–2.99) |
|               |        | Former drinker: |
|               |        | <80 g ethanol/day: 1.46 (0.56–3.79) |
|               |        | ≥80 g ethanol/day: 1.66 (0.69–3.96) |
|               |        | Current drinker: |
|               |        | <80 g ethanol/day: 1.10 (0.39–3.07) |
|               |        | ≥80 g ethanol/day: 1.15 (0.35–3.78) |
|               |        | Ex-drinker: 4 |
|               |        | Quit ≥16 years ago: 0.96 (0.33–2.77) |
| Goodman et al. | 1980–89 | 36133 | 242 (156 men and 86 women) | Atomic bomb survivors |
|               |        | For men: |
|               |        | Never-drinker: 25 |
|               |        | Ever-drinker: 126 |
|               |        | Ex-drinker: 25 |
|               |        | Quit ≥16 years ago: 4 |
|               |        | For women: |
|               |        | Never-drinker: |
|               |        | Ever-drinker: |
|               |        | Ex-drinker: |
|               |        | Quit ≥16 years ago: |

Continued
| Reference          | Study period | Study population | Event followed | Number of cases | Category | Number among cases | Relative risk (95% CI or P) | P for trend | Confounding variables considered | Comments |
|--------------------|--------------|------------------|----------------|---------------|----------|--------------------|-----------------------------|-------------|----------------------------------|----------|
| Chiba et al.       | 1977–93      | Patients with HCV-associated chronic hepatitis or compensated cirrhosis at Tsukuba University Hospital | Incidence       | 63 (54 men and 9 women) | Nondrinker | 1.00               | 1.00                        |            | Sex, age, stage of disease, serum alpha-fetoprotein, anti-HBs, anti-HBc, histories of blood transfusion, surgical procedure and liver cancer in family, smoking | All subjects were anti-HCV-positive and HBsAg-negative. |
| Ikeda et al.       | 1980–?       | Patients with chronic hepatitis at Toranomon Hospital | Incidence       | 89 (2215 men and 671 women) | HBsAg(+) anti-HCV(−) subjects (n = 610) | 1.00 | 3.04 (1.79–5.14) | 0.04 | Stage of hepatitis, gamma-glutamyl transpeptidase | HBsAg and anti-HCV status was available for all subjects. |
| Authors          | Year(s) | Subjects | Study Details                                                                 |
|------------------|---------|----------|------------------------------------------------------------------------------|
| Tanaka et al.    | 1985–95| 96 (62 men and 34 women) | Patients with liver cirrhosis at Kyushu University Hospital Incidence 37 (27 men and 10 women) |
| Matsushita et al. | 1985–94| 267 (165 men and 102 women) | Patients with liver cirrhosis at Kanazawa University Hospital Incidence 67 |
| Aizawa et al.    | 1981–98| 153 (115 men and 38 women) | Patients with chronic hepatitis or cirrhosis positive for anti-HCV at Jikei University Hospital Incidence Not described |
| Mori et al.      | 1992–97| 3052 (974 men and 2078 women) | Residents in a town in Saga prefecture Incidence 22 (14 men and 8 women) |

| Risk Factor | Reference | Odds Ratio (95% CI) |
|-------------|-----------|---------------------|
| <500 kg ethanol | 1.00 |
| ≥500 kg ethanol | 8.37 (2.70–25.93) |
| HBsAg (–) anti-HCV(+) subjects | $(n = 1500)$ Stage of hepatitis, γ-glutamyl transpeptidase, history of blood transfusion, albumin |
| <500 kg ethanol | 1.00 |
| ≥500 kg ethanol | 1.96 (1.06–3.62) |
| Sex, years since LC diagnosis, department, hospitalization status, serum albumin, AST, alpha-fetoprotein, HBsAg, anti-HCV, smoking | |
| Never | 1.00 |
| Past | 0.59 (0.20–1.73) |
| Current | |
| <2.4 drinks/day | 0.06 (0.01–0.57) |
| ≥2.4 drinks/day | 0.17 (0.02–1.42) |
| Type B or C cirrhosis | $(n = 202)$ Age, anti-HCV |
| Positive drinking history | 1.83 (1.00–3.36) |
| Type C cirrhosis | $(n = 140)$ Age |
| Positive drinking history | 2.36 (1.23–4.54) |
| Habitual heavy drinking | |
| No | 1.00 |
| Yes | 3.04 (1.31–7.09) |
| Sex, age, ALT, interferon therapy, histologic staging, irregular regeneration | All subjects were anti-HCV-positive and HBsAg-negative. Habitual heavy drinking was defined as an average daily consumption of 65 g of ethanol for >5 years. |
| History of habitual alcohol consumption | |
| No | 1.00 |
| Yes | 1.27 (0.46–3.47) |
| Sex, age | Anti-HCV and HBsAg status was available but not adjusted for. |
| Never drinker | 1.00 |
| 1–19 drink-years | 2.05 (0.48–8.79) |
| 1–19 drink-years | 0.87 |
| One ‘drink’ corresponds to 23 ml of ethanol. | |

Continued
| Reference  | Study period | Study population | Category | Number of incident cases or deaths | Relative risk (95% CI or P) | P for trend | Confounding variables considered | Comments |
|------------|--------------|------------------|----------|-----------------------------------|-----------------------------|-------------|--------------------------------|----------|
| Noda et al. (26) | 1972–92 | 306 men Alcoholics in Takatsuki city, Osaka, who had been diagnosed at a psychiatric institution | Death | Not described | ≥20 drink-years 1.14 (0.40–3.26) | | | Age, calendar year | Anti-HCV and HBsAg were not tested. |
| Hamada et al. (27) | 1980–2000 | 469 (227 men and 242 women) Patients with clinically compensated chronic hepatitis C due to blood transfusion at National Nagasaki Medical Center | Incidence | 52 | Alcohol consumption | Not excessive 1.00 Excessive 2.21 (1.00–3.58) | | Age, serum bilirubin, platelets, interferon therapy, duration from infection, fibrosis | All subjects were anti-HCV-positive and HBsAg-negative. Excessive alcohol consumption was defined as an alcohol consumption of >50 g/day for 5 years. |
| Takimoto et al. (28) | 1989–? | 356 Patients with histologically proven chronic hepatitis C at Niigata University Hospital and one hospital in Niigata, who did not respond to interferon therapy | Incidence | Not described | Alcohol drinking | No 1.00 Yes 4.30 (P = 0.048) | | Age, sex, blood transfusion, viral load, viral subtype, stage of fibrosis, ALT, platelets, interferon dose | All subjects were anti-HCV-positive and HBsAg-negative. Alcohol drinking was defined as having consumed >80 g ethanol daily for >5 years. |
| Uetake et al. (29) | 1988–2000 | 91 men Patients with HBsAg-negative anti-HCV-negative alcoholic cirrhosis at Jikei University Hospital | Incidence | 13 men | Cumulative alcohol intake (kg) | 1200 kg increase 7.7 (1.9–31.5) 0.0047 | | Anti-HBc | All patients were HBsAg-negative, anti-HCV-negative, and alcoholic. The hazard ratio (and 95% confidence interval) was not described in the original paper, and was estimated by one of the authors (KT). |
| Iwasaki et al. (30) | 1986–2003 | 792 (533 men and 259 women) Hepatitis C patients with or without Child A cirrhosis at Okayama University Hospital and participating institutions, with sustained response to interferon therapy | Incidence | 23 (20 men and 3 women) | Alcohol consumption | <50 g/day 1.00 ≥50 g/day 3.86 (1.58–9.44) | | Fibrosis staging, age | All subjects were anti-HCV-positive and HBsAg-negative. |
| Ogimoto et al. (31) | 1988–99 | 66974 (28343 men and 38631 women) Residents in 45 areas throughout Japan | Death | 184 (number by sex and age not described) | Male, 40–59 years ( n = 16715) | | Collaborating institute | HBsAg and anti-HCV were not tested. |
| Study          | Period  | Total | Incidence | Patients with chronic hepatitis | Patients with cirrhosis | Sex, age, smoking, alcohol consumption, response to interferon therapy, anti-HBc | All subjects were anti-HCV-positive and HBsAg-negative |
|---------------|---------|-------|-----------|-------------------------------|-------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------|
| Nakaya et al. (32) | 1990–97 | 21201 | 48 men   | Incidence 48 men              |                         | Age, smoking, education, daily consumption of orange and other fruit juice, spinach, carrot or pumpkin, and tomato | HBsAg and anti-HCV were not tested.                        |
| Ikeda et al. (33) | 1995–2005 | 846 (473 men and 373 women) | 237 (151 men and 86 women) | Incidence 237 (151 men and 86 women) | (n = 576) | Sex, age, smoking, alcohol consumption, response to interferon therapy, anti-HBc | All subjects were anti-HCV-positive and HBsAg-negative.                         |
similar classification was possible based on the type of controls: hospital or community controls (35,37,40–46,48,49,51–56,58) \((n = 18)\) vs. patients with CLD (39,47,50,56,57) or HBV carriers (36) \((n = 6;\) one study (56) included hospital controls as well) (Table 2). In six case–control studies, both HCV and HBV infections were taken into account or were controlled for (46,47,50,56–58).

A summary of the magnitude of association for the cohort and case–control studies is shown in Tables 3 and 4, respectively. Among all 22 cohort studies identified, nine (13,16,21,23,24,27–30) reported strong positive associations between alcohol drinking and liver cancer, three (14,19,32) reported moderate positive associations and two reported weak positive associations (26,34) (Tables 1 and 3). Of the remaining eight studies, three (18,20,25) observed no association and five (15,17,22,31,33) demonstrated weak to moderate inverse associations; such inverse associations were detected mostly in follow-up studies of patients with CLD (particularly, cirrhotic patients) (15,17,22,33). In some cohort studies targeting mostly healthy subjects, the observed risk was higher in former than current drinkers (19,31,32).

Among the seven cohort studies in which mostly healthy subjects were followed, five (13,14,16,19,32) revealed at least weak positive associations, whereas eight (21,23,24,27–30,34) out of the 14 follow-up studies of patients with CLD showed such positive associations.

Among all 24 case–control studies identified, strong positive associations were found in 14 (35,36,40,42–44,47,49–51,54–56,58), moderate positive associations in four (38,41,45,53) and a weak positive association in one (37) (Tables 2 and 4). For the remainder, no association was reported in four (39,46,48,52) and a moderate inverse association was reported in one (57). In the 18 case–control studies employing hospital or community controls, 15 (35,37,40–45,49,51,53–56,58) demonstrated at least weak positive associations, whereas four (36,47,50,56) out of six case–control studies using controls of CLD patients or HBV carriers afforded such positive associations.

Overall, about 60% of the cohort studies identified reported weak to strong positive associations between alcohol drinking and liver cancer risk, although all such studies are done on mostly healthy subjects lacking information on hepatitis virus infection. Since there is no reason to consider that individuals with chronic HCV or HBV infection tend to consume more alcohol than those without, potential confounding by such viral infection is unlikely to explain the positive associations found. Cohort studies of mostly healthy subjects demonstrated fairly consistent positive associations, yet several follow-up studies on CLD patients (particularly, cirrhotic patients) reported no association (18,20) or even inverse associations (15,17,22,33), which may be due to the following reasons.

First, among CLD patients, the severity of liver disease may confound the association with alcohol consumption. If patients with more severe liver disease tend to drink less alcohol at baseline for any reason (e.g. impaired liver function).
Table 2. Case–control studies on alcohol drinking and liver cancer among Japanese

| Reference       | Study period | Study subjects                             | Category | Relative risk (95% CI or P) | P for trend | Confounding variables considered | Comments |
|-----------------|--------------|--------------------------------------------|----------|----------------------------|------------|----------------------------------|----------|
| Inaba et al. (35) | 1977–79      | Hospital-based (7 hospitals in Yamanashi)   | Cases: 58% were histologically confirmed; Controls: patients without hepatic disease | Not daily | 1.0 | 3.2 (P < 0.05) | Matched (1:1) for sex, age, and hospital Adjusted for matching factors | HBsAg was tested but not adjusted for. Anti-HCV was not tested. |
| Oshima et al. (36) | 1972–80      | Nested case–control (HBsAg-positive blood donors at Osaka Red Cross Blood Center) | Cases: confirmed by record linkage with the Osaka Cancer Registry; Controls: healthy HBV carriers | None or < 1 go/day, 1–<3 go/day, ≥3 go/day | 1.0, 5.4, 8.0 | <0.05 Matched (1:2) for birth year Adjusted for smoking | All subjects were HBsAg-positive. Anti-HCV was not tested. |
| Hiraga et al. (37) | 1981–85      | Hospital-based (one university hospital) | Cases: 50% were histologically confirmed as HCC; Controls: inpatients or outpatients with various diseases | Not daily | 1.0 | 1.7 (0.8–4.0) | Matched (1:1) for age and residential area Adjusted for matching factors | HBsAg was tested but not adjusted for. Anti-HCV was not tested. |
| Kiyosawa et al. (38) | 1980–87      | Nested case–control (military men who had undergone angiography with thorotrast between 1943 and 1946) | Cases: confirmed by autopsy and/or serological and imaging examinations; Controls: no liver tumor by biochemical and serological tests and imaging examinations | For primary liver cancer | 1.0 | | No matching | HBsAg was tested but not adjusted for. |
| Kobayashi et al. (39) | 1975–88      | Hospital-based (Kanazawa University Hospital) | Cases: cirrhotic patients with HCC at autopsy; Controls: cirrhotic patients without HCC at autopsy | Alcohol intake (≥75 g/day, ≥10 years) | No, Yes | 1.0, 1.4 (0.6–3.4) | No matching | HBsAg was tested but not adjusted for. |
| Tsukuma et al. (40) | 1983–87      | 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 | Not heavy | 1.0 | 3.2 (2.0–5.1) | Frequency-matched for sex and age Adjusted for sex, age, HBsAg, history of blood transfusion, smoking, and family history of liver cancer | Anti-HCV was not tested. Heavy drinking was defined as drinking 3 ‘go’s of sake per day for >10 years. |

Continued
| 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                                                                 |
|-----------------|--------------|----------------|-----------------|------------|----------------|-------------------|----------|-------------------------------|----------------|---------------------------------|-------------------------------------------------------------------------|
| Tanaka et al. (41) | 1985–89      | Hospital-based (Kyushu University Hospital) | Cases: 40% were histologically confirmed as HCC; Controls: health examinees at a public health center | ≥40 000 ‘go’s disease, cancer, or smoking/alcohol-related disease | 204 (168 men and 36 women) | 410 (291 men and 119 women) | Non-drinker | 1.0                           |                     | Frequency-matched for sex and age. Adjusted for sex, age, HBsAg, history of blood transfusion, smoking, and family history of liver disease | Anti-HCV status was available for part of the subjects, but not adjusted for. |
|                 |              |                |                 |            |                |                   | Ever-drinker | 1.3 (0.9–2.0)               | 0.02           |                                 | Heavy drinking was defined as having consumed ≥80 ml of ethanol per day for ≥10 years. |
|                 |              |                |                 |            |                |                   | Not heavy    | 1.0                           |                     |                                 | The ‘drink-years’ was calculated by multiplying the daily alcohol use in ‘drink’ (23 ml of ethanol) by the number of years of consumption. |
|                 |              |                |                 |            |                |                   | Heavy        | 2.0 (1.2–3.1)               |                  |                                 |                                                                         |
|                 |              |                |                 |            |                |                   | Non-drinker  | 1.0                           | 0.02           |                                 |                                                                         |
|                 |              |                |                 |            |                |                   | 0.1–33.9 drink-years | 1.2 (0.7–2.1)               |                  |                                 |                                                                         |
|                 |              |                |                 |            |                |                   | 34.0–76.6 drink-years | 1.0 (0.5–1.8)               |                  |                                 |                                                                         |
|                 |              |                |                 |            |                |                   | ≥76.7 drink-years | 2.0 (1.2–3.5)               |                  |                                 |                                                                         |
|                 |              |                |                 |            |                |                   | Sake         | 1.0                           |                  |                                 |                                                                         |
|                 |              |                |                 |            |                |                   | <10 drink-years | 1.0                           |                  |                                 |                                                                         |
|                 |              |                |                 |            |                |                   | ≥10 drink-years | 1.6 (1.1–2.3)               |                  |                                 |                                                                         |
|                 |              |                |                 |            |                |                   | Beer         | 1.0                           |                  |                                 |                                                                         |
|                 |              |                |                 |            |                |                   | <10 drink-years | 1.0                           |                  |                                 |                                                                         |
|                 |              |                |                 |            |                |                   | ≥10 drink-years | 1.0 (0.7–1.5)               |                  |                                 |                                                                         |
|                 |              |                |                 |            |                |                   | Shochu       | 1.0                           |                  |                                 |                                                                         |
|                 |              |                |                 |            |                |                   | <10 drink-years | 1.0                           |                  |                                 |                                                                         |
|                 |              |                |                 |            |                |                   | ≥10 drink-years | 1.0 (0.6–1.6)               |                  |                                 |                                                                         |
|                 |              |                |                 |            |                |                   | Whisky       | 1.0                           |                  |                                 |                                                                         |
| Study            | Year       | Setting                                      | Cases                                      | Controls                                    | Alcohol Index | Frequency-Matched OR | 95% CI          |
|------------------|------------|----------------------------------------------|--------------------------------------------|---------------------------------------------|---------------|---------------------|-----------------|
| Haratake et al.  | 1980-1990  | Hospital-based (University of Occupational and Environmental Health) | Patients with surgically resected HCC; Controls: patients without liver disease |                                             |               |                     |                 |
|                  |            |                                              | 145 (120 men and 25 women)                 |                                             |               |                     |                 |
| Fukuda et al.    | 1986-1992  | Hospital-based (Kurume University Hospital)  | 77% were histologically confirmed as HCC; Controls: inpatients without chronic hepatit or cirrhosis in 2 general hospitals in Kurume |                                             |               |                     |                 |
|                  |            |                                              | 368 (287 men and 81 women)                 |                                             |               |                     |                 |
| Yamaguchi        | 1986       | Hospital-based (Kilme University Hospital)   | Patients with surgically resected HCC; Controls: patients without liver disease |                                             |               |                     |                 |
|                  |            |                                              | 466 (325 men and 141 women)                |                                             |               |                     |                 |
|                  |            |                                              | ≥ 60 drink-years                           | Male, HBsAg-negative                        | 1.0           | 1.0                 |                 |
|                  |            |                                              | 1-29 drink-years                           |                                             |               |                     |                 |
|                  |            |                                              | 30-59 drink-years                          |                                             |               |                     |                 |
|                  |            |                                              | 60 drink-years                             |                                             |               |                     |                 |
| Yamaguchi        | 1976-1985  | Hospital-based (Kurume University Hospital)  | Patients with histologically or clinically confirmed as HCC; Controls: patients without chronic hepatic disorders |                                             |               |                     |                 |
|                  |            |                                              | 466 (385 men and 81 women)                 |                                             |               |                     |                 |
|                  |            |                                              | Male, HBsAg-negative                       | Matched (1:1) for the year of admission, sex, and age |               |                     |                 |
|                  |            |                                              | Analysis was done in male HBsAg-negative subjects alone. |                                             |               |                     |                 |
|                  |            |                                              | None                                       | Matched (1:1 for males and 1:4 for females) for sex, age, residence, and time of hospitalization |               |                     |                 |

The alcohol index was calculated by multiplying the daily alcohol use in 'drink' (23 ml of ethanol) by the number of years of consumption. The 'drink-years' represented the accumulated amount of alcohol intake by age 40, which was calculated by multiplying the daily alcohol use in 'drink' (23 ml of ethanol) by the number of years of consumption.
| Reference          | Study period | Type and source                                      | Definition                                                                                           | Number of cases | Number of controls | Category       | Relative risk (95% CI or $P$) | $P$ for trend | Confounding variables considered                                                                 | Comments                                      |
|-------------------|--------------|------------------------------------------------------|------------------------------------------------------------------------------------------------------|-----------------|-------------------|----------------|--------------------------------|------------|---------------------------------------------------------------------------------|------------------------------------------------|
| Une et al. (45)   | 1986–88      | Hospital-based (hospitals or clinics located in Iizuka Health Center District) | Cases: identified by death certificates in the district; Controls: patients treated for diseases other than liver diseases in three large hospitals in the district | 133 (96 men and 37 women) | 132 (92 men and 40 women) | Male Positive drinking | 1.08 (0.57–2.05) |          | Matched (1:1) for sex and age Adjusted for sex, age, HBsAg, history of blood transfusion, and smoking | Anti-HCV was not tested. |
|                   |              |                                                      |                                                                                                       |                 |                   | Female Positive drinking | 2.87 (0.57–14.40) |          |                                                                                  |                                                |
|                   |              |                                                      |                                                                                                       |                 |                   | Both sexes Positive drinking | 1.20 (0.66–2.18)  |          |                                                                                  |                                                |
| Tanaka et al. (46) | 1992–93      | Hospital-based (Center for Adult Diseases, Osaka)   | Cases: patients with HCC who responded to questionnaire (no details described); Controls: patients with cancer of stomach, colon, rectum, or breast, or large intestine polyp | 137 (116 men and 21 women) | 334 (202 men and 132 women) | Nondrinker | 1.0 | No matching Adjusted for sex, age, education, smoking, HBsAg, and anti-HCV       | HBsAg and anti-HCV status was adjusted for. |
|                   |              |                                                      |                                                                                                       |                 |                   | Former drinker 8.7 (1.6–46.3) |              |          |                                                                                  |                                                |
|                   |              |                                                      |                                                                                                       |                 |                   | Occasional drinker 0.7 (0.2–2.0) |              |          |                                                                                  |                                                |
|                   |              |                                                      |                                                                                                       |                 |                   | <80 g ethanol/day 0.4 (0.1–1.4) |              |          |                                                                                  |                                                |
|                   |              |                                                      |                                                                                                       |                 |                   | ≥80 g ethanol/day 1.4 (0.4–5.5) |              |          |                                                                                  |                                                |
| Chiba et al. (47) | 1991–93      | Hospital-based (Tsukuba University Hospital)        | Cases: HCV-associated cirrhotic patients with HCC established by histology or elevated alpha-fetoprotein together with positive imaging study; Controls: HCV-associated cirrhotic patients without HCC | 76 (38 men and 38 women) | 128 (63 men and 65 women) | Habitual drinking 3.27 (1.46–7.30) |              |          | No matching Adjusted for sex, age, and anti-HBV                                   | All subjects were anti-HCV-positive and HBsAg-negative. Habitual drinking was defined as the average daily alcohol consumption of 80 g or more over a period of more than 5 years. |
| Murata et al. (48) | 1984–93      | Nested case–control (male participants in a gastric mass screening by Chiba Cancer Association) | Cases: confirmed by record linkage with Chiba Cancer Registry; Controls: participants in the screening without liver cancer | 66 men | 132 men | Alcohol intake (cups/day) | 1.0 | 0.3                  | Matched (1:2) for sex, birth year, and the first digit of the address code No adjustment | Anti-HCV and HBsAg were not tested. One cup corresponds to 180 ml of sake containing 27 ml of ethanol. |
|                   |              |                                                      |                                                                                                       |                 |                   | 0                         | 0.6 |          |                                                                                  |                                                |
|                   |              |                                                      |                                                                                                       |                 |                   | 1.1–2.0                  | 0.4 |          |                                                                                  |                                                |
|                   |              |                                                      |                                                                                                       |                 |                   | 2.1+                     | 1.5 |          |                                                                                  |                                                |
| Study       | Year | Hospital Type | Case Definition                                                                 | Control Definition                                      | Number | Matched | Matched Factors                                                                 | Adjusted for | Additional Adjustment |
|------------|------|---------------|--------------------------------------------------------------------------------|---------------------------------------------------------|--------|---------|--------------------------------------------------------------------------------|--------------|-----------------------|
| Shibata et al. (49) | 1992–95 | 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 | 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 | 115 males | HCs and CCs | Based on HCs Non-drinker 1.0 | Matched (1:1) for sex, age, residence (for HCs), and time of hospitalization (for HCs) Adjusted for matching factors | Anti-HCV and HBsAg status was available, but not adjusted for. The ‘drink-years’ represented the accumulated amount of alcohol intake by age 40, which was calculated by multiplying the daily alcohol use in ‘drink’ (23 ml of ethanol) by the number of years of consumption. |
| Mukaiya et al. (50) | 1991–93 | Hospital-based (Sapporo Medical University Hospital) | Cases: histologically and/or clinically confirmed as HCC; Controls: chronic liver disease (hepatitis or cirrhosis) without HCC | Cases: histologically and/or clinically confirmed as HCC; Controls: chronic liver disease (hepatitis or cirrhosis) without HCC | 104 men | 104 men | Not daily 1.00 Daily 2.31 (1.20–4.42) | Matched (1:1) for age Adjusted for age | Additional adjustment for cigarette smoking, and HBV and HCV infections did not materially alter the results. |
| Takeshita et al. (51) | 1993–96 | 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. | 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. | 102 (85 men and 17 women) | 125 (101 men and 24 women) | Men 0–19 drink-years 1.0 0.007 | Frequency-matched for hospital, sex, age, and living area Adjusted for age and smoking | All the controls were HBsAg-negative and anti-HCV-negative by definition. The ‘drink-years’ was calculated by multiplying the daily alcohol use in ‘drink’ (23 ml of ethanol) by the number of years of consumption. |
| Reference | Study period | Study subjects | Type and source | Number of cases | Number of controls | Category | Relative risk (95% CI or P) | P for trend | Confounding variables considered | Comments |
|-----------|--------------|----------------|----------------|----------------|------------------|----------|--------------------------|------------|-------------------------------|----------|
| Koide et al. (52) | 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 | Anti-HCV and HBsAg status was available, but not adjusted for. |
| | | | | | | Current + former | 1.23 (0.59–2.56) | | | |
| | | | | | | 'drink' (15 ml of ethanol) by the number of years of consumption. |
| Iida et al. (53) | 1999–2001 | Hospital-based (hospitals in Yamanashi prefecture) | Cases: patients with HCC (no details described); Controls: inpatients at the hospitals same as cases (no details described) | 495 (363 men and 132 women) | 194 (132 men and 62 women) | Non-heavy drinker | 1.00 | | Matched for sex, age, and time of hospitalization | Anti-HCV and HBsAg status was available, but not adjusted for. |
| | | | | | | Heavy drinker | 1.84 (1.13–2.99) | | | |
| | | | | | | Matched for sex and age | Adjusted for sex | | |
| Matsuo et al. (54) | 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) | Male based on HCs | 1.00 | | Matched for sex (1:4 for female HCs and 1:1 for other controls), age, residence (for HCs), and time of hospitalization (for HCs) | Anti-HCV and HBsAg status was available except for CCs, but not adjusted for. |
| | | | | | | Non-drinker | | | Adjusted for matching factors | |
| | | | | | | 1–29 drink-years | 1.31 | | | |
| | | | | | | 30–59 drink-years | 1.65 | | | |
| | | | | | | ≥60 drink-years | 1.95 (P < 0.05) | | | |
| | | | | | | Male based on CCs | | | | |
| | | | | | | Non-drinker | 1.00 | | | |
| | | | | | | 1–29 drink-years | 2.02 (P < 0.05) | | | |
| | | | | | | 30–59 drink-years | 1.53 | | | |
| | | | | | | ≥60 drink-years | | | | |
Munaka et al. (55) 1997–98
Hospital-based
(University of Occupational and Environmental Health Hospital)
Cases: no detailed description of HCC cases
Controls: no evidence of cancer in any organ

Female

Non-drinker 1.00
1–29 drink-years 1.25
30 drink-years 1.15

Based on HCs

Never drinker 1.00
Unmatched
Adjusted for sex and age

Munaka et al. (55) 1997–98
Hospital-based (University of Occupational and Environmental Health Hospital)
Cases: no detailed description of HCC cases
Controls: no evidence of cancer in any organ

Female

Non-drinker 1.00
1–29 drink-years 1.25
30 drink-years 1.15

Based on HCs

Never drinker 1.00
Unmatched
Adjusted for sex and age

Sakamoto et al. (56) 2001–04
Hospital-based (Saga Medical School Hospital and Saga Prefectural Hospital)
Cases: confirmed as HCC by histological, angiographical, or other radiological findings;
Hospital controls (HCs): first-time visitors at the general outpatient clinic of Saga Medical School Hospital;
Patients with chronic liver disease without HCC (CLDs): patients with chronic hepatitis or cirrhosis not classified as special types (e.g., biliary cirrhosis)

Female

Non-drinker 1.00
1–29 drink-years 1.30
30 drink-years 1.25

Based on CLDs

Never drinker 1.00
Former drinker 1.3 (0.7–2.2)
Current drinker 1.8 (1.0–3.0)

Based on HCs

Never drinker 1.00
1–29 drink-years 3.4 (1.1–10.1)
30 drink-years 4.5 (2.3–8.5)

Alcohol intake (’go’s/day) during last 1–2 years, based on HCs

Never drinker 1.00
1–0.9 3.4 (1.1–10.1)
1.0–1.9 4.5 (2.3–8.5)

One ‘go’ corresponds to 180 ml of sake containing 23 g of ethanol.

Unmatched
Adjusted for sex, age, smoking, HBsAg, and anti-HCV status

Unmatched
Based on HCs

Anti-HCV and HBsAg status was available, but not adjusted for.

Continued
| Reference        | Study period | Study subjects                                                                 | Category | Relative risk (95% CI or \(P\)) | \(P\) for trend | Confounding variables considered | Comments                                                                 |
|------------------|--------------|-------------------------------------------------------------------------------|----------|---------------------------------|-----------------|----------------------------------|--------------------------------------------------------------------------|
| Fukushima et al. (57) | 2001–02      | Hospital-based (Osaka City University Hospital) Cases: HCV-RNA positive patients with HCC confirmed by either histology or radiological findings; Controls: HCV-RNA positive patients without HCC | 0        | 0.8 (0.2–2.9)                   |                 |                                  | All patients were HCV-RNA-positive and HBsAg-negative.                    |
|                  |              |                                                                                | 2.0–2.9  | 0.6 (0.2–2.4)                   |                 |                                  |                                                                          |
|                  |              |                                                                                | 3.0–3.9  | 10.2 (1.7–60.5)                 |                 |                                  |                                                                          |
|                  |              |                                                                                | 4.0+     | 18.0 (3.0–107.9)                |                 |                                  |                                                                          |
|                  |              | Alcohol intake (‘go’s/day) during last 1–2 years, based on CLDs                |          |                                 |                 |                                  |                                                                          |
|                  |              |                                                                                | 0        | 1.0                             |                 |                                  |                                                                          |
|                  |              |                                                                                | 0.1–0.9  | 1.2 (0.7–2.2)                   |                 |                                  |                                                                          |
|                  |              |                                                                                | 1.0–1.9  | 1.0 (0.5–2.1)                   |                 |                                  |                                                                          |
|                  |              |                                                                                | 2.0–2.9  | 1.8 (0.8–4.4)                   |                 |                                  |                                                                          |
|                  |              |                                                                                | 3.0–3.9  | 5.0 (1.3–19.2)                  |                 |                                  |                                                                          |
|                  |              |                                                                                | 4.0+     | 9.4 (2.5–35.4)                  |                 |                                  |                                                                          |
|                  |              | Cumulative ethanol consumption (kg) during lifetime                            |          |                                 |                 |                                  |                                                                          |
|                  |              |                                                                                | Non-drinker | 1.00                       | 0.07            |                                  |                                                                          |
|                  |              |                                                                                | < 260    | 0.48 (0.18–1.31)                |                 |                                  |                                                                          |
|                  |              |                                                                                | ≥ 260    | 0.37 (0.13–1.07)                |                 |                                  |                                                                          |
|                  |              | Cumulative ethanol consumption (kg) after the first identification of liver disease |          |                                 |                 |                                  |                                                                          |
|                  |              |                                                                                | Non-drinker | 1.00                       | 0.3             |                                  |                                                                          |
|                  |              |                                                                                | < 200    | 0.48 (0.16–1.41)                |                 |                                  |                                                                          |
|                  |              |                                                                                | ≥ 200    |                                 |                 |                                  |                                                                          |
|                  | Cumulative ethanol consumption (kg) after the first identification of liver disease |
|------------------|-------------------------------------------------------------------------------------|
|                  | Non-drinker | < 53 | ≥ 53 |
|                  | 1.00        | 1.22 | 1.09 |
|                  | (0.8)       | (0.48–3.10) | (0.35–3.36) |

Ohishi et al. (58) 1970–2002

Nested case–control (atomic bomb survivors in Hiroshima and Nagasaki)

Cases: patients with incident HCC who had stored serum samples available; Controls: survivors without HCC who had stored serum samples available

| Alcohol consumption (g of ethanol per day) | Cases: 224 (136 men and 88 women) | Controls: 644 (387 men and 257 women) |
|--------------------------------------------|----------------------------------|--------------------------------------|
| 0                                          | 1.00                             | 1.00                                 |
| 1–19                                       | 1.27                             | 1.27                                 |
| (0.56–2.87)                                | (0.56–2.87)                      | (0.56–2.87)                          |
| 20–39                                      | 1.02                             | 1.02                                 |
| (0.34–3.05)                                | (0.34–3.05)                      | (0.34–3.05)                          |
| 40+                                        | 4.36                             | 4.36                                 |
| (1.48–13.0)                                | (1.48–13.0)                      | (1.48–13.0)                          |

Matched (1:3) for sex, age, city, time and method of serum storage, and radiation exposure. Adjusted for matching factors, hepatitis virus infection, smoking, coffee, body mass index, diabetes, and radiation dose to the liver. HBsAg and anti-HCV status was adjusted for.

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HC, hospital control; CC, community control; CLD, chronic liver disease.
| Reference          | Study period | Study population | Sex          | Number of subjects | Age range (years) | Event | Number of incident cases or deaths |
|--------------------|--------------|------------------|--------------|-------------------|------------------|-------|-----------------------------------|
| Kono et al. (13)   | 1965–83      | Men              | 5130         | Not specified     | Death            | 51    |                                   |
| Hirayama (14)      | 1966–82      | Men              | 122261       | ≥40               | Death            | 788   |                                   |
| Inaba et al. (15)  | 1973–88      | Men              | 270 (liver cirrhosis) | Not specified | Death            | 46    | ↓↓                               |
| Shibata et al. (16)| 1958–86      | Men              | 639 (farming area) | 40–69             | Death            | 11    | –                                 |
|                    |              |                  | 677 (fishing area) | 40–69             |                  |       |                                   |
| Kato et al. (17)   | 1987–90      | Men and women    | 1784 (cirrhosis and posttransfusion hepatitis) | ≥16              | Incidence        | 122   | ↓↓                               |
| Tsukuma et al. (18)| 1987–91      | Men and women    | 917 (chronic liver disease) | 40–69             | Incidence        | 54    | –                                 |
| Goodman et al. (19)| 1980–89      | Men              | 36 133 (men and women) | Not specified | Incidence        | 156   | –                                 |
| Chiba et al. (20)  | 1977–93      | Men and women    | 412 (HCV-associated chronic liver disease) | 40–72             | Incidence        | 63    | –                                 |
| Ikeda et al. (21)  | 1980–?       | Men and women    | 2215 (chronic hepatitis) | 13–75             | Incidence        | 89    | ↑↑                                |
| Tanaka et al. (22) | 1985–95      | Men and women    | 96 (liver cirrhosis) | 40–69             | Incidence        | 37    | ↓↓                               |
| Matsushita et al. (23)| 1985–94     | Men and women    | 267 (liver cirrhosis) | Not specified | Incidence        | 67    | ↑↑ (type B or C) ↑↑↑ (type C) |
| Aizawa et al. (24) | 1981–98      | Men and women    | 153 (HCV-associated chronic liver disease) | 20–65             | Incidence        | Not described | ↑↑↑   |
| Mori et al. (25)   | 1992–97      | Men and women    | 3052         | ≥30               | Incidence        | 22    | –                                 |
| Noda et al. (26)   | 1972–92      | Men              | 306 (alcoholic) | 21–77             | Death            | Not described | ↑     |
| Hamada et al. (27) | 1980–2000    | Men and women    | 469 (HCV-associated chronic liver disease) | Not specified | Incidence        | 52    | ↑↑↑                              |
| Takimoto et al. (28)| 1989–?      | Men and women    | 356 (HCV-associated chronic hepatitis) | Not specified | Incidence        | Not described | ↑↑↑   |
| Uetake et al. (29) | 1988–2000    | Men              | 91 (alcoholic cirrhosis) | 34–72             | Incidence        | 13    | ↑↑↑                              |
| Iwasaki et al. (30)| 1986–2003    | Men and women    | 792 (HCV-associated chronic liver disease with sustained response to interferon) | Not specified | Incidence        | 23    | ↑↑↑                              |
| Ogimoto et al. (31)| 1988–99      | Men              | 16 715       | 40–59             | Death            | 184 (number by sex and age not described) | ↓     |
|                    |              | Women            | 11 628       | 60–79             | Death            | –     |                                   |
|                    |              | Women            | 22 528       | 40–59             | Death            | –     |                                   |
| Nakaya et al. (32) | 1990–97      | Men              | 21 201       | 40–64             | Incidence        | 48    | ↑↑                                |
| Ikeda et al. (33)  | 1995–2005    | Men and women    | 576 (HCV-associated chronic hepatitis) | Not specified | Incidence        | 94    | ↓                                |
|                    |              |                  | 270 (HCV-associated cirrhosis) | Not specified | Incidence        | 143   | –                                 |
| Ohki et al. (34)   | 1994–2006    | Men and women    | 1431 (HCV-associated chronic liver disease) | Not specified | Incidence        | 340   | ↑                                 |

↑↑↑, strongly positive; ↑↑, moderately positive; ↑, weakly positive; −, no association; ↓, weakly inverse; ↓↓, moderately inverse.
function or physicians’ advice), even in those with a similar diagnosis (e.g. chronic hepatitis or cirrhosis), alcohol drinking may seem to play no, or even protective, role. Second, among cirrhotic patients, competing risks (i.e. deaths from causes other than liver cancer) may be responsible. For example, if cirrhotic patients with alcoholism continue to drink heavily, they may die of hepatic failure or variceal bleeding before the development of liver cancer. Third, drinking habits at baseline among CLD patients may have changed substantially during follow-up, and the resultant misclassification may have distorted a true association. Fourth, alcohol consumption may actually play no important role in the development of liver cancer from cirrhosis. However, it appears difficult to differentiate these possibilities by observational studies.

In some cohort studies based on mostly healthy subjects, former drinkers experienced a higher risk of liver cancer than never drinkers (19,31,32); in all such studies,...

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

| Reference          | Study period | Study subjects          | Sex            | Age range (years) | Number of cases | Number of controls | Magnitude of association |
|--------------------|--------------|-------------------------|----------------|-------------------|-----------------|--------------------|-------------------------|
| Inaba et al. (35)  | 1977–79      | Men and women           | Not specified  | 62                | 62              |                    | ↑↑↑                     |
| Oshima et al. (36) | 1972–80      | Men                     | Not specified  | 20                | 40              |                    | ↑↑↑                     |
| Hiraga et al. (37) | 1981–85      | Men                     | Not specified  | 78                | 78              |                    | ↑                       |
| Kiyosawa et al. (38)| 1980–87     | Men                     | Not specified  | 36 (primary liver cancer) | 67 (exposed to thorotrast) |                    | —                      |
|                    |              |                         |                | 20 (hepatocellular carcinoma) | 67 (exposed to thorotrast) |                    | ↑↑↑                     |
| Kobayashi et al. (39)| 1975–88    | Men and women           | Not specified  | 48                | 40 (cirrhotic patients) |                    | —                      |
| Tsukuma et al. (40)| 1983–87      | Men and women           | ≤74            | 229               | 266             |                    | ↑↑↑                     |
| Tanaka et al. (41) | 1985–89      | Men and women           | 40–69          | 204               | 410             |                    | ↑↑↑                     |
| Haratake et al. (42)| 1980–90     | Men                     | Not specified  | 145               | 83              |                    | ↑↑↑                     |
| Fukuda et al. (43) | 1986–92      | Men and women           | 40–69          | 368               | 485             |                    | ↑↑↑                     |
| Yamaguchi (44)     | 1976–85      | Men                     | Not specified  | 466               | 466             |                    | ↑↑↑                     |
|                    |              |                         |                |                   | (HBsAg-negative) |                    |                         |
| Une et al. (45)    | 1986–88      | Men                     | Not specified  | 96                | 92              |                    | —                      |
|                    |              | Women                   | Not specified  | 37                | 40              |                    | ↑↑↑                     |
| Tanaka et al. (46) | 1992–93      | Men and women           | 40–79          | 137               | 334             |                    | —                      |
| Chiba et al. (47)  | 1991–93      | Men and women           | Not specified  | 76                | 128 (HCV-associated cirrhosis) | ↑↑↑         |
| Murata et al. (48) | 1984–93      | Men                     | Not specified  | 66                | 132             |                    | —                      |
| Shibata et al. (49)| 1992–95      | Men                     | 40–69          | 115               | 115 hospital controls | ↑↑↑       |
|                    |              |                         |                |                   | 115 community controls | ↑↑↑       |
| Mukaiya et al. (50)| 1991–93      | Men                     | Not specified  | 104               | 104 (chronic liver disease) | ↑↑↑       |
| Takeshita et al. (51)| 1993–96   | Men                     | Not specified  | 85                | 101             |                    | ↑↑↑                     |
| Koide et al. (52)  | 1994         | Men and women           | 46–79          | 84                | 84              |                    | —                      |
| Iida et al. (53)   | 1999–2001    | Men and women           | Not specified  | 495               | 194             |                    | ↑↑                     |
| Matsuo et al. (54) | 1995–2000    | Men                     | 40–75          | 177               | 177 hospital controls | ↑↑        |
|                    |              | Women                   | 40–75          | 45                | 177 community controls | ↑↑↑       |
|                    |              |                         |                |                   | 149 hospital controls | —          |
| Munaka et al. (55) | 1997–98      | Men and women           | 34–92          | 78                | 138             |                    | ↑↑↑                     |
| Sakamoto et al. (56)| 2001–2004   | Men and women           | 40–79          | 209               | 275 hospital controls | ↑↑↑       |
|                    |              |                         |                |                   | 381 patients with chronic liver disease | ↑↑↑       |
| Fukushima et al. (57)| 2001–2002 | Men and women           | 17–85          | 73                | 253 (HCV-RNA-positive) | ↓↓        |
| Ohashi et al. (58) | 1970–2002    | Men and women           | Not specified  | 224               | 644             |                    | ↑↑↑                     |

↑↑↑↑, strongly positive; ↑↑↑, moderately positive; ↑↑, weakly positive; —, no association; ↓↓↓↓, moderately inverse.
information on hepatitis virus infection and the presence or absence of CLD was missing. In this regard, a plausible explanation is that former drinkers may have included high-risk individuals such as hepatitis virus carriers and CLD patients who had abstained from alcohol because of illness.

In the case-control studies identified, alcohol consumption was almost consistently associated with increased liver cancer risk. This was the case regardless of the type of controls (mostly healthy subjects vs. CLD patients or hepatitis virus carriers), and only one study on patients with chronic hepatitis C reported an inverse association (57), which somewhat differs from the situation in the cohort studies. A possible change in recent drinking habits among CLD patients can be taken into account in case-control studies, but not usually in cohort studies, and this matter might partly account for the above difference, although the exact reason remains unknown.

Since about 90% of patients with HCC in Japan are known to be chronically infected with HCV or HBV (6), the postulation that heavy alcohol consumption causes alcoholic cirrhosis and thereby leads to the development of HCC does not appear to play a major role. Instead, the potential modifying effect of alcohol on HCC risk among HCV- or HBV-infected individuals is likely to be more important. In this connection, most follow-up studies of patients with chronic hepatitis C over the past decade showed fairly consistent positive associations between alcohol drinking and HCC risk (21,24,27,28,30,34), with few exceptions (33). It remains unclear to what extent alcohol consumption increases the HCC risk among the Japanese general population who are not infected with HCV or HBV because no study exists on this issue.

Potential mechanisms linking the use of alcohol with the development of liver cancer are discussed elsewhere (3). As for the role of alcohol among those with HCV infection, which is the most important risk factor of HCC in Japan, several mechanisms including increased viral replication, enhanced HCV quasispecies complexity, increased liver-cell death, suppression of immune responses, iron overload and increased oxidative stress have been suggested (59,60).

The Japanese may be more susceptible than other ethnic groups, to potential carcinogenic effects of alcohol because about half of them represent heterozygous or homozygous carriers of the inactive aldehyde dehydrogenase (ALDH) 2 allele (ALDH2*2) (9), who have an excessive accumulation of acetaldehyde after alcohol intake; acetaldehyde has been classified as being possibly carcinogenic to humans (10). Epidemiologic data on the role of the ALDH2 genotype in hepatocarcinogenesis has been conflicting (49,51,52,55,56,61). Overall, no material differences have been observed in the ALDH2 genotype distribution between liver cancer patients and control subjects, although two studies of relatively small size reported a significantly increased risk among heterozygous or homozygous carriers of ALDH2*2 (55,61). Two studies suggested a significantly elevated risk of HCC for ALDH2*2 carriers vs. non-carriers among drinkers, but not among non-drinkers (55,66).

The IARC has concluded that there is sufficient evidence for the carcinogenicity of ethanol in experimental animals (3). Taken together, this systematic review confirms a biologically plausible positive association between alcohol drinking and liver cancer risk among the Japanese, and a meta-analysis should be conducted to obtain summary estimates for the overall magnitude of association. However, the studies included in this review employed very different categories of alcohol consumption (particularly in reference categories), which has made a meaningful meta-analysis unfeasible. A meta-analysis of several large-cohort studies using common alcohol consumption categories is now underway, and we hope it will address the above issue.

EVALUATION OF EVIDENCE ON ALCOHOL DRINKING AND LIVER CANCER RISK AMONG JAPANESE

From these results and based on assumed biological plausibility as previously evaluated by the IARC (3), we conclude that there is ‘convincing’ evidence that alcohol drinking increases the risk of primary liver cancer among the Japanese population. High-risk individuals such as patients with CLD and hepatitis virus carriers are strongly recommended to abstain from alcohol use.

Funding

This work was supported by a Grant-in-Aid for the Third Term Comprehensive Control Research for Cancer from the Ministry of Health, Labor and Welfare, Japan.

Conflict of interest statement

None declared.

References

1. Lieber CS. Alcohol and the liver: 1994 update. Gastroenterology 1994;106:1085–105.
2. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004;127: S35–50.
3. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 96. Consumption of Alcoholic Beverages and Ethyl Carbamate (Urethane). Lyon, France: IARC (in press).
4. World Cancer Research Fund. American Institute for Cancer Research. Diet, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: AICR 2007.
5. Gann Monograph on Cancer Research No. 51. Cancer Mortality and Morbidity Statistics: Japan and the World-2004. Tokyo, Japan: Scientific Societies Press 2004.
6. Ikai I, Arri S, Okazaki M, Okita K, Omoat M, Kojo M, et al. Report of the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan. Hepatol Res 2007;37:676–91.
7. Tanaka K, Ikematsu H, Hirohata T, Kashiwagi S. Hepatitis C virus infection and risk of hepatocellular carcinoma among Japanese: Possible role of type Ib (B) infection. J Natl Cancer Inst 1996;88:742–6.
8. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907–17.
9. Goedde HW, Agarwal DP, Fritze G, Meier-Tackmann D, Singh S, Beckmann G, et al. Distribution of ADH2 and ALDH2 genotypes in different populations. Hum Genet 1992;88:344–6.
10. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 71. Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. Lyon, France: IARC 1999.
11. Inoue M, Tsuji I, Wakai K, Nagata C, Mizoue T, Tanaka K, et al. Evaluation based on systematic review of epidemiological evidence among Japanese populations: tobacco smoking and total cancer risk. Jpn J Clin Oncol 2005;35:40–11.
12. World Health Organization. WHO Technical Reports Series 916. Diet, Nutrition and the Prevention of Chronic Diseases: Report of a Joint WHO/FAO Expert Consultation. Geneva, WHO 2003.
13. Kono S, Ikeda M, Tokudome S, Nishizumi M, Kuratsune M. Cigarette smoking, alcohol and cancer mortality: a cohort study of male Japanese physicians. Jpn J Cancer Res 1987;78:1323–8.
14. Hirayama T. A large-scale cohort study on risk factors for primary liver cancer, with special reference to the role of cigarette smoking. Cancer Chemother Pharmacol 1989;23(Suppl.):S114–7.
15. Inaba Y, Ikuchi S, Namishita T, Ichikawa S. The effect of smoking and drinking habit on the process from liver cirrhosis to liver cancer. Gan No Rinsho 1990;36:299–304 (in Japanese).
16. Shibata A, Fukuda K, Toshima H, Hirohata T, Hirohata I. The role of cigarette smoking and drinking in the development of liver cancer: 28 years of observations on male cohort members in a farming and fishing area. Cancer Detect Prev 1990;14:617–23.
17. Kato I, Tominaga S, Ikari A. The risk and predictive factors for developing liver cancer among patients with uncompensated decompensated liver cirrhosis. N Engl J Med 1993;328:1797–801.
18. Goodman MT, Moriwaki H, Vaeth M, Akiba S, Hayabuchi H, Mabuchi K. Prospective cohort study of risk factors for primary liver cancer in Hiroshima and Nagasaki. Japan. Epidemiology 1995;6:36–41.
19. Chiba T, Matsuzaki Y, Abei M, Osakada S, Osuga T, et al. The role of previous hepatitis B virus infection and heavy smoking in hepatocellular carcinoma-related hepatocellular carcinoma. Am J Gastroenterol 1996;91:1195–203.
20. Ikeda K, Saiioh S, Suzuki Y, Kobayashi M, Tsutoba A, Koida I, et al. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. J Hepatol 1998;28:930–8.
21. Tanaka K, Sakai H, Hashizume M, Hirohata T. A long-term follow-up study on risk factors for hepatocellular carcinoma among Japanese patients with liver cirrhosis. Jpn J Cancer Res 1998;89:1241–50.
22. Matsuhashi E, Kaneko S, Kobayashi K. Evaluation of background factors related to carcinogenesis in cirrhosis. Proceedings of 20th Inuyama Symposium. Tokyo: Chugai-igakusha 1998,159–64 (in Japanese).
23. Aizawa Y, Shibamoto Y, Takagi I, Zeniya M, Toda G. Analysis of factors affecting the appearance of hepatocellular carcinoma in patients with chronic hepatitis C. A long term follow-up study after histologic diagnosis. Cancer 2000;89:53–9.
24. Mori M, Haru M, Wada I, Hara T, Yamamoto K, Honda M, et al. Prospective study of hepatitis B and C viral infections, cigarette smoking, alcohol consumption, and other factors associated with hepatocellular carcinoma risk in Japan. Am J Epidemiol 2000;151:131–9.
25. Noda T, Imamichi H, Tanaka H, Kawata A, Hirano K, Ando T, et al. Cause-specific mortality risk among male alcoholics residing in the Osaka metropolitan area. Psychiatry Clin Neurosci 2001;55:465–72.
26. Hamada H, Yatsushahi H, Yano K, Daikoku M, Arisawa M, Inoue O, et al. Impact of aging on the development of hepatocellular carcinoma in patients with posttransfusion chronic hepatitis C. Cancer 2002;95:338–47.
27. Takimoto M, Ohkoshi S, Ichida T, Takeda Y, Nomoto M, Asakura H, et al. Interferon inhibits progression of liver fibrosis and reduces the risk of hepatocarcinogenesis in patients with chronic hepatitis C: a retrospective multicenter analysis of 652 patients. Dig Dis Sci 2007;52:170–6.
28. Uetake S, Yamamura M, Itoh S, Kawashima O, Takeda K, Ohata M. Analysis of risk factors for hepatocellular carcinoma in patients with HBs antigen- and anti-HCV antibody-negative alcoholic cirrhosis: clinical significance of prior hepatitis B virus infection. Alcohol Clin Exp Res 2003;27:475–81.
29. Iwasaki Y, Takaguchi K, Ikeda H, Makino Y, Araki Y, Ando M, et al. Risk factors for hepatocellular carcinoma in hepatitis C patients with sustained virologic response to interferon therapy. Liver Int 2004;24:603–10.
30. Ogimoto I, Shibata A, Kurozawa Y, Nose T, Yoshimura T, Suzuki H, et al. Risk of death due to hepatocellular carcinoma among drinkers and ex-drinkers. Univariate analysis of JACC study data. Kurume Med J 2004;51:59–70.
31. Nakaya N, Tsukumo Y, Kuriyama S, Hozawa A, Shimazu T, Kurashima K, et al. Alcohol consumption and the risk of cancer in Japanese men: the Miyagi cohort study. Eur J Cancer Prev 2005;14:169–74.
32. Ikeda K, Marusawa H, Osaki Y, Nakamura T, Kitajima N, Yamashita Y, et al. Antibody to hepatitis B core antigen and risk for hepatitis C-related hepatocellular carcinoma: a prospective study. Ann Intern Med 2007;146:649–56.
33. Okhi T, Tateishi R, Sato T, Masuzaki R, Imamura J, Goto T, et al. Obesity is an independent risk factor for hepatocellular carcinoma development in chronic hepatitis C patients. Clin Gastroenterol Hepatol 2008;6:459–64.
34. Inaba Y, Maruchi N, Matsuda M, Yoshihara N, Yamamoto S. A case-control study on liver cancer with special emphasis on the possible aetiological role of schistosomiasis. Int J Epidemiol 1984;13:408–12.
35. Oshima A, Tsukuma H, Hiyama T, Fujimoto I, Yamano H, Tanaka M. Follow-up study of HBs Ag-positive blood donors with special reference to effect of drinking and smoking on development of liver cancer. Int J Cancer 1984;34:775–9.
36. Hiraga M, Araki S, Murata K, Yokoyama K, Terao H. Assessment of the interaction of hepatitis B antigen and alcohol in primary hepatocellular carcinoma: a case-control study. Jpn J Public Health 1986;33:636–9 (in Japanese).
37. Kiyosawa K, Inmai H, Sodeyama T, Franca ST, Yousuf M, Furuta S, et al. Comparison of anamnestic history, alcohol intake and smoking, nutritional status, and liver dysfunction between thorotrust patients who developed primary liver cancer and those who did not. Environ Res 1989;49:166–72.
38. Kobayashi K, Ono M, Tanaka N, Hattori N. A comparison between hepatocellular carcinoma-developing and non-carcinoma-developing patients with cirrhosis over a long follow-up period. Hepatogastroenterology 1990;37:445–8.
39. Tsukuma H, Hiyama T, Ohkoshi S, Ohno M, Fujimoto I, Kasugai H, et al. A case-control study of hepatocellular carcinoma in Osaka, Japan. Jpn J Cancer Res 1990;91:231–6.
40. Tanaka K, Hirohata T, Takeshita H, Hirohata I, Koga S, Sugimachi K, et al. Hepatitis B virus, cigarette smoking and alcohol consumption in the development of hepatocellular carcinoma: a case-control study in Fukuoka, Japan. Int J Cancer 1992;51:509–14.
41. Haratake J, Kasai T, Takeda S. An epidemiologic comparative study of hepatocellular carcinoma caused by various etiologic factors. Shokaki Gan Rinsho 1992;38:297–301 (in Japanese).
42. Fujikawa K, Shibata A, Hirohata I, Tanikawa K, Yamaguchi G, Ishii M. A hospital-based case-control study on hepatocellular carcinoma in Fukuoka and Saga Prefectures, northern Kyushu, Japan. Jpn J Cancer Res 1993;84:708–14.
43. Yamaguchi G. Hepatocellular carcinoma and its risk factors—their annual changes and effects on the age at onset. Kurume Med J 1993;40:33–40.
44. Une H, Osajima K, Momose Y, Esaki H. A case-control study on liver cancer in the Chikuko area, Fukuoka prefecture. Minzoku Iseki 1993;59:241–7.
45. Tanaka H, Hiyama T, Tsukuma H, Imaoka S, Morisada K, Iwanaga T, et al. Impact of alcohol consumption on the development of hepatocellular carcinoma: a case-control study using hospitalized patients. Shokaki Gan 1995;5:117–22 (in Japanese).
46. Chiba T, Matsuzaki Y, Abei M, Shoda J, Aikawa T, Tanaka N, et al. Multivariable analysis of risk factors for hepatocellular carcinoma in Japan.
patients with hepatitis C virus-related liver cirrhosis. J Gastroenterol 1996;31:552–8.
48. Murata M, Takeyama K, Choi BC, Pak AW. A nested case-control study on alcohol drinking, tobacco smoking, and cancer. Cancer Detect Prev 1996;20:557–65.
49. Shibata A, Fukuda K, Nishiyori A, Ogimoto I, Sakata R, Yonikawa K. A case-control study on male hepatocellular carcinoma based on hospital and community controls. J Epidemiol 1998;8:1–5.
50. Mukaiya M, Nishi M, Miyake H, Hirata K. Chronic liver diseases for the risk of hepatocellular carcinoma: a case-control study in Japan. Etiologic association of alcohol consumption, cigarette smoking and the development of chronic liver diseases. Hepatogastroenterology 1998;45:2328–32.
51. Takeshita T, Yang X, Inoue Y, Sato S, Morimoto K. Relationship between alcohol drinking, ADH2 and ALDH2 genotypes, and risk for hepatocellular carcinoma in Japanese. Cancer Lett 2000;149:69–76.
52. Koide T, Ohno T, Huang XE, Iijima Y, Sugihara K, Mizokami M, et al. HBV/HCV infection, alcohol, tobacco and genetic polymorphisms for hepatocellular carcinoma in Nagoya, Japan. Asian Pac J Cancer Prev 2000;1:237–43.
53. Iida F, Yamagata Z, Iida R, Hosoda K, Okada S, Matsuda M, et al. Hepatocellular carcinoma in Yamanashi prefecture—a trial of case-control study (third report). Yamanashi Igaku 2002;30:1–7 (in Japanese).
54. Matsuo M. Association between diabetes mellitus and hepatocellular carcinoma: results of a hospital- and community-based case-control study. Kurume Med J 2003;50:91–8.
55. Munaka M, Kohshi K, Kawamoto T, Takasawa S, Nagata N, Itoh H, et al. Genetic polymorphisms of tobacco- and alcohol-related metabolizing enzymes and the risk of hepatocellular carcinoma. J Cancer Res Clin Oncol 2003;129:355–60.
56. Sakamoto T, Hara M, Higaki Y, Ichiba M, Horiita M, Mizuta T, et al. Influence of alcohol consumption and gene polymorphisms of ADH2 and ALDH2 on hepatocellular carcinoma in a Japanese population. Int J Cancer 2006;118:1501–7.
57. Fukushima W, Tanaka T, Ohfuji S, Habu D, Tamori A, Kawada N, et al. Does alcohol increase the risk of hepatocellular carcinoma among patients with hepatitis C virus infection? Hepatol Res 2006;34:141–9.
58. Ohishi W, Fujiwara S, Cologne JB, Suzuki G, Akahoshi M, Nishi N, et al. Risk factors for hepatocellular carcinoma in a Japanese population: a nested case-control study. Cancer Epidemiol Biomarkers Prev 2008;17:846–54.
59. Vento S, Cainelli F. Does hepatitis C virus cause severe liver disease only in people who drink alcohol? Lancet Infect Dis 2002;2303–9.
60. Koike K, Tsutsumi T, Miyoshi H, Shinzawa S, Shintani Y, Fujie H, et al. Molecular basis for the synergy between alcohol and hepatitis C virus in hepatocarcinogenesis. J Gastroenterol Hepatol 2008;23(Suppl. 1):S87–91.
61. Kato S, Tajiri T, Matsukura N, Matsuda N, Tanai N, Mamada H, et al. Genetic polymorphisms of aldehyde dehydrogenase 2, cytochrome p450 2E1 for liver cancer risk in HCV antibody-positive Japanese patients and the variations of CYP2E1 mRNA expression levels in the liver due to its polymorphism. Scand J Gastroenterol 2003;38:886–93.

Appendix

Research group members: Shoichiro Tsugane [principal investigator], Manami Inoue, Shizuka Sasazuki, Motoki Iwasaki, Tetsuya Otani [until 2006], Norie Kurahashi [since 2007], Taichi Shimazu [since 2007] (National Cancer Center, Tokyo); Ichiro Tsuji [since 2004], Yoshitaka Tsubono [in 2003] (Tohoku University, Sendai); Yoshikazu Nishino (Miyagi Cancer Research Institute, Natori, Miyagi); Kenji Wakai (Nagoya University, Nagoya); Keitaro Matsuo [since 2006] (Aichi Cancer Center, Nagoya); Chisato Nagata (Gifu University, Gifu); Tetsuya Mizoue (International Medical Center of Japan, Tokyo); Keitaro Tanaka (Saga University, Saga).