TABLE VII. Factors Associated With Non-Virological Response to Combination Therapy of Interferon Plus Ribavirin Identified by Multivariate Analysis in Patients With Genotype 1b

| Factor | Category | Odds ratio (95% CI) | P |
|---|---|---|---|
| Amino acid substitutions in the core region[a] | 0: No double-mutant | 1 | 0.028 |
| | 1: Double-mutant | 7.000 (1.238–39.566) | |

Only the variable that achieved statistical significance ($P < 0.05$) on multivariate logistic regression is shown.
[a]The mutant aa 70 and 91 pattern was evaluated as double-mutant, and other patterns as non-double-mutant.

RBV combination therapy, a different dose of IFN was used in the present study to test whether a larger dosage of IFN improves the outcome of IFN therapy.

In this study, the larger dose did not increase sustained virological response nor decrease non-virological response. Instead, the dose reduction of IFN and/or RBV was significantly higher in the higher dose group (Table III). Furthermore, the incidence of depression was significantly higher in the high-dose group (Table III). These results suggest that a high dose of IFN is not beneficial to patients who receive IFN and RBV combination therapy, and probably who will receive the PEG-IFN and RBV combination therapy.

The predictive factors for sustained virological response and non-virological response to the combination therapy for patients with genotype 1b were analyzed. Logistic regression analyses identified pretreatment substitutions at both aa 70 and 91 in the core region (double-mutant) as a singular predictive factor for non-virological response (Table VII). Furthermore, the existence of aa substitution in the ISDR was significantly more frequent in virological responders compared to non-virological responders (Table VI), in agreement with previous reports [Puig-Basagoiti et al., 2001; Pascu et al., 2004]. It has been reported that the numbers of aa substitutions in the ISDR correlate with serum HCV RNA levels [Enomoto et al., 1996]. However, no apparent correlation was observed in this study. As shown in Figures 3 and 4, patients who had substitutions of aa 70 and/or 91 in the core region or no aa substitutions in ISDR had poor initial reduction in the HCV core antigen. These results are consistent with recent studies that have shown the importance of a rapid initial decline of the viral load in obtaining a better response rate [Fried et al., 2002; Davis et al., 2003]. These results suggest that aa substitution analysis should provide important information on treatment of patients with genotype 1b.

The core protein of the HCV has been reported to disturb the IFN signaling by interacting with STAT1 SH2 domain [Lin et al., 2006] or repressing IRF1 [Ciccaglione et al., 2007]. These studies did not analyze the effect of aa substitutions in the core region. Further study is necessary to clarify the effect of aa substitutions in the core region and to identify a molecular target to improve the therapy.

Although aa substitution in the core region was identified as an important predictor in patients with genotype 1b in this study, aa substitutions of the core region and ISDR in patients with genotype 2a/b infection were not analyzed. Although the sustained virological response rate in patients who completed the therapy was high (26/28 [93%], per protocol analysis), few patients were unable to achieve sustained virological response. Furthermore, a significant number of patients could not complete the treatment course because of adverse effects. A more effective and easy to complete therapy should be developed to treat such patients. The predictive factors in such patients should also be clarified.

The recent development of a new type of drug targeting NS3/4 protease may improve the outcome of treatment in patients with chronic hepatitis C [Reesink et al., 2006; Forestier et al., 2007; Kieffer et al., 2007; Sarrazin et al., 2007a,b]. However, drug resistant mutants might emerge against such a small molecule therapy targeting viral enzyme(s). The functions of virus proteins that resist IFN including core, ISDR and PePHD should be clarified further to develop a better therapy that can achieve a higher sustained virological response rate with fewer and milder side-effects.

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## REFERENCES

Akuta N, Suzuki F, Sezaki H, Suzuki Y, Hosaka T, Someya T, Kobayashi M, Saitoh S, Watahiki S, Sato J, Matsuda M, Kobayashi M, Arase Y, Ikeda K, Kumada H. 2005. Association of amino acid substitution pattern in core protein of hepatitis C virus genotype 1b high viral load and non-virological response to interferon-ribavirin combination therapy. Intervirology 48:372–380.

Akuta N, Suzuki F, Sezaki H, Suzuki Y, Hosaka T, Someya T, Kobayashi M, Saitoh S, Watahiki S, Sato J, Kobayashi M, Arase Y, Ikeda K, Kumada H. 2006. Predictive factors of virological non-response to interferon-ribavirin combination therapy for patients infected with hepatitis C virus of genotype 1b and high viral load. J Med Virol 78:83–90.

Akuta N, Suzuki F, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M, Kobayashi M, Arase Y, Ikeda K, Kumada H. 2007a. Predictive factors of early and sustained responses to peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype 1b: Amino acid substitutions in the core region and low-density lipoprotein cholesterol levels. J Hepatol 46:403–410.

Akuta N, Suzuki F, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M, Kobayashi M, Arase Y, Ikeda K, Kumada H. 2007b. Predictors of viral kinetics to peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype. 1b. J Med Virol 79:1686–1695.

Aoyagi K, Ohue C, Iida K, Kimura T, Tanaka E, Kiyosawa K, Yagi S. 1999. Development of a simple and highly sensitive enzyme immunoassay for hepatitis C virus core antigen. J Clin Microbiol 37:1802–1808.

Berg T, von Wagner M, Nasser S, Sarrazin C, Heintges T, Gerlach T, Buggisch P, Goeser T, Rasenack J, Pape GR, Schmidt WE, Kallinowski B, Klinker H, Spengler U, Martus P, Alshuth U, Zeuzem S. 2006. Extended treatment duration for hepatitis C virus type 1: Comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. Gastroenterology 130:1086–1097.

Blindenbacher A, Duong FH, Hunziker L, Stutvoet ST, Wang X, Terracciano L, Moradpour D, Blum HE, Alonzi T, Tripodi M, La Monica N, Heim MH. 2003. Expression of hepatitis C virus proteins inhibits interferon alpha signaling in the liver of transgenic mice. Gastroenterology 124:1465–1475.

Bode JLS, Ehrhardt C, Albrecht U, Erhardt A, Schaper F, Heinrich P, Haussinger D. 2003. IFN-α antagonistic activity of HCV core protein involves induction of suppressor of cytokine signaling. FASEB J 17:488–490.

Brillet R, Penin F, Hezode C, Chouteau P, Dhumeaux D, Pawlotsky JM. 2007. The nonstructural 5A protein of hepatitis C virus genotype 1b does not contain an interferon sensitivity-determining region. J Infect Dis 195:432–441.

Brouwer JT, Nevens F, Bekkering FC, Bourgeois N, Van Vlierberghe H, Weegink CJ, Lefebvre V, Van Hattum J, Henrion J, Delwaide J, Hansen BE, Schalm SW, for the Benelux Study Group on Treatment of Chronic Hepatitis C. 2004. Reduction of relapse rates by 18-month treatment in chronic hepatitis C. A Benelux randomized trial in 300 patients. J Hepatology 40:689–695.

Chayama K, Tsubota A, Kobayashi M, Okamoto K, Hashimoto M, Miyano Y, Koike H, Kobayashi M, Koida I, Arase Y, Saitoh S, Suzuki Y, Murashima N, Ikeda K, Kumada H. 1997. Pretreatment virus load and multiple amino acid substitutions in the interferon sensitivity-determining region predict the outcome of interferon treatment in patients with chronic genotype 1b hepatitis C virus infection. Hepatology 25:745–749.

Chayama K, Suzuki F, Tsubota A, Kobayashi M, Arase Y, Saitoh S, Suzuki Y, Murashima N, Ikeda K, Takahashi N, Kinoshita M, Kumada H. 2000. Association of aa sequence in the PKR-eIF2 phosphorylation homology domain and response to interferon therapy. Hepatology 32:1138–1144.

Ciccaglione AR, Stellacci E, Marcantonio C, Muto V, Equestre M, Marsili G, Rapicetta M, Battistini A. 2007. Repression of interferon regulatory factor 1 by hepatitis C virus core protein results in inhibition of antiviral and immunomodulatory genes. J Virol 81: 202–214.

Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. 2003. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. Hepatology 38:645–652.

Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. 1994. Classification of chronic hepatitis: Diagnosis, grading and staging. Hepatology 19:1513–1520.

Di Marco V, Ferraro D, Almasio P, Vaccaro A, Parisi P, Cappello M, Cino N, Di Stefano R, Craxi A. 2002. Early viral clearance and sustained response in chronic hepatitis C: A controlled trial of interferon and ribavirin after high-dose interferon induction. J Viral Hepat 9:354–359.

Enomoto N, Sakuma I, Asahina Y, Kurosaki M, Murakami T, Yamamoto C, Ogura Y, Izumi N, Marumo F, Sato C. 1996. Mutations in the nonstructural protein 5A gene and response to interferon in patients with chronic hepatitis C virus 1b infection. N Engl J Med 334:77–81.

Ferenci P, Brunner H, Nachbaur K, Datz C, Gschwantler M, Hofer H, Stauber R, Hackl F, Jessner W, Rosenbeiger M, Munda-Steindl P, Hegenbarth K, Gangl A, Vogel W, Australian Hepatitis Study Group. 2001. Combination of interferon induction therapy and ribavirin in chronic hepatitis C. Hepatology 34:1006–1011.

Forestier N, Reesink HW, Weegink CJ, McNair L, Kieffer TL, Chu HM, Purdy S, Jansen PL, Zeuzem S. 2007. Antiviral activity of telaprevir (VX-950) and peginterferon alfa-2a in patients with hepatitis C. Hepatology 46:640–648.

Foy E, Li K, Wang C, Sumpter R, Jr., Ikeda M, Lemon SM, Gale M, Jr. 2003. Regulation of interferon regulatory factor-3 by the hepatitis C virus serine protease. Science 300:1145–1148.

Fried MW, Shiffman M, Sterling RK, Weinstein J, Crippin J, Garcia G, Wright TL, Conjeevaram H, Reddy KR, Peter J, Cotsonis GA, Nolte FS. 2000. A multicenter, randomized trial of daily high-dose interferon-alfa 2b for the treatment of chronic hepatitis C: Pretreatment stratification by viral burden and genotype. Am J Gastroenterol 95:3225–3229.

Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, Jr., Haussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. 2002. Peginterferon alfa-2a plus ribavirin for patients with chronic hepatitis C virus infection. N Engl J Med 347:975–982.

Gale MJ, Jr., Korth MJ, Tang NM, Tan SL, Hopkins DA, Dever TE, Polyak SJ, Gretch DR, Katze MG. 1997. Evidence that hepatitis C virus resistance to interferon is mediated through repression of the PKR protein kinase by the nonstructural 5A protein. Virology 230:217–227.

Gaudy C, Lambelé M, Moreau A, Veillon P, Lunel F, Goudeau A. 2005. Mutations within the hepatitis C virus genotype 1b E2-PePHD domain do not correlate with treatment outcome. J Clin Microbiol 43:750–754.

Hadziyannis AS, Papaioannou C, Spanou F, Manesis EK, Hadziyannis SJ. 2001. Induction interferon therapy in naive patients with chronic hepatitis C: Increased end-of-treatment virological responses but absence of long-term benefit. Aliment Pharmacol Ther 15:551–557.

Hashimoto M, Chayama K, Kobayashi M, Tsubota A, Arase Y, Saitoh S, Suzuki Y, Ikeda K, Matsuda M, Koike H, Kobayashi M, Handa H, Kumada H. 1999. Fluctuations of hepatitis C virus load are not related to amino acid substitutions in hypervariable region 1 and interferon sensitivity determining region. J Med Virol 58:247–255.

Hoofnagle JH, Ghany MG, Kleiner DE, Doo E, Heller T, Promrat K, Ong J, Khokhar F, Soza A, Herion D, Park Y, Everhart JE, Liang TJ. 2003. Maintenance therapy with ribavirin in patients with chronic hepatitis C who fail to respond to combination therapy with interferon alfa and ribavirin. Hepatology 38:66–74.

Kato N, Hijikata M, Ootsuyama Y, Nakagawa M, Ohkoshi S, Sugimura T, Shimotohno K. 1990. Molecular cloning of the human hepatitis C virus genome from Japanese patients with non-A, non-B hepatitis. Proc Natl Acad Sci USA 87:9524–9528.

Kieffer TL, Sarrazin C, Miller JS, Welker MW, Forestier N, Reesink HW, Kwong AD, Zeuzem S. 2007. Telaprevir and pegylated interferon-alpha-2a inhibit wild-type and resistant genotype 1 hepatitis C virus replication in patients. Hepatology 46:631–639.

Kiyosawa K, Sodeyama T, Tanaka E, Gibo Y, Yoshizawa K, Nakano Y, Furuta S, Akahane Y, Nishioka K, Purcell RH, Alter MJ. 1990. Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma: Analysis by detection of antibody to hepatitis C virus. Hepatology 12:671–675.

Lin W, Kim SS, Yeung E, Kamegaya Y, Blackard JT, Kim KA, Holtzman MJ, Chung RT. 2006. Hepatitis C virus core protein blocks interferon signaling by interaction with the STAT1 SH2 domain. J Virol 80:9226–9235.

Lindsay KL, Davis GL, Schiff ER, Bodenheimer HC, Balart LA, Dienstag JL, Perrillo RP, Tamburro CH, Goff JS, Everson GT, Silva M, Katkov WN, Goodman Z, Lau JY, Maertens G, Gogate J, Sanghvi B, Albrecht J. 1996. Response to higher doses of interferon alfa-2b in patients with chronic hepatitis C: A randomized multicenter trial. Hepatology 24:1034–1040.

Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. 2001. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: A randomised trial. Lancet 358:958–965.

McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, Goodman ZD, Ling MH, Cort S, Albrecht JK. 1998. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 339:1485–1492.

Niederau C, Lange S, Heintges T, Erhardt A, Buschkamp M, Hurter D, Nawrocki M, Kruska L, Hensel F, Petry W, Haussinger D. 1998. Prognosis of chronic hepatitis C: Results of a large, prospective cohort study. Hepatology 28:1687–1695.

Pascu M, Martus P, Höhne M, Wiedenmann B, Hopf U, Schreier E, Breg T. 2004. Sustained virological response in hepatitis C virus type 1b infected patients is predicted by the number of mutations

within the NS5A-ISDR: A meta-analysis focused on geographical differences. Gut 53:1345–1351.

Polyak SJ, McArdle S, Liu SL, Sullivan DG, Chung M, Hofgärtner WT, Carithers RL, Jr., McMahon BJ, Mullins JI, Corey L, Gretch DR. 1998. Evolution of hepatitis C virus quasispecies in hypervariable region 1 and the putative interferon sensitivity-determining region during interferon therapy and natural infection. J Virol 72:4288–4296.

Polyak SJ, Nousbaum JB, Larson AM, Cotler S, Carithers RL, Jr., Gretch DR. 2000. The protein kinase-interacting domain in the hepatitis C virus envelope glycoprotein-2 gene is highly conserved in genotype 1-infected patients treated with interferon. J Infect Dis 182:397–404.

Puig-Basagoiti F, Sáiz JC, Forns X, Ampurdanès S, Giménez-Barcons M, Franco S, Sánchez-Fueyo A, Costa J, Sánchez-Tapias JM, Rodés J. 2001. Influence of the genetic heterogeneity of the ISDR and PePHD regions of hepatitis C virus on the response to interferon therapy in chronic hepatitis C. J Med Virol 65: 35–44.

Reesink HW, Zeuzem S, Weegink CJ, Forestier N, van Vliet A, van de Wetering de Rooij J, McNair L, Purdy S, Kauffman R, Alam J, Jansen PL. 2006. Rapid decline of viral RNA in hepatitis C patients treated with VX-950: A phase Ib, placebo-controlled, randomized study. Gastroenterology 131:997–1002.

Sánchez-Tapias JM, Diago M, Escartín P, Enríquez J, Romero-Gómez M, Bárcena R, Crespo J, Andrade R, Martínez-Bauer E, Pérez R, Testillano M, Planas R, Solá R, García-Bengoechea M, Garcia-Samaniego J, Muñoz-Sánchez M, Moreno-Otero R, TeraViC-4 Study Group. 2006. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. Gastroenterology 131:451–460.

Sarrazin C, Kieffer TL, Bartels D, Hanzelka B, Müh U, Welker M, Wincheringer D, Zhou Y, Chu HM, Lin C, Weegink C, Reesink H, Zeuzem S, Kwong AD. 2007a. Dynamic hepatitis C virus genotypic and phenotypic changes in patients treated with the protease inhibitor telaprevir. Gastroenterology 132:1767–1777.

Sarrazin C, Rouzier R, Wagner F, Forestier N, Larrey D, Gupta SK, Hussain M, Shah A, Cutler D, Zhang J, Zeuzem S. 2007b. SCH 503034, a novel hepatitis C virus protease inhibitor, plus pegylated interferon alpha-2b for genotype 1 nonresponders. Gastroenterology 132:1270–1278.

Taliani G, Gemignani G, Ferrari C, Aceti A, Bartolozzi D, Blanc PL, Capanni M, Esperti F, Forte P, Guadagnino V, Mari T, Marino N, Milani S, Pasquazzi C, Rosina F, Tacconi D, Toti M, Zignego AL, Messerini L, Stroffolini T, Nonresponder Retreatment Group. 2006. Pegylated interferon alfa-2b plus ribavirin in the retreatment of interferon-ribavirin nonresponder patients. Gastroenterology 130: 1098–1106.

Taylor DR, Shi ST, Romano PR, Barber GN, Lai MM. 1999. Inhibition of the interferon-inducible protein kinase PKR by HCV E2 protein. Science 285:107–110.

Torres-Puente M, Cuevas JM, Jiménez-Hernández N, Bracho MA, García-Robles I, Carnicer F, del Olmo J, Ortega E, Moya A, González-Candelas F. 2008. Hepatitis C virus and the controversial role of the interferon sensitivity determining region in the response to interferon treatment. J Med Virol 80:247–253.

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# Epidemiology of hepatocellular carcinoma in Japan

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Primary liver cancer, 95% of which is hepatocellular carcinoma (HCC), is ranked third in men and fifth in women as a cause of death from malignant neoplasms in Japan. The number of deaths and death rate of HCC began to increase sharply in 1975. These numbers peaked at 34510 and 27.4/100000, respectively, in 2004, but decreased to 33662 annual deaths and a 26.7/100000 death rate in 2006. Although hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are both major causes of HCC, HCV-related HCC represents 70% of all cases. The incidence of HCC without hepatitis B surface antigen (HBsAg) or antibodies to HCV (anti-HCV) accounts for 8%–15% of HCC patients nationwide. Geographically, HCC is more frequent in western than eastern Japan, and death rates of HCC in each prefecture correlate with anti-HCV, but not HBsAg, prevalence. Interferon therapy for chronic hepatitis C reduces the risk of development of HCC, especially among patients with sustained virological response. Further research should focus on the mechanisms of carcinogenesis by HCV and HBV, development of more effective treatments, and establishment of early detection and preventative approaches. Better understanding of HCC unrelated to HCV and HBV, possibly caused by steatohepatitis and diabetes, should also be a major concern in future studies.

**Key words:** HCC, HCV, HBV, nonalcoholic steatohepatitis (NASH), interferon

## Introduction

The three leading causes of death in Japan since 1981 are malignant neoplasms, cardiovascular diseases, and cerebrovascular diseases. For the past 30 years, liver cancer has been the third leading cause of death from malignant neoplasms in men, following lung and stomach cancer. In women, liver cancer has ranked fifth as a cause of death during the past decade, following colon, stomach, lung, and breast cancer. Primary liver cancer can be classified into three types according to the cell from which the cancer originated, namely, hepatocellular carcinoma (HCC), cholangiocellular carcinoma, and other. As HCC accounts for up 95% of all primary cancer cases, the term "liver cancer" usually means HCC.[1]

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the two major causes of HCC in Japan.[2,3] The increase in incidence of HCC in Japan, however, is largely attributable to the increase of HCV infection in the general population during the past 50 to 60 years.[2]

## Changes in deaths and death rates of primary liver cancer

Changes in annual deaths from primary liver cancer among different age groups between 1958 and 2006 are shown in Fig. 1. The total number of deaths from HCC was stable at fewer than 10000 persons/year until 1975 before showing a sharp increase. The spike in 1995 resulted from a change in the International Classification of Disease (ICD) code from ICD 9 to ICD 10, which included intrahepatic bile duct cancer, accounting for approximately 5% of HCC deaths.

The majority of HCC mortalities were in patients below the age of 69 until 1999, when this age reached 70 years. In 2006, 66% of patients with HCC were over 70. The number of deaths from HCC reached 34510 in 2004, but decreased to 33662 in 2006.

The death rates of liver cancer by sex (Fig. 2) are consistently higher in men than in women. A sharp rise in the death rate of primary liver cancer in men began

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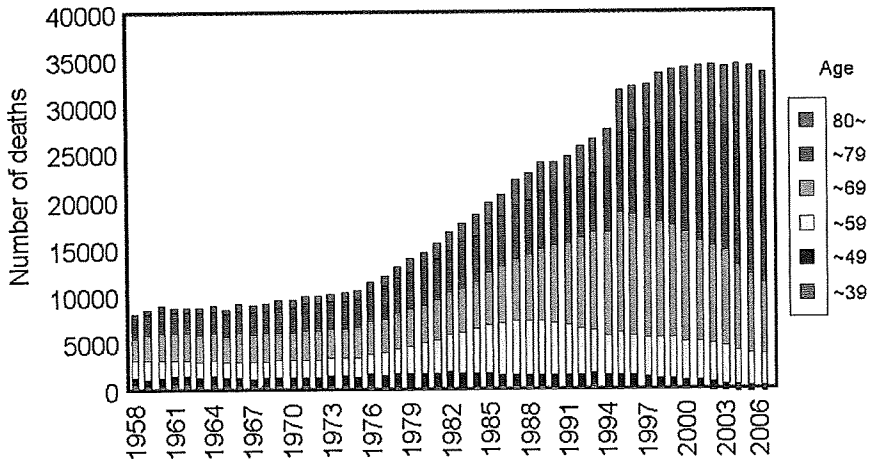


**Fig. 1.** Changes in annual deaths of patients (by age, in years) with primary liver cancer between 1958 and 2006. (Taken from the Vital Statistics of Japan, released every year by the Ministry of Health, Labour, and Welfare)

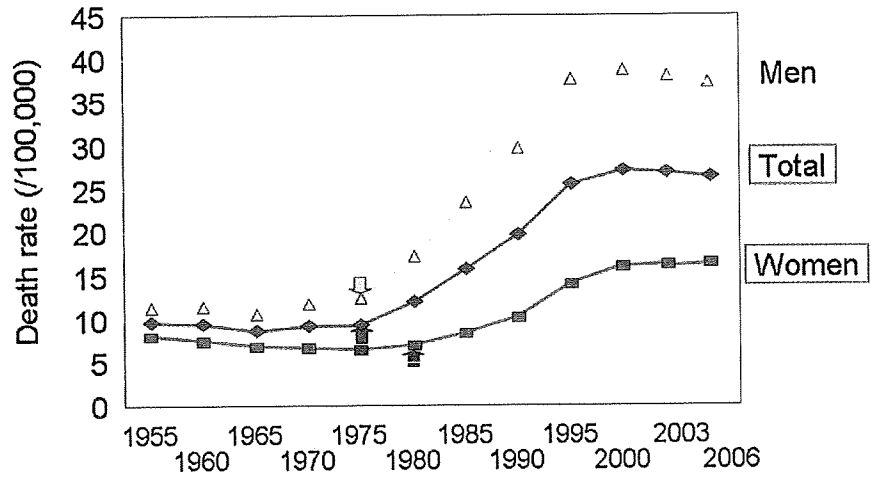


**Fig. 2.** Changes in the death rate of primary liver cancer in men (*triangles, yellow*), women (*rectangles, pink*), and in total (*diamonds, blue*)

in 1975, and a more gradual rise in women commenced in 1980. The total age-adjusted death rate peaked in 2002 (27.5/100000 persons in 2002), and decreased to 27.0 in 2003. In 2006, the total age-adjusted death rate stood at 26.7/100000, which is caused by a decrease in death rate (36.7) in men, but offset by an increase in women to 17.2.

## Age and sex in HCC

Changes in the mean age of HCC patients and male/female ratio every 2 years between 1984 and 2003 are shown in Fig. 3. In that period, the mean age of female HCC patients was higher than that of males, and the mean ages of both sexes progressively increased. As reported previously, however, HBV-related HCC was stable from 1982 to 2003, implying that this change originated from HCV-related HCC patients. The male/female ratio was 4.5 in 1984–1985 and 2.5 in 2002–2003 (see Fig. 3), showing that the proportion of female patients with HCC had increased. This increase in female patients is also considered as a consequence of increased HCV-related HCC.

## Changes in etiology of HCC in Japan

A nationwide survey on primary liver cancer has been conducted every 2 years since 1968 by the Liver Cancer Study Group of Japan.[1,4–9] Five serological surveys performed between 1990 and 2001 have documented that most patients with HCC are positive for either HBsAg or antibodies to HCV (anti-HCV). Tests for HBsAg became available in 1975 and those for anti-HCV in 1990. HBsAg-positive cases of HCC constituted 42% of patients in 1977–1978, but only 15.5% in 2002–2003 (Fig. 4). In contrast, anti-HCV-positive cases of HCC accounted for more than 70% of cases diagnosed until 2000–2001. However, this number dipped to 69.6% in 2002–2003, and has since remained at less than 70%. In contrast, HCV of unknown origin and other cases of HCC have been increasing gradually, and constituted 14.9% of all cases in 2002–2003.

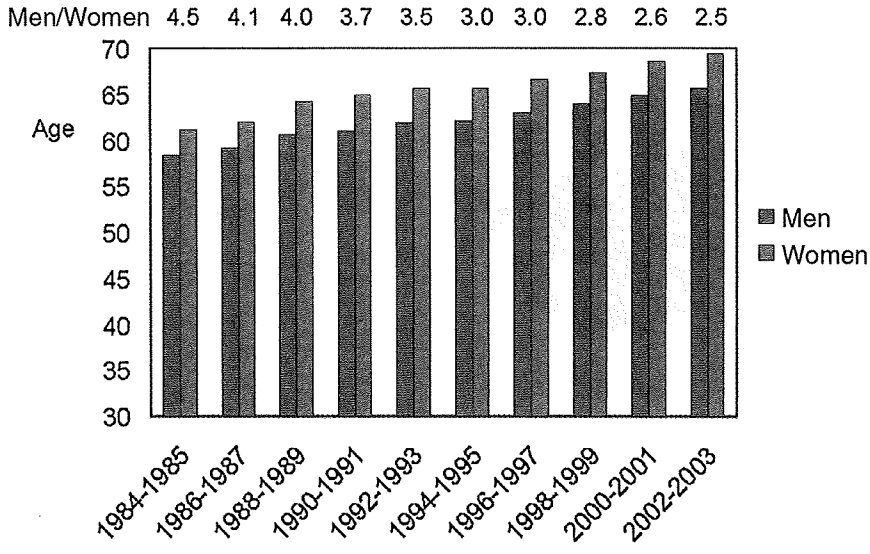


**Fig. 3.** Changes in the mean age (in years) of men (*blue bars*) and women (*pink bars*) patients with hepatocellular carcinoma (HCC) between 1984 and 2003

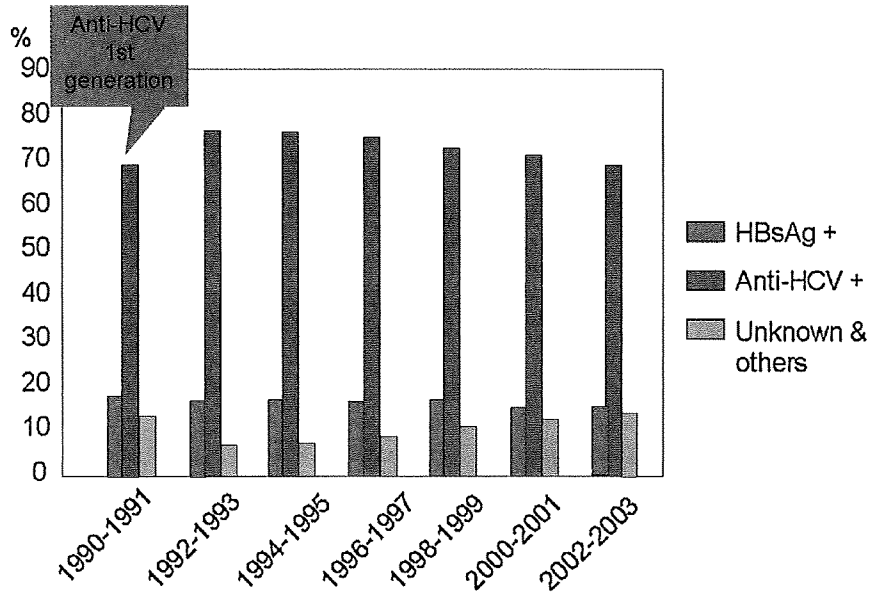


**Fig. 4.** Changes in the etiology of HCC between 1990 and 2003: hepatitis B surface antigen (*HBsAg+, pink*), antihepatitis C virus (*anti-HCV+, blue*), and *unknown* and *others* (*green*)

In cross-sectional studies conducted at Shinshu University Hospital, HCV-related HCC was found in the majority of cases (72%) (Fig. 5). Non-B non-C HCC (NBNC-HCC) accounted for 10% of cases in 2002–2007. In these 28 patients, nonalcoholic steatohepatitis (NASH) accounted for 14%.

## Geographic variation of liver cancer and HBV/HCV infection

Although Japan is a relatively small country with a homogeneous population, the incidence of HCC varies greatly among different regions. The Vital Statistics of Japan for 2005 published in 2007 by the Japanese Ministry of Health, Labour, and Welfare on the incidence of deaths as a result of HCC in its 48 prefectures shows a steady increase in death rates of HCC from east to west in Japan. The average age-adjusted death rate of HCC among 48 prefectures was 27.2 per 100000 persons in 2005 (Fig. 6). Furthermore, nationwide health screening for HBsAg and anti-HCV in citizens over 40 years of age has been performed since 2002, and the prevalence rates of these markers have been analyzed for each prefecture in Japan. In 2006, the average HBsAg and anti-HCV prevalences were 1.0% and 0.7%, respectively, in this group (see Fig. 6). There was a highly significant association between the death rate of HCC and prevalence of anti-HCV in each prefecture (Fig. 7; correlation coefficient = 0.66; $P < 0.001$,

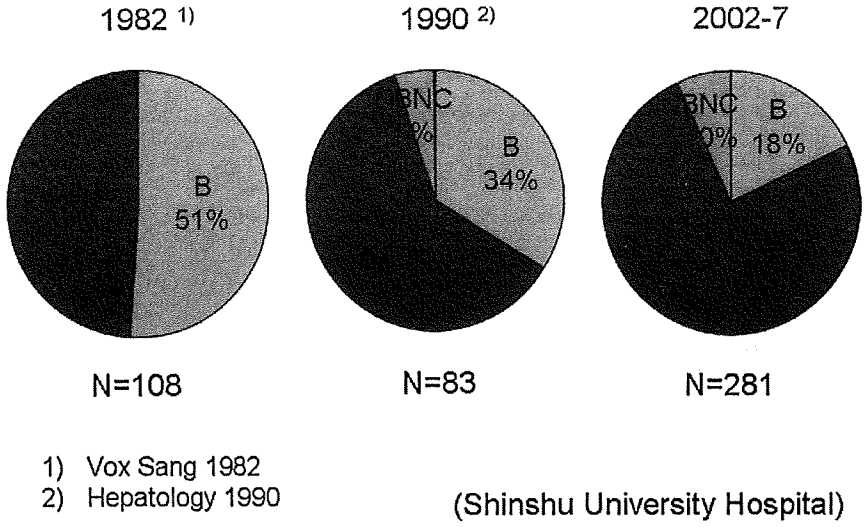


**Fig. 5.** Clinical features of hepatitis B (*B*) virus (HBV)- and hepatitis C (*C*) virus (HCV)-related HCC in 1982, 1990, and 2002–2005 at Shinshu University Hospital. *NBNC*, non-B non-C

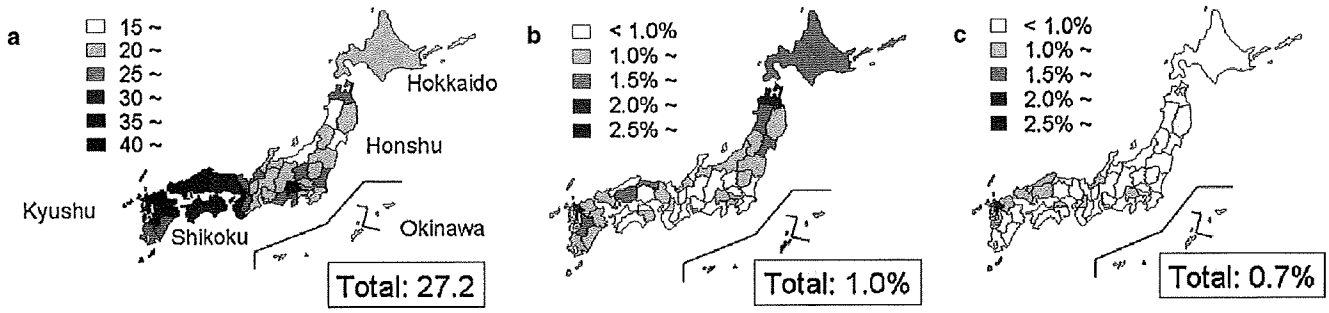


**Fig. 6.** **a** Death rate of primary liver cancer was 27.2 per 100000 in 2005 among people over 40 years of age in 48 prefectures in Japan. In the same group in 2006, HBsAg prevalence was 1.0% (**b**) and anti-HCV prevalence was 0.7% (**c**)

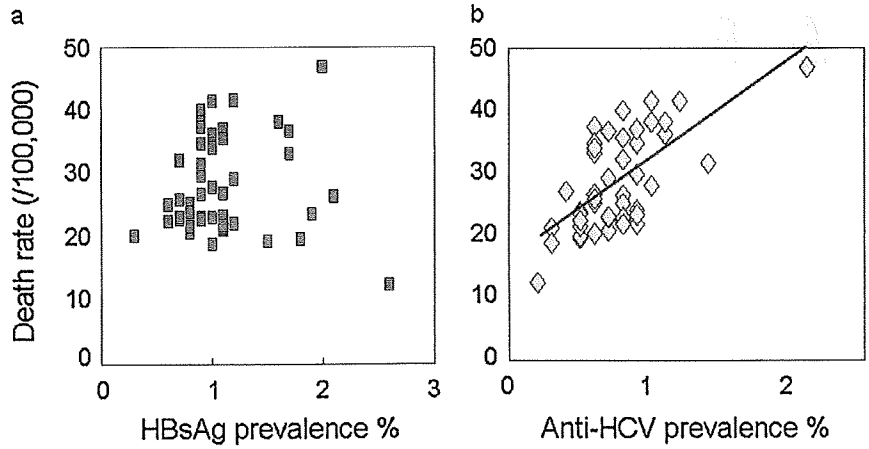


**Fig. 7.** Relationship between the death rate of primary liver cancer and prevalence of (**a**) HBsAg ($r = 0.02$, $P$ = NS) and (**b**) anti-HCV ($r = 0.66$, $P < 0.001$, $y = 16.3x + 16.1$) among the general population over 40 years of age in 2006

$y = 16.3x + 16.1$), but no correlation with the prevalence of HBsAg was seen (Fig. 6). For instance, although Okinawa Prefecture had the highest prevalence of HBsAg (2.6%), its HCC death rate was the lowest (12.5/100000 persons). A possible explanation for this discrepancy is that the HBV genotype Bj, which shows good clinical prognosis,[10,11] is the dominant HBV genotype in Okinawa. In contrast, areas with high rates of anti-HCV, especially in western Japan, had high death rates from HCC. HCV appears to be the major contributor to primary liver cancer in these regions; Saga Prefecture shows both the highest HCC death rate (46.9/100000) and highest prevalence rate of anti-HCV (2.1%) in Japan.

**Table 1.** Summary of findings in representative studies on the incidence of hepatocellular carcinoma (HCC) among patients with chronic hepatitis C virus (HCV) infection treated with interferon alone in Japan

| | Treated | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Untreated | | Non-SVR | | SVR | | Total | |
| Author | No. HCC/no. cases | % | No. HCC/no. cases | % | No. HCC/no. cases | % | No. HCC/no. cases | % |
| Kasahara[12] | | | 41/709 | 5.8 | 5/313 | 1.6 | 46/1022 | 4.5 |
| Imai[13] | 19/140 | 13 | | | | | 18/419 | 4.3 |
| Ikeda[14] | 67/452 | 15 | 23/730 | 3.2 | 5/461 | 1.1 | 28/1191 | 2.4 |
| Yoshida[15] | 67/395 | 17 | 214/1556 | 13.8 | 27/836 | 3.2 | 241/2392 | 10.1 |
| Okanoue[16] | | | 119/849 | 14.0 | 8/397 | 2.0 | 127/1246 | 10.2 |
| Ikeda[17] | 59/352 | 17 | 34/171 | 19.9 | 1/53 | 1.9 | 94/576 | 16.3 |
| Total | 212/1339 | 16 | 432/4015 | 10.8 | 46/2060 | 2.2 | 554/6846 | 8.1 |

SVR: sustained virological response

## Antiviral therapy suppresses the incidence of HCC

As described in prior sections, HCV infection is the major cause of HCC in Japan, suggesting that eradication of HCV may decrease the incidence of HCC. A summary of different studies on the incidence of HCC among patients with chronic hepatitis C who were treated with interferon in Japan can be found in Table 1.[12–17] These studies show a moderate decrease in the risk of HCC in patients with chronic hepatitis C treated with interferon, especially in patients with sustained virological response as compared with nonresponders and nontreated patients.

Recently, Ikeda et al. prospectively studied patients with chronic HCV infection and evidence of occult HBV infection [negative results for HBsAg and HBV DNA but positive results for antibodies to hepatitis B core antigen (anti-HBc) in serological testing].[17] Patients with HCV-related cirrhosis and positive results for anti-HBc were at high risk for HCC, even in patients with a sustained virological response to interferon (IFN) therapy. Thus, anti-HBc positivity is a marker of high risk for HCC among patients with HCV-related cirrhosis.

Between 1992 and 2001, approximately 300000 patients with chronic hepatitis C received IFN monotherapy in Japan. As shown in Fig. 1, it is remarkable that the number of deaths and the death rate of HCC began to decrease in 2005. These phenomena suggest that antiviral treatment indeed reduces the risk of HCC in patients with HCV infection.

## Conclusion

The number of deaths and death rate of HCC showed a sharp increase from 1975 onward but had begun to decrease in 2006. Although both HBV and HCV infection play a major role in HCC in Japan, HCV-related HCC represents 70% of all cases. The incidence of HCC without HBsAg or anti-HCV accounts for 7%–15% in Japan, and half of NBNC-HCC cases are of unknown origin. Geographically, HCC is more frequent in western than eastern Japan, and the death rates of HCC in each prefecture correlate with anti-HCV, but not HBsAg, prevalence. IFN therapy for chronic hepatitis C reduces the risk of development of HCC, especially in patients with sustained viral response.

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## References

1. Ikai I, Arii S, Okazaki M, Okita K, Omata M, Kojiro M, Takayasu K, et al. Report of the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan. Hepatol Res 2007;37:676–91.
2. Kiyosawa K, Umemura T, Ichijo T, Matsumoto A, Yoshizawa K, Gad A, Tanaka E. Hepatocellular carcinoma: recent trends in Japan. Gastroenterology 2004;127:S17–26.
3. Umemura T, Kiyosawa K. Epidemiology of hepatocellular carcinoma in Japan. Hepatol Res 2007;37(suppl 2):S95–100.
4. Japan LCSGi. Survey and follow-up study of primary liver cancer in Japan. Report 11. Kanzo 1995;36:208–18.
5. Japan LCSGi. Survey and follow-up study of primary liver cancer in Japan. Report 12. Kanzo 1997;38:317–30.
6. Japan LCSGi. Survey and follow-up study of primary liver cancer in Japan. Report 13. Kanzo 1999;40:288–300.
7. Japan LCSGi. Survey and follow-up study of primary liver cancer in Japan. Report 14. Kanzo 2000;41:799–811.
8. Japan LCSGi. Survey and follow-up study of primary liver cancer in Japan. Report 15. Kanzo 2003;44:157–75.
9. Ikai I, Arii S, Ichida T, Okita K, Omata M, Kojiro M, Takayasu K, et al. Report of the 16th follow-up survey of primary liver cancer. Hepatol Res 2005;32:163–72.
10. Orito E, Sugauchi F, Tanaka Y, Ichida T, Sata M, Tanaka E, Okanoue T, et al. Differences of hepatocellular carcinoma patients with hepatitis B virus genotypes of Ba, Bj or C in Japan. Intervirology 2005;48:239–45.
11. Sumi H, Yokosuka O, Seki N, Arai M, Imazeki F, Kurihara T, Kanda T, et al. Influence of hepatitis B virus genotypes on the progression of chronic type B liver disease. Hepatology 2003;37:19–26.
12. Kasahara A, Hayashi N, Mochizuki K, Takayanagi M, Yoshioka K, Kakumu S, Iijima A, et al. Risk factors for hepatocellular car-

cinoma and its incidence after interferon treatment in patients with chronic hepatitis C. Osaka Liver Disease Study Group. Hepatology 1998;27:1394–402.
13. Imai Y, Kawata S, Tamura S, Yabuuchi I, Noda S, Inada M, Maeda Y, et al. Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Osaka Hepatocellular Carcinoma Prevention Study Group. Ann Intern Med 1998;129:94–9.
14. Ikeda K, Saitoh S, Arase Y, Chayama K, Suzuki Y, Kobayashi M, Tsubota A, et al. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. Hepatology 1999;29: 1124–30.
15. Yoshida H, Tateishi R, Arakawa Y, Sata M, Fujiyama S, Nishiguchi S, Ishibashi H, et al. Benefit of interferon therapy in hepatocellular carcinoma prevention for individual patients with chronic hepatitis C. Gut 2004;53:425–30.
16. Okanoue T, Minami M, Makiyama A, Sumida Y, Yasui K, Itoh Y. Natural course of asymptomatic hepatitis C virus-infected patients and hepatocellular carcinoma after interferon therapy. Clin Gastroenterol Hepatol 2005;3:S89–91.
17. Ikeda K, Marusawa H, Osaki Y, Nakamura T, Kitajima N, Yamashita Y, Kudo M, 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.