引用文献リスト

大腸がん

食物繊維と大腸がんとの関連に関するコホート研究（付表 S-1）

(1) Otani T, Iwasaki M, Ishihara J, Sasazuki S, Inoue M, Tsugane S; Japan Public Health Center-Based Prospective Study Group. Dietary fiber intake and subsequent risk of colorectal cancer: the Japan Public Health Center-based prospective study. Int J Cancer 2006; 119: 1475-1480.

(2) Wakai K, Date C, Fukui M, Tamakoshi K, Watanabe Y, Hayakawa N, Kojima M, Kawado M, Suzuki K, Hashimoto S, Tokudome S, Ozasa K, Suzuki S, Toyoshima H, Ito Y, Tamakoshi A; JACC Study Group. Dietary fiber and risk of colorectal cancer in the Japan collaborative cohort study. Cancer Epidemiol Biomarkers Prev 2007; 16: 668-675.

食物繊維と大腸がんとの関連に関するケースコントロール研究（付表 S-2）

(3) Wakai K, Hirose K, Matsuo K, Ito H, Kuriki K, Suzuki T, Kato T, Hirai T, Kanemitsu Y, Tajima K. Dietary risk factors for colon and rectal cancers: a comparative case-control study. J Epidemiol 2006; 16: 125-135.

カルシウム及びビタミンDと大腸がんとの関連に関するコホート研究（表 I-5）

(1) Otani T, Iwasaki M , Sasazuki S, Inoue M, Tsugane S for the Japan Public Health Center-Based Prospective Study Group. Plasma vitamin D and risk of colorectal cancer: the Japan Public Health Center-Based Prospective Study. Br J Cancer 2007; 97: 446–451.

(2) Ishihara J, Inoue M, Iwasaki M, Sasazuki S, Tsugane S. Dietary calcium, vitamin D, and the risk of colorectal cancer. Am J Clin Nutr 2008; 88: 1576-1583.

カルシウム及びビタミンDと大腸がんとの関連に関するケースコントロール研究（表 I-6）

(1) Wakai K, Hirose K, Matsuo K, Ito H, Kuriki K, Suzuki T, Kato T, Hirai T, Kanemitsu Y, Tajima K. Dietary risk factors for colon and rectal cancers: a comparative case-control study. J Epidemiol 2006; 16: 125-135.

(2) Mizoue T, Kimura Y, Toyomura K, Nagano J, Kono S, Mibu R, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Ikejiri K, Futami K, Yasunami Y, Maekawa T, Takenaka K, Ichimiya H, Imaizumi N. Calcium, dairy foods, vitamin D, and colorectal cancer risk: the Fukuoka Colorectal Cancer Study. Cancer Epidemiol Biomarkers Prev 2008; 17: 2800-2807.

身長と大腸がんとの関連に関するコホート研究（付表 S-3）

(1) Shimizu N, Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T, Matsushita S. Height,

weight, and alcohol consumption in relation to the risk of colorectal cancer in Japan: a prospective study. Br J Cancer 2003; 88: 1038–1043.

(2) Tamakoshi K, Wakai K, Kojima M, Watanabe Y, Hayakawa N, Toyoshima H, Yatsuya H, Kondo T, Tokudome S, Hashimoto S, Suzuki K, Ito Y, Tamakoshi A; for the JACC Study Group. A prospective study of body size and colon cancer mortality in Japan: The JACC Study. Int J Obes Relat Metab Disord 2004; 28: 551–558.

(3) Otani T, Iwasaki M, Inoue M, Tsugane S for the Japan Public Health Center-based Prospective Study Group. Body mass index, body height, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan Public Health Center-based Prospective Study. Cancer Causes Control 2005; 16: 839–850.

肺がん

BMI と肺がんとの関連に関するコホート研究（付表 S-4）

(1) Kuriyama S, Tsubono Y, Hozawa A, Shimazu T, Suzuki Y, Koizumi Y, Suzuki Y, Ohmori K, Nishino Y, Tsuji I. Obesity and risk of cancer in Japan. Int J Cancer 2005; 113: 148-157.

(2) Kondo T, Hori Y, Yatsuya H, Tamakoshi K, Toyoshima H, Nishino Y, Seki N, Ito Y, Suzuki K, Ozasa K, Watanabe Y, Ando M, Wakai K, Tamakoshi A for the JACC Study Group. Lung cancer mortality and body mass index in a Japanese cohort: findings from the Japan Collaborative Cohort Study (JACC Study). Cancer Cause Control 2007; 18: 229-234.

BMI と肺がんとの関連に関するケースコントロール研究（付表 S-5）

(1) Kanashiki M, Sairenchi T, Saito Y, Ishikawa H, Satoh H, Sekizawa K. Body mass index and lung cancer: a case-control study of subjects participating in a mass-screening program. Chest 2005; 128: 1490-1496.

大豆製品と肺がんとの関連に関するコホート研究（付表 S-6）

(1) Hirayama T. Life-style and mortality. Karger, Basel, 1990.

(2) Ozasa K, Watanabe Y, Ito Y, Suzuki K, Tamakoshi A, Seki N, Nishino Y, Kondo T, Wakai K, Ando M, Ohno Y for the JACC Study Group. Dietary habits and risk of lung cancer death in a large-scale cohort study (JACC Study) in Japan by sex and smoking habit. Jpn J Cancer Res 2001; 92: 1259-1269.

(3) Takezaki T, Inoue M, Kataoka H, Ikeda S, Yoshida M, Ohashi Y, Tajima K, Tominaga S. Diet

and lung cancer risk from a 14-year population-based prospective study in Japan: with special reference to fish consumption. Nutr Cancer 2003; 45: 160-167.

(4) Khan MMH, Goto R, Kobayashi K, Suzumura S, Nagata Y, Sonoda T, Sakauchi F, Washio M, Mori M. Dietary habits and cancer mortality among middle aged and older Japanese living in Hokkaido, Japan by cancer site and sex. Asian Pac J Cancer Prev 2004; 5: 58-65.

大豆製品と肺がんとの関連に関するケースコントロール研究（付表 S-7）

(1) Wakai K, Ohno Y, Genka K, Ohmine K, Kawamura T, Tamakoshi A, Lin Y, Nakayama T, Aoki K, Fukuma S. Risk modification in lung cancer by a dietary intake of preserved foods and soyfoods: findings from a case-control study in Okinawa, Japan. Lung Cancer 1999; 25: 147-159.

(2) Takezaki T, Hirose K, Inoue M, Hamajima N, Yatabe Y, Mitsumomi T, Sugiura T, Kuroishi T, Tajima K. Dietary factors and lung cancer risk in Japanese: with special reference to fish consumption and adenocarcinomas. Br J Cancer 2001; 84: 1199-1206.

(3) Huang XE, Hirose K, Wakai K, Matsuo K, Ito H, Xiang J, Takezaki T, Tajima K. Comparison of lifestyle risk factors by family history for gastric, breast, lung and colorectal cancer. Asian Pac J Cancer Prev 2004; 5: 419-427.

(4) Matsuo K, Hiraki A, Ito H, Kosaka T, Suzuki T, Hirose K, Wakai K, Yatabe Y, Mitsudomi T, Tajima K. Soy consumption reduces the risk of non-small-cell lung cancers with epidermal growth factor receptor mutations among Japanese. Cancer Sci 2008; 99: 1202-1208.

乳がん

乳製品と乳がんとの関連に関するケース・コントロール研究（付表 S-8）

(1) Hirohata T, Shigematsu T, Nomura AMY, Nomura Y. Occurrence of breast cancer in relation to diet and reproductive history: a case-control study in Fukuoka, Japan. Natl Cancer Inst Monogr 1985; 69: 187-90.

(2) Kikuchi S, Okamoto N, Suzuki T, Kawahara S, Nagai H, Sakiyama T, Wada O, Inaba Y.A case control study of breast cancer, mammary cyst and dietary, drinking or smoking habit in Japan. Gan No Rinsho 1990; Spec No: 365-9.

(3) Kato I, Miura S, Kastumi F, Iwase T, Tashiro H, Fujita Y, et al. A case-control study of breast cancer among Japanese women: with special reference to family history and reproductive and dietary factors. Breast Cancer Res Treat 1992; 24: 51-59.

(4) Hirose K, Imaeda N, Tokudome Y, Goto C, Wakai K, Matsuo K, et al. Soybean products and

reduction of breast cancer risk: a case-control study in Japan. Br J Cancer 2005; 93: 15-22.

魚と乳がんとの関連に関するコホート研究（付表 S-9）

(5) Key T, Key TJ, Sharp GB, Appleby PN, Beral V, Goodman MT, Soda M, et al. Soya foods and breast cancer risk: a prospective study in Hiroshima and Nagasaki, Japan. Br J Cancer. 1999; 81: 1248-56.

魚と乳がんとの関連に関するケース・コントロール研究（付表S-10）

(1)Hirohata T, Shigematsu T, Nomura AMY, Nomura Y. Occurrence of breast cancer in relation to diet and reproductive history: a case-control study in Fukuoka, Japan. Natl Cancer Inst Monogr 1985; 69: 187-90.

(2)Kikuchi S, Okamoto N, Suzuki T, Kawahara S, Nagai H, Sakiyama T, Wada O, Inaba Y.A case control study of breast cancer, mammary cyst and dietary, drinking or smoking habit in Japan. Gan No Rinsho 1990; Spec No: 365-9.

(3) Kato I, Miura S, Kastumi F, Iwase T, Tashiro H, Fujita Y, et al. A case-control study of breast cance among Japanese women: with special reference to family history and reproductive and dietary factors. Breast Cancer Res Treat 1992; 24: 51-59.

(4)Hirose K, Imaeda N, Tokudome Y, Goto C, Wakai K, Matsuo K, et al. Soybean products and reduction of breast cancer risk: a case-control study in Japan. Br J Cancer 2005; 93: 15-22.

肝がん

糖尿病と肝がんとの関連に関するコホート研究（付表 S-11）

(1) 津熊秀明, 神田勤, 上松一郎. 糖尿病教育入院患者の長期予後－特に肝癌, 肝硬変死亡の要因について－. 糖尿病 1987; 30: 349-56.

(2) Sasaki A, Uehara M, Horiuchi N, Hasegawa K, Shimizu T. A 15 year follow-up study of patients with non-insulin dependent diabetes mellitus (NIDDM) in Osaka, Japan. Long-term prognosis and causes of death. *Diabetes Res Clin Pract* 1996; 34: 47-55.

(3) 加藤活気, 杉本吉行, 村松雅人, 金山均, 片田直幸. ウイルス性慢性肝疾患における糖尿病の合併および長期予後に及ぼす糖尿病合併の影響. プラクティス 1997; 14: 187-91.

(4) Ohata K, Hamasaki K, Toriyama K, Matsumoto K, Saeki A, Yanagi K, Abiru S, Nakagawa Y, Shigeno M, Miyazoe S, Ichikawa T, Ishikawa H, Nakao K, Eguchi K. Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. *Cancer* 2003; 97: 3036-43.

(5) Shibata A, Ogimoto I, Kurozawa Y, Nose T, Yoshimura T, Suzuki H, Iwai N, Sakata R, Fujita

Y, Ichikawa S, Fukuda K, Tamakoshi A. Past medical history and risk of death due to hepatocellular carcinoma, univariate analysis of JACC study data. *Kurume Med J* 2003; 50: 109-19.

(6) Uetake S, Yamauchi 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: 47S-51S.

(7) Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. *Arch Intern Med* 2006; 166: 1871-7.

(8) Khan MM, Saito S, Takagi S, Ohnishi H, Izumi H, Sakauchi F, Washio M, Sonoda T, Nagata Y, Asakura S, Kobayashi K, Mori M, Shimamoto K. Relationship between hepatocellular carcinoma and impaired glucose tolerance among Japanese. *Hepatogastroenterology* 2006; 53: 742-6.

(9) Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, Kato M, Nakamura T, Higuchi K, Nishiguchi S, Kumada H, Ohashi Y. Overweight and obesity increase the risk for liver cancer in patients with liver cirrhosis and long-term oral supplementation with branched-chain amino acid granules inhibits liver carcinogenesis in heavier patients with liver cirrhosis. *Hepatol Res* 2006; 35: 204-14.

(10) Torisu Y, Ikeda K, Kobayashi M, Hosaka T, Sezaki H, Akuta N, Kawamura Y, Yatsuji H, Suzuki F, Suzuki Y, Arase Y, Kumada H. Diabetes mellitus increases the risk of hepatocarcinogenesis in patients with alcoholic cirrhosis: A preliminary report. *Hepatol Res* 2007; 37: 517-23.

(11) Ohki T, Tateishi R, Sato T, Masuzaki R, Imamura J, Goto T, Yamashiki N, Yoshida H, Kanai F, Kato N, Shiina S, Yoshida H, Kawabe T, Omata M. Obesity is an independent risk factor for hepatocellular carcinoma development in chronic hepatitis C patients. *Clin Gastroenterol Hepatol* 2008; 6: 459-64.

糖尿病と肝がんとの関連に関するケースコントロール研究（付表 S-12）

(1) Shibata A, Fukuda K, Nishiyori A, Ogimoto I, Sakata R, Tanikawa K. A case-control study on male hepatocellular carcinoma based on hospital and community controls. *J Epidemiol* 1998; 8: 1-5.

(2) 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.

(3) Kuriki K, Hirose K, Tajima K. Diabetes and cancer risk for all and specific sites among Japanese men and women. *Eur J Cancer Prev* 2007; 16: 83-9.

(4) Ohishi W, Fujiwara S, Cologne JB, Suzuki G, Akahoshi M, Nishi N, Takahashi I, Chayama K. Risk factors for hepatocellular carcinoma in a Japanese population: a nested case-control study. *Cancer Epidemiol Biomarkers Prev* 2008; 17: 846-54.

食道がん

野菜摂取と食道がんの関連に関するコホート研究（付表 S-13）

(2) Kinjo Y, Cui Y, Akiba S, Watanabe S, Yamaguchi N, Sobue T, Mizuno S, Beral V. Mortality risks of oesophageal cancer associated with hot tea, alcohol, tobacco and diet in Japan. J Epidemiol 1998; 8; 235-243.

(3) Sauvaget C, Nagano J, Hayashi M, Spencer E, Shimizu Y, Allen N. Vegetables and fruit intake and cancer mortality in the Hiroshima/Nagasaki Life Span Study. Br J Cancer 2003; 88: 689-694.

(4) Yamaji T, Inoue M, Sasazuki S, Iwasaki M, Kurahashi N, Shimazu T, Tsugane S. Fruit and vegetable consumption and squamous cell carcinoma of the esophagus in Japan: The JPHC study. Int J Cancer 2008;123: 1935-1940.

野菜摂取と食道がんの関連に関するケースコントロール研究（付表 S-14）

(1) Nakachi K, Imai K, Hoshiyama Y, Sasab T. The joint effects of two factors in the aetiology of oesophageal cancer in Japan. J Epidemiol Commun Health 1988;42: 355-364.

(2) Sasaki R, Aoki K, Takeda S. Contribution of dietary habits to esophageal cancer in Japan. Prog Clin Biol Res 1990; 346: 83-92.

(3) Hanaoka T, Tsugane S, Ando N, Ishida K, Kakegawa T, Isono K, Takiyama W, Takagi I, Ide H, Watanabe H, Iizuka T. Alcohol consumption and risk of esophageal cancer in Japan: a case-control study in seven hospitals. Jpn J Clin Oncol 1994;24:241-246.

(4) Takezaki T, Shinoda M, Hatooka S, Hasegawa S, Nakamura S, Hirose K, Inoue M, Hamajima N, Kuroishi T, Matsuura H, Tajima K. Subsite-specific risk factors for hypopharyngeal and esophageal cancer (Japan). Cancer Causes Control 2000; 11: 597-608.

(5) Yokoyama A, Kato H, Yokoyama T< Tsujinaka T, Muto M, Omori T, Haneda T, Kumagai Y, Igaki H, Yokoyama M, Watanabe H, Fukuda H, Yoshimizu H. Genetic polymorphisms of alcohol and aldehyde dehydrogenases and glutathione S-transferase M1 and drinking, smoking, and diet in Japanese men with esophageal squamous cell carcinoma. Carcinognesis 2002; 23: 1851-1859.

果物摂取と食道がんの関連に関するコホート研究（付表 S-15）

(1) Sauvaget C, Nagano J, Hayashi M, Spencer E, Shimizu Y, Allen N. Vegetables and fruit intake and cancer mortality in the Hiroshima/Nagasaki Life Span Study. Br J Cancer 2003; 88: 689-694.

(2) Yamaji T, Inoue M, Sasazuki S, Iwasaki M, Kurahashi N, Shimazu T, Tsugane S. Fruit and vegetable consumption and squamous cell carcinoma of the esophagus in Japan: The JPHC study. Int J Cancer 2008;123: 1935-1940.

果物摂取と食道がんの関連に関するケースコントロール研究（付表 S-16）

(1) Nakachi K, Imai K, Hoshiyama Y, Sasab T. The joint effects of two factors in the aetiology of oesophageal cancer in Japan. J Epidemiol Commun Health 1988;42: 355-364.

(2) Sasaki R, Aoki K, Takeda S. Contribution of dietary habits to esophageal cancer in Japan. Prog Clin Biol Res 1990; 346: 83-92.

(3) Hanaoka T, Tsugane S, Ando N, Ishida K, Kakegawa T, Isono K, Takiyama W, Takagi I, Ide H, Watanabe H, Iizuka T. Alcohol consumption and risk of esophageal cancer in Japan: a case-control study in seven hospitals. Jpn J Clin Oncol 1994;24:241-246.

(4) Takezaki T, Shinoda M, Hatooka S, Hasegawa S, Nakamura S, Hirose K, Inoue M, Hamajima N, Kuroishi T, Matsuura H, Tajima K. Subsite-specific risk factors for hypopharyngeal and esophageal cancer (Japan). Cancer Causes Control 2000; 11: 597-608.

(5) Yokoyama A, Kato H, Yokoyama T< Tsujinaka T, Muto M, Omori T, Haneda T, Kumagai Y, Igaki H, Yokoyama M, Watanabe H, Fukuda H, Yoshimizu H. Genetic polymorphisms of alcohol and aldehyde dehydrogenases and glutathione S-transferase M1 and drinking, smoking, and diet in Japanese men with esophageal squamous cell carcinoma. Carcinognesis 2002; 23: 1851-1859.

膵臓がん

野菜摂取と膵臓がんの関連に関するコホート研究（付表 S-17）

(1) Hirayama T. Life-style and mortality: a large-scale census-based cohort study in Japan. Karger, Basel, 1990.

(2) Sauvaget C, Nagano J, Hayahashi M, Spencer E, Shimizu Y, Allen N. Vegetable and fruit intake and cancer mortality in the Hiroshima/Nagasaki Life Span Study. Br J Cancer 2003; 88: 689-694.

野菜摂取と膵臓がんの関連に関するケースコントロール研究（付表 S-18）

(1) Mizuno S, Watanabe S, Nakamura K, Omata M, Oguchi H, Ohashi K, Ohyanagi H, Fujiki T, Motojima K. A multi-institute case-control study on the risk factors of developing pancreatic cancer. Jpn J Clin Oncol 1992; 22: 286-291.

(2) Ohba S, Nishi M, Miyake H. Eating habits and pancreas cancer. Int J Pancreatology. 1996; 20: 37-42.
(3) Inoue M, Tajima K, Takezaki T, Hamajima N, Hirose K, Ito H, Tominaga S. Int J Epidemiol 2003; 32: 257-262.

果物摂取と膵臓がんの関連に関するコホート研究（付表 S-19）

(1) Sauvaget C, Nagano J, Hayahashi M, Spencer E, Shimizu Y, Allen N. Vegetable and fruit intake and cancer mortality in the Hiroshima/Nagasaki Life Span Study. Br J Cancer 2003; 88: 689-694.

果物摂取と膵臓がんの関連に関するケースコントロール研究（付表 S-20）

(1) Mizuno S, Watanabe S, Nakamura K, Omata M, Oguchi H, Ohashi K, Ohyanagi H, Fujiki T, Motojima K. A multi-institute case-control study on the risk factors of developing pancreatic cancer. Jpn J Clin Oncol 1992; 22: 286-291.
(2) Ohba S, Nishi M, Miyake H. Eating habits and pancreas cancer. Int J Pancreatology. 1996; 20: 37-42.

前立腺がん

乳製品と前立腺がんの関連に関するコホート研究（付表 S-21）

(1) Allen NE, Sauvaget C, Roddam AW, Appleby P, Nagano J, Suzuki G, Key TJ, Koyama K. A prospective study of diet and prostate cancer in Japanese men. Cancer Causes Control. 2004;15:911-20.
(2) Kurahashi N, Inoue M, Iwasaki M, Sasazuki S, Tsugane S. Dairy product, saturated fatty acid, and calcium intake and prostate cancer in a prospective cohort of Japanese men. Cancer Epidemiol Biomarkers Prev. 2008;17:930-7.

乳製品と前立腺がんの関連に関するケースコントロール研究（付表 S-22）

(1) Mishina T, Watanabe H, Araki H, Nakao M. Epidemiological study of prostatic cancer by matched-pair analysis. Prostate. 1985;6:423-36.
(2) Sonoda T, Nagata Y, Mori M, Miyanaga N, Takashima N, Okumura K, Goto K, Naito S, Fujimoto K, Hirao Y, Takahashi A, Tsukamoto T, Fujioka T, Akaza H. A case-control study of diet and prostate cancer in Japan: possible protective effect of traditional Japanese diet. Cancer Sci. 2004;95:238-42.

カルシウムと前立腺がんの関連に関するコホート研究（付表 S-23）

(1) Kurahashi N, Inoue M, Iwasaki M, Sasazuki S, Tsugane S. Dairy product, saturated fatty acid, and calcium intake and prostate cancer in a prospective cohort of Japanese men. Cancer Epidemiol Biomarkers Prev. 2008;17:930-7.

カルシウムと前立腺がんの関連に関するケースコントロール研究（付表 S-24）

(1) Oishi K, Okada K, Yoshida O, Yamabe H, Ohno Y, Hayes RB, Schroeder FH.A case-control study of prostatic cancer with reference to dietary habits. Prostate. 1988;12:179-90.

(2) Nagata Y, Sonoda T, Mori M, Miyanaga N, Okumura K, Goto K, Naito S, Fujimoto K, Hirao Y, Takahashi A, Tsukamoto T, Akaza H. Dietary isoflavones may protect against prostate cancer in Japanese men. J Nutr. 2007;137:1974-9.

緑茶と前立腺がんの関連に関するコホート研究（付表 S-25）

(1) Allen NE, Sauvaget C, Roddam AW, Appleby P, Nagano J, Suzuki G, Key TJ, Koyama K. A prospective study of diet and prostate cancer in Japanese men. Cancer Causes Control. 2004;15:911-20.

(2) Kikuchi N, Ohmori K, Shimazu T, Nakaya N, Kuriyama S, Nishino Y, Tsubono Y, Tsuji I. No association between green tea and prostate cancer risk in Japanese men: the Ohsaki Cohort Study. Br J Cancer. 2006;95:371-3.

(3) Kurahashi N, Sasazuki S, Iwasaki M, Inoue M, Tsugane S. Green tea consumption and prostate cancer risk in Japanese men: a prospective study. Am J Epidemiol. 2008;167:71-7.

緑茶と前立腺がんの関連に関するケースコントロール研究（付表 S-26）

(1) Mishina T, Watanabe H, Araki H, Nakao M. Epidemiological study of prostatic cancer by matched-pair analysis. Prostate. 1985;6:423-36.

(2) Sonoda T, Nagata Y, Mori M, Miyanaga N, Takashima N, Okumura K, Goto K, Naito S, Fujimoto K, Hirao Y, Takahashi A, Tsukamoto T, Fujioka T, Akaza H. A case-control study of diet and prostate cancer in Japan: possible protective effect of traditional Japanese diet. Cancer Sci. 2004;95:238-42.

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書 籍 名	出版社名	出版地	出版年	ページ

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Tanaka K, Tsuji I, Wakai K, Nagata C, Mizoue T, Tsugane S, 他	Alcohol drinking and liver cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population.	Jpn J Clin Oncol.	38	816-38	2008
Mizoue T, Wakai K, Nagata C, Tsuji I, Tanaka K, Matsuo K, Tsugane S, 他	Alcohol drinking and colorectal cancer in Japanese: a pooled analysis of results from five cohort studies.	Am J Epidemiol.	167	1397-406	2008

Jpn J Clin Oncol 2008;38(12)816–838
doi:10.1093/jjco/hyn108

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

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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

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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 south-east 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 $\downarrow\downarrow\downarrow$ 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), $0.5 \leq RR < 0.67$ (SS), $1.5 < RR \leq 2.0$ (SS) or $RR > 2.0$ (NS); (iii) 'weak' (symbol $\downarrow$ or $\uparrow$) when $0.5 \leq RR < 0.67$ (NS), $0.67 \leq RR \leq 1.5$ (SS) or $1.5 < RR \leq 2.0$ (NS) and (iv) 'no association' (symbol $-$) when $0.67 \leq RR \leq 1.5$ (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				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
Kono et al. (13)	1965–83	5130 men	Male physicians in western Japan	Death	51 men (primary 9, unspecified 42)	Never/past		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	122261 men	95% of the census population in 29 health-center-covered areas in six prefectures	Death	788 men (liver cancer) or 123 men (primary liver cancer)	For liver cancer				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			
						Daily		1.89 ($P < 0.01$)			
Inaba et al. (15)	1973–88	270 men	Patients with liver cirrhosis at Juntendo University Hospital	Death	46 men	Never		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	639 men in a farming area and 677 men in a fishing area	Residents in a farming area or a fishing area in Kyushu	Death	11 men (farming area) and 22 men (fishing area)	Farming area					
						Non-drinker	2	1.0	>0.1	Age	HBsAg and anti-HCV were not tested
						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)			

						Fishing area					
						Shochu none	4	1.00	<0.01	Age, smoking	
						Shochu <2 go/day	14	5.85 (1.31–26.18)			
						Shochu ≥2 go/day	4	14.02 (2.34–83.89)			
Kato et al. (17)	1987–90	1784	Patients with decompensated liver cirrhosis or post-transfusion hepatitis	Incidence	122	Never drinker	46	1.00		Sex, age	HBsAg and anti-HCV status was unknown. The total alcohol index was obtained by multiplying the daily ethanol intake (ml) by the number of years of drinking
						Past drinker	19	0.58 (0.32–1.04)			
						Occasional drinker	4	0.43 (0.15–1.24)			
						Current drinker	5	0.41 (0.16–1.06)			
						Total alcohol index					
						0	46	1.00	0.046		
						1–1999	10	0.49 (0.23–1.02)			
						2000+	13	0.53 (0.27–1.04)			
Tsukuma et al. (18)	1987–91	917 (548 men and 369 women)	Patients with chronic hepatitis or compensated cirrhosis at Center for Adult Diseases, Osaka	Incidence	54	Nondrinker		1.00		Age, sex, stage of disease, serum alpha-fetoprotein, HBsAg, anti-HBc, anti-HCV, smoking	HBsAg and anti-HCV status was adjusted for.
						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)			
Goodman et al. (19)	1980–89	36133	Atomic bomb survivors	Incidence	242 (156 men and 86 women)	For men				Sex, city, age at the time of bombing, age, radiation dose to the liver	HBsAg and anti-HCV were not tested.
						Never-drinker	25	1.00			
						Ever-drinker	126	1.11 (0.72–1.70)			
						Ex-drinker	25	2.33 (1.34–4.07)			
						Quit ≥16 years ago	4	0.96 (0.33–2.77)			

Continued

Table 1. *Continued*

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
						Quit 11–15 years ago	8	2.08 (0.93–4.67)			
						Quit ≤10 years ago	12	7.87 (3.89–16.0)			
						Present drinker	100	0.98 (0.63–1.52)			
						<135 ml/week	37	1.09 (0.65–1.81)			
						135–299 ml/week	37	1.11 (0.67–1.86)			
						≥300 ml/week	37	1.12 (0.67–1.87)			
						For women					
						Never/past drinker	56	1.00			
						Present drinker	27	1.25 (0.78–1.98)			
						<27 ml/week	1	0.28 (0.04–2.02)			
						27–69 ml/week	6	1.20 (0.52–2.79)			
						≥70 ml/week	9	2.02 (0.99–4.09)			
Chiba et al. (20)	1977–93	412 (249 men and 163 women)	Patients with HCV-associated chronic hepatitis or compensated cirrhosis at Tsukuba University Hospital	Incidence	63 (54 men and 9 women)	Nondrinker		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.
						<150 kg ethanol		1.33 (0.60–2.93)			
						150–449 kg ethanol		1.50 (0.71–3.17)			
						≥450 kg ethanol		0.98 (0.43–2.23)			
Ikeda et al. (21)	1980–?	2215 (1544 men and 671 women)	Patients with chronic hepatitis at Toranomon Hospital	Incidence	89	All subjects	($n = 2215$)			Stage of hepatitis, gamma-glutamyl transpeptidase	HBsAg and anti-HCV status was available for all subjects.
						<500 kg ethanol		1.00			
						≥500 kg ethanol		3.04 (1.79–5.14)			
						HBsAg(+) anti-HCV(−) subjects	($n = 610$)			Indocyanine green retention rate	

						<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)			
Tanaka et al. (22)	1985–95	96 (62 men and 34 women)	Patients with liver cirrhosis at Kyushu University Hospital	Incidence	37 (27 men and 10 women)	Never	16	1.00		Sex, age, years since LC diagnosis, department, hospitalization status, serum albumin, AST, alpha-fetoprotein, HBsAg, anti-HCV, smoking	HBsAg and anti-HCV status was adjusted for. The relative risks were not described in the original paper, and were reestimated by one of the authors (KT). One 'drink' corresponds to 23 ml of ethanol.
						Past	17	0.59 (0.20–1.73)			
						Current					
						<2.4 drinks/day	1	0.06 (0.01–0.57)			
						≥2.4 drinks/day	3	0.17 (0.02–1.42)			
Matsushita et al. (23)	1985–94	267 (165 men and 102 women)	Patients with liver cirrhosis at Kanazawa University Hospital	Incidence	67	Type B or C cirrhosis	($n = 202$)			Age, anti-HCV	All subjects analyzed were positive for anti-HCV or HBsAg.
						Positive drinking history		1.83 (1.00–3.36)			
						Type C cirrhosis	($n = 140$)			Age	
						Positive drinking history		2.36 (1.23–4.54)			
Aizawa et al. (24)	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	Habitual heavy drinking				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.
						No		1.00			
						Yes		3.04 (1.31–7.09)			
Mori et al. (25)	1992–97	3052 (974 men and 2078 women)	Residents in a town in Saga prefecture	Incidence	22 (14 men and 8 women)	History of habitual alcohol consumption				Sex, age	Anti-HCV and HBsAg status was available but not adjusted for.
						No	10	1.00			
						Yes	22	1.27 (0.46–3.47)			
						Never drinker	10	1.00	0.87		One 'drink' corresponds to a glass of sake.
						1–19 drink-years	3	2.05 (0.48–8.79)			
							9				

Continued

Table 1. *Continued*

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
						≥20 drink-years		1.14 (0.40–3.26)			
Noda et al. (26)	1972–92	306 men	Alcoholics in Takatsuki city, Osaka, who had been diagnosed at a psychiatric institution	Death	Not described	O/E ratio for hepatocellular carinoma		1.6 (0.3–4.7)		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				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.
						Not excessive		1.00			
						Excessive		2.21 (1.00–3.58)			
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				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.
						No		1.00			
						Yes		4.30 ($P = 0.048$)			
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)				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).
						1200 kg increase		7.7 (1.9–31.5)	0.0047		
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	Incidence	23 (20 men and 3 women)	Alcohol consumption				Fibrosis staging, age	All subjects were anti-HCV-positive and HBsAg-negative.
						<50 g/day		1.00			
						≥50 g/day		3.86 (1.58–9.44)			
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.
						Never drinker		1.00			
						Ex-drinker		8.11 (3.17–20.77)			
						Current drinker		0.65 (0.27–1.52)			

						Male, 60–79 years	($n = 11628$)				
						Never drinker		1.00			
						Ex-drinker		3.48 (1.86–6.54)			
						Current drinker		0.75 (0.43–1.31)			
						Female, 40–59 years	($n = 22528$)				
						Never drinker		1.00			
						Ex-drinker		3.85 (0.48–30.93)			
						Current drinker		0.23 (0.03–1.80)			
						Female, 60–79 years	($n = 16103$)				
						Never drinker		1.00			
						Ex-drinker		4.18 (1.47–11.88)			
						Current drinker		0.59 (0.25–1.43)			
Nakaya et al. (32)	1990–97	21201 men	Residents in 14 municipalities of Miyagi prefecture	Incidence	48 men	Never drinker	3	1.0	0.21	Age, smoking, education, daily consumption of orange and other fruit juice, spinach, carrot or pumpkin, and tomato	HBsAg and anti-HCV were not tested.
						Ex-drinker	10	6.6 (1.8–24.2)			
						Current drinker	35	2.7 (0.8–8.9)			
						<22.8 g alcohol/day	11	2.8 (0.8–10.1)			
						≥22.8 g alcohol/day	24	2.7 (0.8–8.9)			
Ikeda et al. (33)	1995–2005	846 (473 men and 373 women)	Patients with HCV-associated chronic hepatitis or cirrhosis at Kyoto University Hospital and 14 affiliated core hospitals	Incidence	237 (151 men and 86 women)	Patients with chronic hepatitis	($n = 576$)			Sex, age, smoking, alcohol consumption, response to interferon therapy, anti-HBc	All subjects were anti-HCV-positive and HBsAg-negative.
						None	57	1.00 (reference)			
						<30 g/day	14	0.75 (0.39–1.44)			
						≥30 g/day	23	0.65 (0.37–1.12)			
						Patients with cirrhosis	($n = 270$)				
						None	99				

Continued

Table 1. *Continued*

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
						<30 g/day	11	1.00 (reference)			
								0.42 (0.22–0.83)			
						≥30 g/day	33	1.03 (0.65–0.83)			
Ohki et al. (34)	1994–2006	1431 (727 men and 704 women)	Patients with positive HCV-RNA at Tokyo University Hospital	Incidence	340	Alcohol consumption				Ages, sex, diabetes, body mass index, serum albumin, bilirubin, ALT, prothrombin time, platelets, alpha-fetoprotein	All subjects were anti-HCV-positive and HBsAg-negative.
						≤80 g/day		1.00			
						>80 g/day		1.41 (1.07–1.86)			

CI, confidence interval; HBsAg, hepatitis B surface antigen; anti-HCV, antibody to hepatitis C virus; anti-HBc, antibody to hepatitis B core antigen; HCV, hepatitis C virus; anti-HBs, antibody to hepatitis B surface antige; LC, liver cirrhosis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; O/E ratio, ratio of observed to expected number; HCV-RNA, hepatitis C virus RNA.

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

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
		Type and source	Definition	Number of cases	Number of controls					
Inaba et al. (35)	1977–79	Hospital-based (7 hospitals in Yamanashi)	Cases: 58% were histologically confirmed; Controls: patients without hepatic disease	62 (49 men and 13 women)	62 (49 men and 13 women)	Not daily	1.0		Matched (1:1) for sex, age, and hospital Adjusted for matching factors	HBsAg was tested but not adjusted for. Anti-HCV was not tested.
						Daily	3.2 ($P < 0.05$)			
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	20 men	40 men	None or <1 go/day	1.0	<0.05	Matched (1:2) for birth year Adjusted for smoking	All subjects were HBsAg-positive. Anti-HCV was not tested.
						1– <3 go/day	5.4			
						≥3 go/day	8.0			
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	78 men	78 men	Not daily	1.0		Matched (1:1) for age and residential area Adjusted for matching factors	HBsAg was tested but not adjusted for. Anti-HCV was not tested.
						Daily	1.7 (0.8–4.0)			
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	36 men	67 men	For primary liver cancer			No matching	HBsAg was tested but not adjusted for.
						≥80 g/day	1.0		No adjustment	Anti-HCV was not tested.
						<80 g/day	1.21 (0.54–2.74)			The relative risk was not described in the original paper, and was estimated by one of the authors (KT).
						For HCC				
						≥80 g/day	1.0			
						<80 g/day	2.91 (0.95–8.92)			
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	48 (40 men and 8 women)	40 (27 men and 13 women)	Alcohol intake (≥75 g/day, ≥10 years)			No matching	HBsAg was tested but not adjusted for.
						No	1.0		No adjustment	Anti-HCV was not tested.
						Yes	1.4 (0.6–3.4)			The relative risk was not described in the original paper, and was estimated by one of the authors (KT).
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	229 (192 men and 37 women)	266 (192 men and 74 women)	Not heavy	1.0		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.
						Heavy	3.2 (2.0–5.1)			
						0–9999 'go's	1.0	0.03		
						10 000–39 999 'go's	1.0 (0.6–1.6)			

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