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

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Received June 10, 2014; accepted July 14, 2014

Objective: The potential associations of diabetes mellitus with malignant neoplasms including liver cancer have become a great concern from both clinical and preventive perspectives. Although sufficient evidence for a positive association between diabetes and liver cancer already exists, it would be informative to summarize up-to-date epidemiologic data in Japan.

Methods: We systematically reviewed epidemiologic studies on diabetes and liver cancer among Japanese populations. Original data were obtained by searching the MEDLINE (PubMed) and Ichushi databases, complemented with manual searches. The evaluation was performed in terms of the magnitude of association in each study and the strength of evidence (‘convincing’, ‘probable’, ‘possible’ or ‘insufficient’), together with biological plausibility.

Results: We identified 19 cohort studies, one pooled-analysis of seven cohort studies, and seven case–control studies. Of 24 relative risk estimates of liver cancer for diabetes reported in those cohort studies, 17 showed a weak to strong positive association, six revealed no association and one demonstrated a weak inverse association (summary relative risk 2.10, 95% confidence interval 1.60–2.76). Ten relative risk estimates from the case–control studies showed a weak to strong positive association (n = 9) or no association (n = 1; summary relative risk 2.32, confidence interval 1.73–3.12). Overall, the summary relative risk became 2.18 (confidence interval 1.78–2.69). Heterogeneity in relative risks was significant for the difference in categories of study population (P = 0.01), but not in study type (P = 0.39) or sex (P = 0.33).

Conclusions: Diabetes mellitus ‘probably’ increases the risk of liver cancer among the Japanese population.

Key words: liver cancer – diabetes – systematic review – epidemiology – Japanese
INTRODUCTION

The prevalence of diabetes mellitus has been increasing in Japan (1), and the potential associations of diabetes with major chronic diseases including malignant neoplasms have become a great concern from both clinical and preventive points of view. For primary liver cancer, most of which (>90%) comprises hepatocellular carcinoma (2), sufficient evidence already exists for a positive association with diabetes mellitus, as illustrated by several meta-analyses showing ~2–4-fold increase of summary relative risk (RR) in diabetic vs. non-diabetic individuals (3–7). Since the publication of these meta-analyses, however, relevant epidemiologic data including those in a large pooled analysis (8) have still been accumulating, particularly in Japan, and summarizing the most recent and previous data would be informative in considering the prevention of liver cancer in this country.

We aimed to review and summarize up-to-date epidemiologic findings on diabetes mellitus and liver cancer among the Japanese, whose dominant risk factors of liver cancer represent hepatitis C and B virus infection (2,9) and alcohol consumption (10). This work was conducted as part of a project of systematic evaluation of the epidemiological evidence regarding lifestyles and cancers in Japan (11).

PATIENTS AND METHODS

The details of the evaluation method have been described elsewhere (11). In brief, original data for this review were identified by searching 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 diabetes mellitus and liver cancer incidence/mortality among the Japanese from 1950 (or 1983 for the Ichushi database) to March 2014, including papers in press if available, were identified using the search terms ‘diabetes’, ‘liver neoplasms’, ‘hepatocellular’, ‘cohort’, ‘follow-up’, ‘case–control’, ‘Japan’ and ‘Japanese’ as keywords. Papers written in either English or Japanese were reviewed, and only studies on Japanese populations living in Japan were included. The individual results were summarized in the tables separately by study design as cohort or case–control studies.

The evaluation was made based on the magnitude of association and the strength of evidence. First, the former was assessed by classifying the RR in each study into the following four categories, while considering statistical significance (SS) or no statistical significance (NS): (i) ‘strong’ (symbol \(\downarrow\downarrow\downarrow\) or \(\uparrow\uparrow\uparrow\)) when RR < 0.5 (SS) or RR > 2.0 (SS); (ii) ‘moderate’ (symbol \(\downarrow\downarrow\) or \(\uparrow\uparrow\)) 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 \(\downarrow\) or \(\uparrow\)) 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. The ratios of observed to expected number of deaths, which were reported in early follow-up studies of only diabetic patients with a general population as a reference group, were also used although their nature was somewhat different from that of RRs. In the case of multiple publications of analyses of the same or overlapping datasets, only data from the largest or most updated results were included. Studies that reported RRs for impaired glucose tolerance only, or did not provide RRs or data necessary for the present authors to calculate relevant RRs were excluded.

After the above process, the strength of evidence was evaluated in a manner similar to that used in the WHO/FAO Expert Consultation Report, in which evidence was classified as ‘convincing’, ‘probable’, ‘possible’ and ‘insufficient’ (12). Biological plausibility was also taken into account for this evaluation. The final judgment was made based on a consensus of the research group members. 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.

In meta-analyses of this paper, we estimated the summary RR of liver cancer for diabetes mellitus by using random effects models according to the method of DerSimonian and Laird because individual RRs across studies were significantly heterogeneous based on the Q statistic (13,14). We also performed random-effects meta-regression analyses with covariates of study type (two categories: cohort or case–control), sex (three categories: men, women or both) and study population (three categories: general population, diabetic patients or patients with chronic liver disease [CLD]) to explore a potential source of the above heterogeneity. The covariate for the difference in event (death or incidence) was not included in these analyses due to the limited number of RRs for liver cancer deaths. All statistical analyses were performed with the STATA statistical package (Stata Corp., College Station, TX, USA). Two-sided \(P\) values <0.05 were considered statistically significant.

RESULTS

We identified 19 cohort studies (15–33) and one pooled analysis including seven cohort studies (8) (Table 1) as well as seven case–control studies (34–40) (Table 2). For convenience, the pooled analysis (8) was treated as a single study hereafter. Of those cohort studies, three presented results by sex (8,15,33), two presented results for men only (20,23) and 15 presented results only for men and women combined (16–19,21,22,24–32). The respective numbers for the case–control studies are three (35,37,40), one (34) and three (36,38,39). In one cohort study (17), RRs were estimated separately for patients with chronic hepatitis and those with cirrhosis. As a result, 24 and 10 RR estimates in the cohort...
| Reference       | Study period | Number of subjects for analysis | Source of subjects | Event followed | Number of incident cases or deaths | Category                        | Number among cases | Relative risk (RR) (95% CI or P) | Confounding variables considered | Comments                                                                 |
|-----------------|--------------|---------------------------------|--------------------|---------------|---------------------------------|--------------------------------|-------------------|----------------------------------|-------------------------------|--------------------------------------------------------------------------|
| Tsukuma et al.  | 1970–82      | 858 (484 Men and 374 women)     | Diabetic patients admitted for education at Osaka Prefectural Hospital | Death         | 20 (19 Men and 1 woman)        | O/E ratio for men         | 19                | 9.50 (5.72–14.84)                | Age and observation period   | The 95% CIs were not described in the original paper and were estimated by one of the authors (K.T.). |
| Sasaki et al.   | 1960–93      | 1939 (1200 Men and 739 women)   | Patients with NIDDM at Osaka Seijinbyo Center | Death         | 73                              | O/E ratio for liver cancer | 73                | 3.02 (2.37–3.80)                 | Sex, age and observation period | The 95% CI was not described in the original paper and were estimated by one of the authors (K.T.). HBsAg and anti-HCV were not tested. |
| Kato et al.     | ?–1995       | 542 (329 Men and 213 women)     | Patients with chronic hepatitis or cirrhosis due to hepatitis B or C virus infection | Incidence     | Not described                   | Chronic hepatitis (n = 355) | No adjustment      | No diabetes (n = 30) = 1.00     |                                | The RRs and 95% CIs were not described in the original paper and were estimated by one of the authors (K.T.). |
|                 |              |                                 |                    |               |                                 |                               |                   | Diabetes (n = 325) = 1.73 (0.42–7.15) |                                | All patients were HBsAg-positive and/or anti-HCV positive. |
|                 |              |                                 |                    |               |                                 |                               |                   | Liver cirrhosis (n = 187) = 1.00 |                                |                                |
|                 |              |                                 |                    |               |                                 |                               |                   | No diabetes (n = 39) = 1.00       |                                |                                |
|                 |              |                                 |                    |               |                                 |                               |                   | Diabetes (n = 148) = 1.17 (0.78–1.75) |                                |                                |
| Tazawa et al.   | 1987–?       | 279 (190 Men and 89 women)      | HCV-infected patients with chronic hepatitis without cirrhosis at Tsuchiura Kyodo General Hospital | Incidence     | 13 (11 Men and 2 women)        | No diabetes (n = 256)       | 1.00               | No adjustment                     | The age-adjusted RR was 9.4 (P = 0.002), but its CI was not shown. | All patients were anti-HCV and HCV-RNA positive. |
|                 |              |                                 |                    |               |                                 |                               |                   | Diabetes (n = 23) = 5.68 (1.80–18.18) |                                |                                |
| Author et al. | Year | Patients | Incidence | No diabetes | Diabetes | Sex, age, body mass index, drinking, ALT, HCV serotype, HCV core titer, interferon treatment, cirrhosis, histological grading and steatosis | Notes |
|--------------|------|----------|-----------|-------------|----------|---------------------------------------------------------------------------------------------------------------------------------|-------|
| Ohata et al. (19) | 1980–2000 | 161 (106 Men and 55 women) | Patients with chronic hepatitis or cirrhosis due to HCV infection | 70 | No diabetes | 1.00 | All patients were anti-HCV-positive and HBsAg-negative. |
| Uetake et al. (20) | 1988–2000 | 91 Men | Patients with HBsAg (−) anti-HCV (−) alcoholic cirrhosis at Jikei University Hospital | Incidence 13 Men | No diabetes | 1.00 | No adjustment |
| | | | | | Diabetes | 3 | 0.75 (0.22–2.51) | The RR and 95% CI were not described in the original paper and were estimated by one of the authors (K.T.). |
| Khan et al. (21) | 1977–2002 | 1989 (908 Men and 1081 women) | Residents of Tanno and Sohbetsu towns of Hokkaido | Death 8 (6 Men and 2 women) | Normal | 1 | Sex, age, albumin and hypertension treatment |
| | | | | | IGT | 5 | 11.36 (1.31–98.38) | HBsAg and anti-HCV were not tested. |
| Muto et al. (22) | Not described | 622 (294 Men and 328 women) | Patients with decompensated cirrhosis who had hypoalbuminemia | Incidence 89 | No diabetes | 1.00 | Treatment group (BCAA supplementation and diet therapy) |
| | | | | | Diabetes | 2 | 3.38 (0.30–38.73) | Anti-HCV and, probably, HBsAg status was available but was not adjusted for. |
| Torisu et al. (23) | 1978–2005 | 47 Men | Patients with alcoholic cirrhosis at Toranomon Hospital | Incidence 9 Men | No diabetes | 1.0 | Age |
| | | | | | Diabetes | 5 | 21.7 (2.4–193.7) | All patients were HBsAg-negative, anti-HCV-negative, and alcoholic. |
| Ohki et al. (24) | 1994–2006 | 1431 (727 Men and 704 women) | Patients with positive HCV-RNA at Tokyo University Hospital | Incidence 340 | No diabetes | 1.00 | Age, sex, alcohol, body mass index, serum albumin, bilirubin, ALT, prothrombin time, platelets and alpha-fetoprotein |
| | | | | | Diabetes | 1.26 (0.92–1.71) | All subjects were anti-HCV-positive and HBsAg-negative. |
| Tomiyama et al. (25) | 1989–2007 | 95 (19 Men and 76 women) | Patients with primary biliary cirrhosis at Kawasaki Medical School Hospital | Incidence 7 (3 Men and 4 women) | No diabetes | 1.00 | Age, history of blood transfusion, platelet count and Scheuer’s histological classification |
| | | | | | Diabetes | 4.54 (0.48–42.93) | All subjects were negative for hepatitis B and C virus markers. |
| Ikeda et al. (26) | 1976–2004 | 82 (67 Men and 15 women) | Patients with non-B, non-C cirrhosis at Toranomon Hospital | Incidence 16 | No diabetes | 1.00 | Sex, age, serum HBV-DNA and total alcohol intake |
| | | | | | Diabetes | 3.89 (1.22–12.47) | All subjects were HBsAg-negative and anti-HCV-negative. |
| Konishi et al. (27) | 1992–? | 197 (126 Men and 71 women) | Patients with HCV who had interferon therapy at Ehime University Hospital | Incidence 18 | Based on 75 g OGTT | 1.00 | Age, hepatic fibrosis stage and γ-GTP |
| | | | | | Normal/IGT | 4.627 (1.677–12.766) | All subjects were anti-HCV-positive and HBsAg-negative. |
| Reference   | Study period | Study population                                                                 | Category          | Number among cases | Relative risk (RR) (95% CI or \(P\)) | Confounding variables considered                                                                                                                                                                                                 | Comments                                                                                      |
|-------------|--------------|-----------------------------------------------------------------------------------|-------------------|--------------------|--------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Kurosaki et al. (28) | 1994—?      | Patients with chronic hepatitis C who received interferon therapy at Musashino Red Cross Hospital | Incidence 68      | No diabetes        | 1.00                                 | Age, sex, stage of fibrosis, grade of steatosis, response to interferon, ethanol consumption and body mass index                                                                 | All subjects were anti-HCV-positive and HBsAg-negative.                                      |
| Kuroda et al. (29)    | 1998—?      | Cirrhotic patients with HCV infection at Iwate Medical School                       | Incidence 60      | No diabetes        | 1.00                                 | No adjustment                                                                                                                                  | All subjects were anti-HCV-positive and HBsAg-negative.                                      |
| Takahashi et al. (30) | 2002—?      | HCV-positive patients who underwent liver biopsy and 75 g OGGT and who were treated with interferon | Incidence 13 (12 Men and 1 woman)     | No diabetes        | 1.00 (0.59—1.59)                    | Sex, age, alcohol, response to interferon therapy, fibrosis stage, alpha-fetoprotein and steatosis                                                                                                                                 | All subjects were anti-HCV-positive and HBsAg-negative.                                      |
| Kawamura et al. (31)  | 1997—?      | Patients with non-alcoholic fatty liver disease at Toranomon Hospital               | Incidence 16      | No diabetes        | 1.00                                 | Age, aspartate aminotransferase and platelet count                                                                                               | All subjects were anti-HCV-negative and HBsAg-negative.                                      |
| Arase et al. (32)     | 1990—?      | HCV-positive patients with chronic hepatitis or cirrhosis who were treated with interferon at Toranomon Hospital | Incidence 393 (272 Men and 121 women) | No diabetes        | 1.00 (1.09—9.50)                    | Age, sex, total alcohol intake, presence of cirrhosis, and response to interferon therapy                                                                                                                                                | All subjects were anti-HCV-positive and HBsAg-negative.                                      |
| Nakamura et al. (33)  | 1992—2008   | Residents of Takayama, Gifu prefecture                                             | Incidence 176 (106 Men and 70 women) | No diabetes        | 1.00                                | Age, smoking, body mass index, physical activity, education, histories of hypertension, stroke and ischemic heart disease, and intakes of total energy, fat, ethanol and coffee                                                                 | HBsAg and anti-HCV were not evaluated.                                                        |
and case–control studies, respectively, were used for this evaluation.

Study populations in the cohort studies were classified broadly into three categories: apparently healthy subjects (local residents) from a general population (8,21,33) \((n = 3)\), diabetic patients (15,16) \((n = 2)\) and patients with CLD (17–20,22–32) \((n = 15)\) (Table 1). Chronic infection with both hepatitis C virus (HCV) and hepatitis B virus (HBV) was taken into account in 13 cohort studies (18–20,23–32). In the case–control studies, a similar classification was possible based on the type of controls: apparently healthy subjects (local residents (34,35), first-visit cancer-free outpatients (37) or atomic bomb survivors (38)) \((n = 4)\) and patients with CLD (36,39,40) \((n = 3)\) (Table 2). Four case–control studies took into account both HCV and HBV infection (36,38–40).

A summary of the magnitude of association for the cohort studies and the case–control studies is shown in Tables 3 and 4, respectively. Of 24 RR estimates reported in 20 cohort studies, 10 (8,15,16,18,23,26,27,30,31,33) showed a strong positive association between diabetes and liver cancer, five (8,21,22,32) revealed a moderate positive association and two (17,19) demonstrated a weak positive association, while the remaining seven presented no association (15,17,20,24,28,29) or a weak inverse association (33). Of 10 RR estimates in seven case–control studies, nine (34–38,40) showed a weak to strong positive association and only one (39) presented no association.

Figure 1 illustrates a forest plot of the RRs of liver cancer for diabetes in individual studies and the corresponding summary RR. In this figure, sex-specific estimates are separately plotted. For both the cohort and case–control studies as well as all studies combined, the RRs were turned out to be significantly heterogeneous \((P < 0.001, 0.011, 0.001, \text{respectively})\) and the summary RR was estimated as 2.10 (95% CI 1.60–2.76) and 2.32 (95% CI 1.73–3.12) for the cohort and case–control studies, respectively. The summary RR for all studies combined became 2.18 (95% CI 1.78–2.69).

To explore a potential source of the heterogeneity between studies, we carried out random-effects meta-regression analyses with covariates of study type, sex and study population (Table 5). Table 5 also presents the summary RR of liver cancer for diabetes in each subgroup by a random-effects model. No significant differences in RRs were evident between subgroups by study type \((\chi^2 = 0.75\text{ with 1 degree of freedom \([DF]\), } P = 0.39\) or sex \((\chi^2 = 2.24\text{ with 2 DF, } P = 0.33)\), but subgroups by study population revealed a significant difference \((\chi^2 = 8.96\text{ with 2 DF, } P = 0.01)\). More specifically, the summary RR in the subgroup of diabetic patients was significantly higher than that in the subgroup of general population \((P = 0.004)\) or CLD patients \((P = 0.01)\). The residual \(I^2\) statistic was 76% without any covariates and 63% with all covariates, and the model with all covariates showed an adjusted \(R^2\) of 28% with an overall model \(P\) of 0.03.
| Reference          | Study period | Study subjects                                                                 | Type and source | Number of cases | Number of controls | Category          | RR (95% CI or p) | Confounding variables considered                                                                 | Comments                                                                 |
|--------------------|--------------|---------------------------------------------------------------------------------|-----------------|-----------------|-------------------|-------------------|-----------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Shibata et al. (34) | 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 two general hospitals in Kurume; Community controls (CCs): randomly sampled citizens of Kurume | 115 Males       | 115 Male HCs and 115 male CCs | Based on CCs     | No diabetes 1.00 | Matched (1:1) for sex, age (± 5 years for HCs and ± 3 years for CCs), residence (for HCs), and time of hospitalization (for HCs) | The RR and 95% CI were not described in the original paper and were estimated by one of the authors (K.T.). Anti-HCV and HBsAg status was not available for CCs. |
| Matsuo (35)        | 1995–2000    | Hospital-based (Kurume University Hospital)                                      | Cases: confirmed as HCC by histological, angiographical, and/or other findings; HCs: inpatients without chronic hepatitis or cirrhosis in two general hospitals in Kurume; 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) | For males based on CCs | No diabetes 1.00 | Matched for sex (1:4 for female HCs and 1:1 for other controls), age (± 5 years for HCs and ± 5 years for CCs), residence (for HCs) and time of hospitalization (for HCs) adjusted for matching factors, history of blood transfusion, smoking and drinking | Anti-HCV and HBsAg status was not available for CCs. |
| Kabutake et al. (36) | 1994–2006  | Hospital-based (Tokyo Women’s Medical University Hospital)                      | Cases: patients with alcoholic liver injury complicated with HCC; Controls: patients with alcoholic cirrhosis without HCC | 96 (92 Men and 4 women) | 65 (58 Men and 7 women) | No diabetes 1.00 | Diabetes 2.29 (1.20–4.37) |                                                                                                         | The RR and 95% CI were not described in the original paper and were estimated by one of the authors (K.T.). |
| Kuriki et al. (37) | 1989–2000    | Hospital-based (details not described)                                           | Cases: patients with primary liver cancer (International Classification of Diseases, 10th revision: C22); HCs: first-visit outpatients without past/present history of cancer | 340 (265 Men and 75 women) | 47 768 (14 199 men and 33 569 women) | For men           | No diabetes 1.00 | No matching adjusted for age, body mass index, drinking and smoking habits, physical exercise, bowel movement, family history of liver cancer, family history of diabetes, dietary restriction, raw vegetable intake, greasy food intake and snacking | Anti-HCV and HBsAg status was unknown. |
| Study                        | Years     | Study Design         | Cases: Details                                                                 | Controls: Details                                                                 | Diabetic Status | Methodology                                                                 | Matched Factors                                                                 | Adjustments                                                                 |
|------------------------------|-----------|----------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|----------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Ohishi et al. (38)           | 1970–2002 | Nested case–control  | Patients with incident HCC who had stored serum samples available;             | Survivors without HCC who had stored serum samples available;                 | Diabetes 10 years before diagnosis | Matched (1:3) for sex, age, city, time and method of serum storage, and radiation exposure adjusted for matching factors, hepatitis virus infection, alcohol consumption, smoking, coffee, body mass index and radiation dose to the liver | HBsAg and anti-HCV status was adjusted for.                                      |
| Taniguchi et al. (39)        | Not described | Hospital-based      | Patients with HCV-associated chronic hepatitis or cirrhosis with HCC;         | Patients with HCV-associated chronic hepatitis or cirrhosis without HCC;     | No diabetes 1.00 | No adjustment                                                             | Diabetes 1.35 (0.93–1.95)                                                      | The RR and 95% CI were not described in the original paper and were estimated by one of the authors (K.T.). All subjects were anti-HCV-positive. |
| Horie et al. (40)            | 2007–08   | Hospital-based       | Patients with alcoholic cirrhosis with HCC;                                  | Patients with alcoholic cirrhosis without HCC;                              | For men                               | No adjustment                                                             | Diabetes 1.71 (1.26–2.33)                                                      | The RR and 95% CIs were not described in the original paper and were estimated by one of the authors (K.T.). All subjects were negative for HBsAg and anti-HCV. |

RR, relative risk; CI, confidence interval; HCC, hepatocellular carcinoma; HCs, hospital controls; CCs, community controls; anti-HCV, antibody to hepatitis C virus; HBsAg, hepatitis B surface antigen.
Table 3. Summary of cohort studies on diabetes mellitus and liver cancer among Japanese

| Reference          | Study period | Study population                                      | Sex   | Number of subjects | Age range | Event   | Number of incident cases or deaths | Magnitude of association |
|--------------------|--------------|-------------------------------------------------------|-------|--------------------|-----------|---------|-------------------------------------|--------------------------|
| Tsukuma et al. (15)| 1970–82      | Men 484                                               |       | Not specified      | Death     | 19      |                                     | ↑↑↑                      |
|                    |              | Women 374                                              |       | Not specified      | Death     | 1       |                                     | –                        |
| Sasaki et al. (16) | 1960–93      | Men and women 1939                                    |       | Not specified      | Death     | 73      |                                     | ↑↑↑                      |
| Kato et al. (17)   | ?–1995       | Men and women 335 (Chronic hepatitis)                 |       | Not specified      | Incidence | Not described | ↑                        |
|                    |              | 187 (Cirrhosis)                                       |       | Not specified      | Incidence | Not described | –                        |
| Tazawa et al. (18) | 1987–?       | Men and women 279 (HCV-associated chronic hepatitis)  |       | Not specified      | Incidence | 13      |                                     | ↑↑↑                      |
| Ohata et al. (19)  | 1980–2000    | Men and women 161 (HCV-associated chronic hepatitis or cirrhosis) |       | Not specified      | Incidence | 70      |                                     | ↑                        |
| Uetake et al. (20) | 1988–2000    | Men 91 (Alcoholic cirrhosis)                          |       | Not specified      | Incidence | 13      |                                     | –                        |
| Khan et al. (21)   | 1977–2002    | Men and women 1989                                    |       | Not specified      | Death     | 8       |                                     | ↑↑                      |
| Muto et al. (22)   | Not described| Men and women 622 ( Decompensated cirrhosis)          |       | Not specified      | Incidence | 89      |                                     | ↑↑                      |
| Torisu et al. (23) | 1978–2005    | Men 47 (Alcoholic cirrhosis)                          |       | Not specified      | Incidence | 9       |                                     | ↑↑↑                      |
| Ohki et al. (24)   | 1994–2006    | Men and women 1431 (HCV-associated chronic liver disease) |       | Not specified      | Incidence | 340     |                                     | –                        |
| Tomiyama et al. (25)| 1989–2007   | Men and women 95 ( Primary biliary cirrhosis)         |       | Not specified      | Incidence | 7       |                                     | ↑↑                      |
| Ikeda et al. (26)  | 1976–2004    | Men and women 82 (Non-B, non-C cirrhosis)             |       | Not specified      | Incidence | 16      |                                     | ↑↑↑                      |
| Konishi et al. (27)| 1992–?       | Men and women 197 (Patients with HCV)                 |       | Not specified      | Incidence | 18      |                                     | ↑↑↑                      |
| Kurosaki et al. (28)| 1994–?       | Men and women 1279 (Patients with chronic hepatitis C) |       | Not specified      | Incidence | 68      |                                     | –                        |
| Kuroda et al. (29) | 1998–?       | Men and women 133 (Cirrhotic patients with HCV infection) |       | Not specified      | Incidence | 60      |                                     | –                        |
| Takahashi et al. (30)| 2002–?       | Men and women 203 (HCV-positive patients treated with interferon) |       | Not specified      | Incidence | 13      |                                     | ↑↑↑                      |
| Kawamura et al. (31)| 1997–?       | Men and women 6508 (Patients with non-alcoholic fatty liver disease) |       | Not specified      | Incidence | 16      |                                     | ↑↑↑                      |
| Arase et al. (32)  | 1990–?       | Men and women 4302 (HCV-positive patients treated with interferon) |       | Not specified      | Incidence | 393     |                                     | ↑↑                      |
| Nakamura et al. (33)| 1992–2008    | Men 14 173                                            |       | Not specified      | Incidence | 106     |                                     | ↑↑↑                      |
|                    |              | Women 16 547                                           |       | Not specified      | Incidence | 70      |                                     | ↓                        |
| Sasazuki et al. (8) | 1984–2009    | Men 142 744                                           |       | Not specified      | Incidence | 1279    |                                     | ↑↑↑                      |
|                    |              | Women 165 995                                          |       | Not specified      | Incidence | 565     |                                     | ↑↑                      |

HCV, hepatitis C virus.
1.6–3.6 (3–7). The overall association was almost similar regarding the two main study designs, with a summary RR estimated at 2.2, which is analogous to those from previous meta-analyses. The overall evidence in Japan strongly supports a strong positive association between diabetes and liver cancer risk, indicating that the overall evidence in Japan strongly supports an increased risk of liver cancer among diabetic patients. The summary RR estimates in the case–control studies showed a weak to positive association, with 17 of the 24 RR estimates in the cohort studies and 9 of the 10 RR estimates in the case–control studies showing a positive association.

**DISCUSSION**

Overall, 17 of the 24 RR estimates in the cohort studies and 9 of the 10 RR estimates in the case–control studies showed a weak to strong positive association between diabetes and liver cancer risk, indicating that the overall evidence in Japan strongly supports an increased risk of liver cancer among diabetic patients. The summary RR was estimated at 2.2, which is analogous to those previously reported in several meta-analyses, with a range of 1.6–3.6 (3–7). The overall association was almost similar regardless of study type (case–control or cohort studies) or sex (men, women, or both) although three RR estimates from two early studies on diabetic patients (15,16) showed a summary RR of 4.6 (Table 5) that was significantly higher than that in subsequent studies on general populations (summary RR = 2.1) or CLD patients (summary RR = 1.9). Both studies (15,16) differed from the others in that they followed only diabetic patients and compared liver cancer mortality in such patients with that in the general population, adjusting only for age and observation period.

A major concern on the association between diabetes and liver cancer may be that diabetic subjects possibly include patients with hepatogenous diabetes as a complication of an advanced stage of CLD, such as cirrhosis (41), thereby showing a higher liver cancer risk in appearance. Hepatogenous diabetes manifests clinically as liver function deteriorates, and it appears difficult to differentiate Type 2 diabetes from hepatogenous diabetes (41). This issue will be particularly problematic for studies on general populations or diabetic patients without clinical information on the status of subjects’ liver disease and hepatitis virus markers. However, the majority of recent cohort studies on CLD patients with adjustment for the severity of CLD and hepatitis virus status (19,24,25,27,28,30–32) also found a positive association between diabetes and liver cancer risk.

As for the diagnosis of diabetes, self-reported histories were used in 6 (8,33–35,37,38) of the 27 studies evaluated, and the method of ascertaining diabetes was not clearly described in five studies (20,25,26,36,39). Virtually no studies took into account onset age, duration and treatment of diabetes, which appear difficult to verify but likely have influence on the disease course if diabetes truly causes a risk increase of liver cancer. Of note, some anti-diabetic drugs have been suspected to be protective (e.g. metformin (42)) or promotive (e.g. insulin and sulfonylurea (43)) in human carcinogenesis. These issues may have caused some underestimation or overestimation of true associations. Although Type 1 and Type 2 diabetes were not clearly distinguished in most studies, it seems reasonable to assume that most study subjects had Type 2 diabetes because Type 1 diabetes is rare in adults. Besides, diabetic patients may undergo more medical checkups than non-diabetic subjects, leading to increased detection of cancer and thus some overestimation of the positive association.

Additional methodological limitations should be considered. First, selection bias and information bias (e.g. recall bias on self-reported history of diabetes) might have distorted the results, especially in the hospital-based case–control studies (34–37,39,40). Second, potential confounders were not always considered in the 27 studies evaluated. Hepatitis status, alcohol drinking or obesity (or body mass index) was not controlled in 10 (8,15–17,21,22,33–35,37), 15 (15–18,20–23,25,27,29,34,36,39,40) or 20 (15–18,20–23,25–27,29–32,34–36,39,40) studies, respectively, although whether or not obesity should be controlled may be open to question due to the possible similarity in etiological mechanisms between diabetes and obesity, as discussed below. Moreover, only five studies (8,33,35,37,38) controlled for smoking that is now regarded as a risk factor (44–46). Finally, publication bias could not be ruled out although statistical tests for the presence of such a bias revealed insignificant results (P = 0.09 and 0.17 by the Begg’s and Egger’s tests, respectively; data not shown) (13,14).
In relation to the biological plausibility for the observed positive association between diabetes and liver cancer, several mechanisms have been proposed. First, Type 2 diabetes is characterized by insulin resistance and resulting hyperinsulinemia. Insulin can exert a potentially mitogenic effect by activating the insulin receptor and then triggering intracellular signaling cascades that have the potential to be both mitogenic and anti-apoptotic (e.g. phosphatidylinositol 3-kinase-AKT pathway) (47) and by interacting with the insulin-like growth factor-1 (IGF-1) receptor playing a pivotal role in cancer cell...
proliferation (48). Elevated insulin can also increase free IGF-1 (i.e. bio-active form of IGF-1) in blood via reducing the production of IGF-1 binding proteins 1 and 2 in the liver, thereby leading to tumor development (49). This is the most frequently proposed hypothesis, which also represents a possible mechanism underlying the association between obesity and liver cancer (49,50). If this mechanism mainly contributes to hepatocarcinogenesis, adjusting for obesity as a common complication of Type 2 diabetes might be overadjustment. Secondly, hyperglycemia among diabetic patients can increase oxidative stress in the cell due to an overload of glucose oxidation and other mechanisms leading to the production of reactive oxygen species (ROS) such as hydroxyl radical (51). ROS can bind DNA, can cause gene mutations and may induce cancer development. Although it is still unclear whether hyperglycemia is associated with the development of cancer via ROS production, it is noteworthy that long-term iron reduction therapy with phlebotomy and low-iron diet, which is believed to suppress the production of ROS including hydroxyl radical (52), has lowered the incidence of hepatocellular carcinoma in patients with chronic hepatitis C (53). Lastly, patients with Type 2 diabetes often have obesity leading to elevated levels of pro-inflammatory factors such as tumor necrosis factor-alpha and interleukin-6 and decreased levels of adiponectin with anti-inflammatory actions, and resulting chronic inflammation can promote hepatocarcinogenesis (50).

**Acknowledgement**

The authors gratefully acknowledge the assistance of Ms Izumi Suenaga.

**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 and the National Cancer Center Research and Development Fund.

**Conflict of interest statement**

None declared.

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**Table 5.** Summary relative risks (RR) and 95% confidence intervals (CI) of liver cancer for diabetes mellitus in subgroups by study type, sex, and study population among Japanese

| Subgroup                  | No. of RR estimates | Summary RR (95% CI) | P for difference between subgroup
|---------------------------|---------------------|---------------------|-------------------------------|
| **Study type**            |                     |                     |                               |
| Cohort                    | 24                  | 2.10 (1.60–2.76)    | 0.39                          |
| Case–control              | 10                  | 2.32 (1.73–3.12)    |                               |
| **Sex**                   |                     |                     |                               |
| Men                       | 9                   | 2.68 (1.81–3.96)    | 0.33                          |
| Women                     | 6                   | 2.56 (1.19–5.50)    |                               |
| Both                      | 19                  | 1.88 (1.44–2.45)    |                               |
| **Study population**      |                     |                     |                               |
| General population        | 11                  | 2.10 (1.82–2.42)    | 0.01                          |
| Diabetic patients         | 3                   | 4.56 (1.64–12.7)    |                               |
| Patients with CLD         | 20                  | 1.90 (1.47–2.47)    |                               |

CLD, chronic liver disease.

*Based on random effects meta-regression including covariates of study type (cohort or case–control), sex (men, women or both) and study population (general population, diabetic patients or CLD patients).
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**Appendix**

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