MINI-REVIEW

Liver Cancer and its Prevention

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Abstract

Liver cancer is one of the leading causes of cancer deaths in Asia and Africa. The epidemiology of liver cancer is distinctive in Japan, where chronic infection with hepatitis C virus (HCV) rather than hepatitis B virus (HBV) plays the major role in the etiology. In this paper, together with a brief review of the descriptive epidemiology of liver cancer and its prevention, Japanese experiences of liver cancer occurrence and some epidemiological studies are described, and Japanese national projects directed against hepatitis and liver cancer are presented.

Distinctive time-trends have been observed for liver cancer incidence in Japan. The rates for over 55-59 year olds (both sexes) showed a peak in the birth cohort of 1931-1935, while the rates for less than 50-54 year old females indicate a decreasing trend. The extremely high incidences among birth cohorts around 1931-1935 seems to be related to endemic HCV infection in this generation in Japan. Follow-up studies not only of patients with chronic hepatitis C but also of apparently healthy carriers of HCV showed an increased risk of hepatocellular carcinoma (HCC). Cumulative risk of HCC (40-74 years of age) was estimated as reaching 21.6% (males) and 8.7% (females) among anti-HCV positive voluntary blood donors. Retrospective cohort studies indicated interferon (IFN), with or without ribavirin, to be effective for reducing the risk of HCC among patients with chronic hepatitis C. Periodic examination with ultrasonography and measurement of alpha-fetoprotein has become common practice for early detection of HCCs among patients with chronic hepatitis or liver cirrhosis in Japan. A non-randomized controlled study was conducted to evaluate the effect of periodic examination on mortality, but we failed to show any beneficial effects of screening for liver cancer.

In the fiscal year 2002, Japanese National Projects directed against hepatitis and HCC were started, in which blood tests for HCV and HBsAg are offered just once at the age of 40, 45, 50, 55, 60, 65 or 70 for five years. Participants are categorized as either HCV carriers or non-carriers. HCV carriers are further examined by liver disease specialists, seeking indications for IFN therapy. Type C chronic hepatitis patients are recommended to receive IFN therapy with or without ribavirin. This project is expected to become a model of liver cancer control in HCV-endemic countries. Recently however, the US Preventive Service Task Force has recommended against routine screening for HCV infection in asymptomatic adults in the general population who are not at increased risk of infection. This divergence of views is also discussed.

Key Words: prevention of liver cancer - risk factors - hepatitis C virus- interferon treatment - screening

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Introduction

Liver cancer is one of the world's greatest disease burdens, with hepatocellular carcinoma (HCC) above all as one of the leading causes of cancer deaths in Asia and Africa. Chronic infection with hepatitis B and/or hepatitis C viruses is a well-known risk factor and the most influential determinant for HCC. Control of hepatitis virus infections has theoretically been well established through screening of donated blood for hepatitis B virus (HBV) and hepatitis C virus (HCV), use of disposable needles and syringes, and passive/active immunization against HBV with HBIG (HB immunoglobulin) and HB vaccine. In most Asian countries HBV plays the major role in hepatocarcinogenesis, but in Japan around 80% of HCC cases are related to HCV. An extremely high prevalence of HCV has been reported in Mongolia and in parts of Africa and south-eastern Asia. High risk behavior, including intravenous drug abuse, was also reported in surveys from the US. Control of HCV infection and prevention of HCC will be very important not only in Japan but also in the rest of the world. In this paper, together with a brief review of the descriptive epidemiology of liver cancer and its prevention, Japanese experiences of liver cancer occurrence and some epidemiological studies are introduced. Present national projects directed against hepatitis and HCC in Japan are also described and discussed.

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Liver Cancer Burden in the World

Using the most recent collected data, the IARC (Ferlay et al., 2004) has estimated cancer incidence and mortality in the world. The number of worldwide liver cancer deaths in 2002 was estimated as 598,412, which amounted to 9% of all cancer deaths and ranked third in site-specific cancer deaths, followed by lung and stomach cancer (Table 1). The burden of liver cancer was more serious among less developed countries. In Eastern Asia, more than 377,000 people were died from liver cancer, accounting for 19% of all cancer deaths. In South-Eastern Asia, liver cancer ranked second and accounted for 12%. Liver cancer deaths in these two areas accounted for 71% of those in the world.

The age-adjusted incidence rate of liver cancer (adjusted to the world population) was estimated as 18.4-98.9 per 100,000 for males in many Asian countries, including China, Japan, Korea, and Thailand, as well as countries in Eastern and Middle Africa (Ferlay et al., 2004). These geographical distributions of extremely high incidence areas were almost the same as those of high incidence areas of liver cancer among females (7.2-57.3 per 100,000). Prevention of liver cancer is surely high priority in Asia.

Chronic infection with HBV and/or HCV is a well-known risk factor and the most influential determinant for HCC. When the geographic pattern of HBV prevalence was referred to (Okuda et al., 1999), high prevalence countries for HBV (6-10%) coincided well with high incidence areas for liver cancer, with a few exceptions; Japan (lower prevalence (1-2%) and higher incidence) and Alaska (higher prevalence (6-10%) and lower incidence). Control of HBV infection has been well established through screening of donated blood for HBV, use of disposable needles and syringes, and HB vaccine. According to the WHO/UNICEF joint reporting form (WHO/UNICEF, 2002), 141 countries have introduced national programs of HB vaccination in 2002, although there are some differences in coverage.

The WHO weekly epidemiological record (WHO, 2000) reported the geographical pattern of HCV prevalence in 2000. Extremely high prevalence (more than 10%) was observed in Mongolia, Egypt, Cameroon and Bolivia. The high prevalence in Egypt was reported to be ascribable to parenteral anti-schistosomal therapy, which typically requires 10 to 12 injections and is usually given with reusable syringes (Cohen, 1999). Although this type of therapy tapered off in the 1970s when oral schisto drugs became available, the schisto-HCV link is well known to be the world's largest iatrogenic transmission scenario to date.

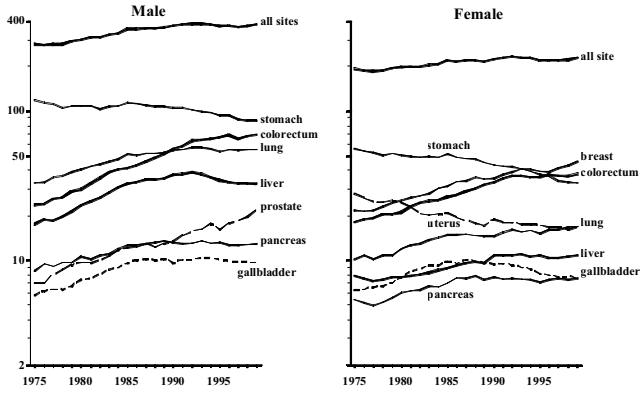

Figure 1. Time-trends of Age-adjusted Incidence Rates of Cancer for Major Sites, Japan, 1975-1999 (Standard: Japanese Model Population of 1985)

Outbreak of HCV Related Liver Cancer in Japan

Figure 1 shows time-trends of age-adjusted incidence rates of cancer for major sites in Japan (adjusted to the Japanese model population of 1985) during the period 1975 to 1999 (Ajiki et al., 2004). The age-adjusted incidence rates of liver cancer for males increased remarkably until the early 1990s, but began to decrease thereafter. For females, it increased moderately until the early 1990s, and reached a plateau thereafter.

Figure 2 indicates age-specific incidence rates of liver cancer by gender and birth cohort in Japan. The horizontal axis shows birth years, ranging from 1886 to 1975. Among

Table 1. Annual Number of Cancer Deaths from Major Sites and Their Rank, both Sexes, all Ages, 2002

	World			More developed			Less developed		
Stomach	699,803	2	10%	212,236	3	8%	485,026	3	14%
Colon/Rectum	529,020	4	8%	313,894	2	12%	214,264	7	6%
Liver	598,412	3	9%	109,236	7	4%	486,684	2	14%
Lung	1,179,074	1	18%	584,979	1	22%	591,313	1	17%
Breast	411,093	5	6%	189,765	4	7%	221,028	6	6%
All sites but skin	6,724,931		100%	2,688,472		100%	3,562,833		100%
	Eastern Asia			South-Eastern Asia					
Stomach	383,972	2	19%	21,900	6	6%	Liver cancer deaths		
Colon/Rectum	131,531	5	7%	28,419	3	8%	in the 2 areas account for		
Liver	377,493	3	19%	45,069	2	12%	71% of those in the world		
Lung	417,717	1	21%	63,690	1	18%	(From GLOBOCAN 2002)		
Breast	47,866	8	2%	26,822	4	7%			
All sites but skin	2,016,310		100%	363,424		100%			

males aged 45-49 and over, the rates were highest in birth cohorts around 1931-1935, while among males aged under 45 the rates were highest in birth cohorts around 1946-1950. Among females aged 50-54 and over, similar peaks were observed in birth cohorts around 1931-1935, while the rates for those aged under 50 decreased in recent birth cohorts. We speculate that the extremely high incidence among birth cohorts around 1931-1935 was related to an endemic of HCV infection among those generations in Japan (who reached ages of fifties and sixties at the beginning of the 1990s), while the decrease was associated with the lower prevalence of HBV among the younger generations.

Circumstantial evidence for the endemic of HCV infection was suggested partly from the report of annual numbers of arrested drug addicts in Japan from 1951 to 1997 (Okada, 1999). The first period of abuse happened in the early 1950s. It was an outbreak of parenteral amphetamine use in the devastated society after World War II. Although it settled down through intensification of penalties, tightening of control, and development of the national movement, people born in 1931 to 1935, who were aged early twenties then, seem to have had a greater chance of HCV infection, irrespective of their drug abuse or not.

Figure 3 shows time-trends of age-adjusted liver cancer mortality rates (adjusted to the world population) for selected countries during the last three decades (Kuroishi et al., 2004). While decreasing trends were observed in Singapore, Greece, and Spain, increasing trends were noticed in some countries, including Japan, USA, and Australia, particularly for males. The increase in liver cancer mortality was reported to be caused by an increase in HCV related liver cancer incidence not only in Japan (Okuda, 1997) but also in USA (EL-Serag, et al., 2003).

Prevalence of Risk Factors for HCC in Japan

Tanaka et al (2004) reported the prevalence of HBs antigen and HCV antibody among the first blood donor candidates in Japan during 1995 to 2000 (Figure 4). The

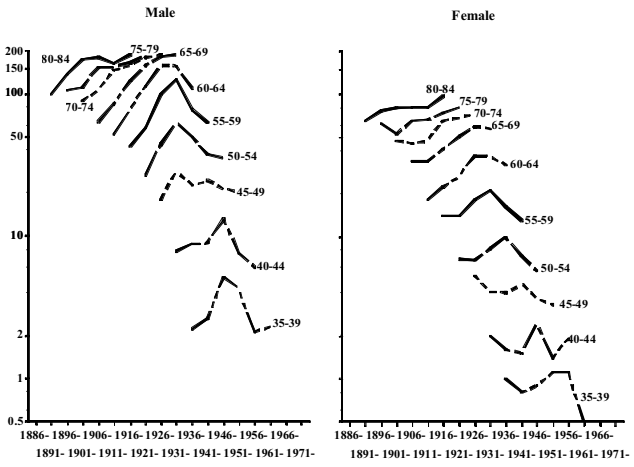

Figure 2. Age-specific Incidence Rates of Liver Cancer by Gender and Birth-year (from 1886 to 1975), Japan

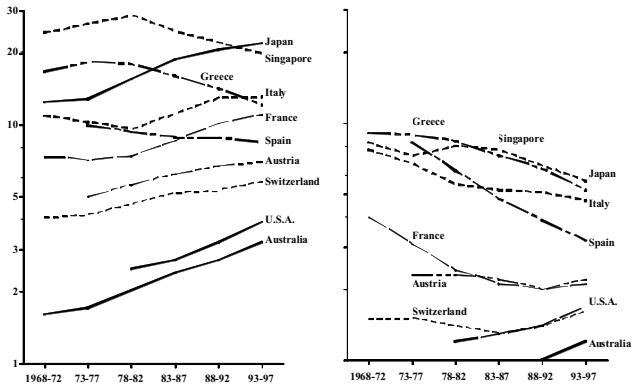

Figure 3. Time-trends of Age-adjusted Liver Cancer Mortality Rates for Selected Countries, 1968-1997 (Standard: World Population)

horizontal axis indicates their age in the year 2000, as well as the average year of their birth. The solid line is for HCV antibody, and the dotted line is for HBs antigen. Prevalence of HCV was high (3.4%) among the generation born around 1935. Regrettably data for older Japanese generations are not available. Prevalence of HBs antigen was highest among the generation born around 1945.

Figure 5 shows age-specific prevalence of hepatitis virus markers among patients with HCC in Osaka, Japan, during 1990-1999 (Tanaka et al., 1999). Osaka is one of the prefectures with the highest liver cancer incidence in Japan. While most of the patients aged 50 and over were HCV antibody positive, more than 60% of the cases aged less than 50 were HBs antigen positive. Thus, age-specific trends of liver cancer incidence in Japan (Figure 2) seem to be well understandable in terms of the past endemic of HCV and HBV infection.

Figure 6 shows gender-specific distributions of established risk factors for HCC; that is, HBV, HCV and heavy drinking among HCC patients in Osaka, Japan, during 1994-2000 (Tsukuma et al., 2001). HCV positive cases were 74.4% for males and 81.8% for females, and HBV positive

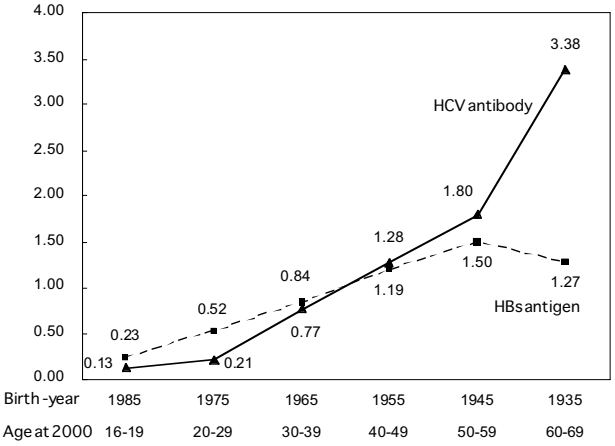

Figure 4. Prevalence of HBs Antigen and HCV Antibodies among the First Blood Donor Candidates, Japan, 1995 to 2000

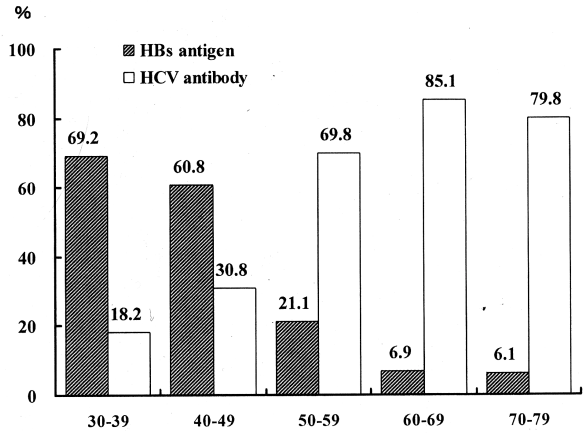

Figure 5. Age-specific Prevalence of HBs Antigen and HCV Antibody among Patients with HCC in Osaka, Japan, 1990 to 1999

rates were 14.3% for males and 10.2% for females. 27.5% of the males were heavy drinkers, defined as those who consumed more than 80 grams of alcohol a day over a period of 10 years. Heavy drinkers were rare among females in Japan.

Associations between Lifestyle and Risk for Hepatocellular Carcinoma

In order to clarify the roles of lifestyle factors in the etiology of HCC, a follow-up study of patients with chronic hepatitis and cirrhosis was conducted in Osaka Medical Center for Cancer and Cardiovascular Diseases (OMCC) (Tsukuma et al., 1993, Tanaka et al., 1999). Table 2 shows patient characteristics at baseline, number of study subjects, and the incidence of HCC during the period of around five

Table 2. Number of Study Subjects and the Incidence of HCC According to Basic Characteristics at Enrollment (Follow-up period: Mean 60.8 months, Range 6-103 months)

Characteristics at baseline	No. of study subjects	Incidence of HCC No.	%
Sex			
Male	580	126	21.7
Female	392	56	14.3
Age			
-44	58	5	8.6
45-54	273	41	15.0
55-64	519	106	20.4
65-	122	30	24.6
Diagnosis			
Chronic hepatitis	714	91	12.7
Liver cirrhosis	258	91	35.3
Virus makers			
HBsAg(+), anti-HCV(+)	13	3	23.1
HBsAg(+), anti-HCV(-)	126	27	21.4
HBsAg(-), anti-HCV(+)	833	152	18.2
(Status of past infection with HBV)			
HBcAb(low titer), anti-HCV(+)	422	88	20.9
HBcAb(-), anti-HCV(+)	278	41	14.7

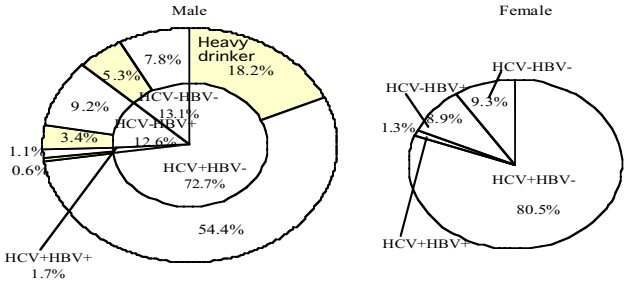

Figure 6. Gender-specific Distributions of Established Risk Factors for HCC among HCC Patients in Osaka, Japan, 1994 to 2000

years. The incidence was 22% for males and 14% for females. Thirty-five percent of the cirrhosis patients developed HCC. Adjusted hazard rate ratios for the development of HCC are presented in Table 3. Males showed a significantly higher risk for HCC. If smoking and drinking were adjusted for, however, the hazard rate ratio became insignificant. Our follow-up study indicated significant associations between smoking and the risk for HCC. Drinking was not associated significantly with risk for HCC in this follow-up study; this seemed to be due partly to a behavior change affecting drinking after the development of chronic liver disease.

National Projects against Hepatitis and HCC in Japan

The history of Japanese projects against hepatitis and HCC is here briefly described. In late 1970s, screening for HBs antigen started at Red Cross Blood Centers, and the

Table 3. Smoking and Drinking Habits and the Risk of HCC among Patients with Anti-HCV Positive Chronic Hepatitis or Liver Cirrhosis

Factors	Adjusted HR	P-value
Sex		
Male/Female	1.91	0.0002
(Adjusted for age and presence of liver cirrhosis)		
Male/Female	1.27	0.36
(Furthermore adjusted for smoking and drinking)		
Smoking		
Current smoker		
≥20 cigarettes/day	2.33	0.002
1-19 cigarettes/day	1.54	0.17
Exsmoker	1.41	0.23
Nonsmoker	1.00	
Drinking		
Current daily drinker		
≥80 g of ethanol/day	1.24	0.57
<80 g of ethanol/day	1.25	0.44
Former daily drinker		
≥80 g of ethanol/day	1.33	0.32
<80 g of ethanol/day	1.28	0.33
Occasional drinker	0.79	0.52
Nondrinker	1.00	

use of disposable needles and syringes was promoted. In 1986, national projects against HBV vertical transmission started, where immunization by HB immuno-globulin and HB vaccine was introduced, in order to prevent HBV infection from HBe antigen positive mothers to infants. In 1989, screening for HCV antibody started at Red Cross Blood Centers. In 1992, medical insurance started to cover interferon (IFN) therapy for type C chronic active hepatitis. The Japanese government has taken urgent comprehensive countermeasures against hepatitis and HCC since April 2002 (fiscal year 2002). In these projects, blood tests for HCV and HBs antigen have been offered just once at the age of 40, 45, 50, 55, 60, 65 and 70, for five years, as part of health check-ups under the Act of Health for the Aged. Participants are categorized as either HCV carriers or non-carriers. HCV carriers are further examined by liver disease specialists, in terms of indication of IFN therapy. Type C chronic hepatitis patients are recommended to receive IFN (with or without ribavirin) therapy. Figure 7 indicates the HCV screening system in 2003; that is a series of tests comprising quantification of HCV antibody titer, detection of HCV antigen, and polymerase chain reaction (PCR) for HCV RNA. Using this system, the screenees are judged accurately as HCV carriers or non-HCV carriers.

Activities accompanying the Japanese hepatitis virus screening projects are as follows; 1) public education on type B and C viral hepatitis, 2) public education of persons at high risk, and providing access to sites for counseling and testing, 3) pretest and post-test counseling, 4) guidelines on treatment for type C chronic hepatitis, 5) surveillance of HCV screening and follow-up of HCV carriers in some municipalities.

Table 4 shows the results of screening for HCV and HBs antigen under the national projects against hepatitis and HCC in 2002. Thirty percent of the target population participated in the screening. Fourteen thousand and six hundred (1.1% of the participants) were positive for HCV, and 16,700 (1.3%) were positive for HBs antigen.

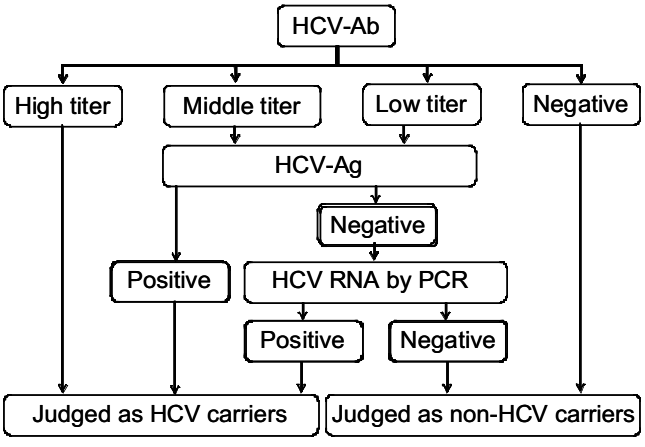

Figure 7. HCV Screening System under the National Projects against Hepatitis and HCC, 2003

Table 4. Blood Tests for HCV and HBsAg under the National Projects against Hepatitis and HCC

	HCV	HBsAg
No. of target population <A>	4,331,521	4,331,521
Participants <B>	1,298,746	1,291,194
B/A	30.0%	29.8%
Positives <C>	14,672	16,721
C/B	1.1%	1.3%

Some Japanese Study Results Supporting the National Projects

Some of our study results supported the Japanese projects against hepatitis and HCC. The first was a retrospective cohort study of patients with type C chronic hepatitis, where we evaluated the effectiveness of IFN therapy for reducing HCC incidence in Osaka, Japan (Tanaka et al., 2000)[15]. Around 740 patients diagnosed as type C chronic hepatitis were followed up and their cumulative risk for HCC was evaluated according to the use of IFN therapy and their response to the therapy. HCC risk was very high among the patients without IFN treatment or those who didn't respond to IFN therapy. In contrast, responders remained at minimal to moderate risk for HCC, according to the duration of response. A sustained response, with patients remaining at minimal risk for HCC, means that transaminase normalization continued over 6 months after completing IFN therapy. As compared to the risk among patients without IFN treatment, the multivariate-adjusted hazard rate ratio for HCC was 0.52 for those who received IFN therapy. Inverse dose-response relationships were also observed between the duration of IFN response and the risk for HCC. The second study was of a controlled trial of early detection for HCC, where we tried to evaluate whether or not early detection would reduce the risk of mortality from HCC and liver disease. Study subjects were outpatients in OMCC, who were diagnosed as type B or type C chronic hepatitis or cirrhosis, and who fitted pre-arranged criteria (Tsukuma et al., 1993). They were assigned to the study group or control group, according to their birth date; that is, either an even or odd year.

The study group was given periodic checkups, using alpha-fetoprotein (AFP) and ultra-sonography (US). The control group was given the usual care. We compared the mortality between the two groups (Figure 8). The eligibility criteria shown in Table 5 were set to exclude those patients with decompensated liver disease who were unlikely to undergo radical treatment for HCC when it was detected. The study results are summarized in Table 6. The study group comprised 654 patients and control group 615. Mean follow-up period was 83 months. As of the end of 2002, 99 of the study group had died; 42% from HCC and 16% from other liver disease. Among the control group, 70 patients had died; 44% from HCC and 17% from other liver disease. Five-year cumulative mortality was 8% for the study group, and 6% for the control group, while the cumulative incidence of

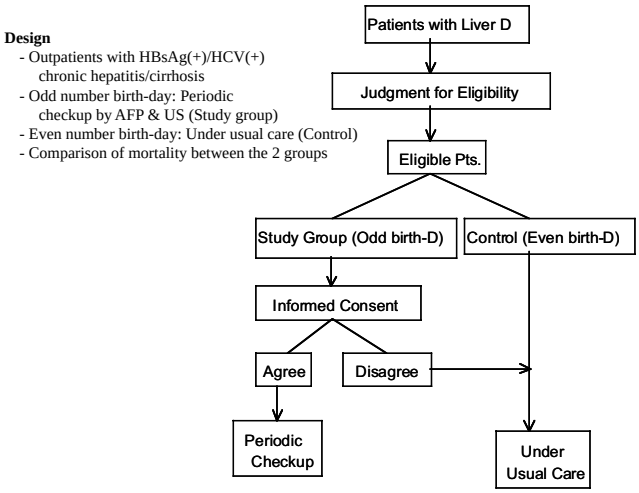

Figure 8. Design of the Controlled Trial of Early Detection for HCC, OMCC

HCC was 11% for the study group and 9% for the control group. Thus we concluded that early detection of HCC was not very effective in reducing mortality from HCC and liver disease, although there were several limitations in the study. One of the limitations was that periodic examination with US and measurement of AFP became common practice for early detection of HCC among patients with chronic hepatitis or liver cirrhosis in Japan, and as patients in the control group have also undergone periodic examinations; that is, so-called "contaminations" may have happened.

US Policy of Screening for HCV, compared with the Japanese Policy

The Japanese Projects against hepatitis and HCC are ongoing, and expected to become a model of HCC control in HCV endemic countries. Recently however the US Preventive Service Task Force (USPSTF) has recommended against routine screening for HCV infection in asymptomatic adults in the general population who are not at increased risk of infection (U.S. Preventive Task Force, 2004, Roger et al., 2004). Their rating is D; that is they have concluded that there is at least fair evidence that the service is ineffective, or that harms outweigh benefits. The USPSTF has also concluded that there is insufficient evidence to recommend for or against routine screening for HCV infection in adults at high risk of infection.

The USPSTF explains its rationale as follows; the prevalence of HCV infection in the general population is low, and most who are infected do not develop cirrhosis or other major negative health outcomes. There is no evidence that screening for HCV infection leads to improved long-term health outcomes, such as decreased incidence of cirrhosis or HCC, or reduced mortality. Although there is good evidence that antiviral therapy improves intermediate outcomes, such as viremia, there is limited evidence that such treatment improves long-term health outcomes. The current treatment regimen is long and costly, and is associated with a high patient dropout rate due to adverse effects. Potential harms of screening include unnecessary biopsies and labeling, although there is limited evidence to determine the magnitude of these harms.

Confronting the USPSTF recommendation, the Japanese

Table 5. Eligibility Criteria for the Controlled Trial of Early Detection for HCC, OMCC

1) Age Male 40_67y.o. Female 50_67y.o
2) No liver cancer
3) No sever esophageal varices No uncontrolable ascites
4) Chronic hepatitis or liver cirrhosis
5) Satisfy all criteria below
   a. HBsAg (+) or HCV-Ab (+)
   b. Serum total bilirubin 2.0mg/dl
   c. Serum albumin 2.8gr/dl
   d. Platelet 50,000/mm^3
   e. Hepaplastin test 40%
6) Collaborative

Table 6. Final Results of the Early Detection for HCC, OMCC (Mean follow-up periods: 82.8 months)

	Study group				Control group			
No. of eligible study subjects	654	100%			615	100%		
Reject enrollment	28	4%						
Vital status (as of Dec 31, 2002)								
Alive	545	83%			539	88%		
Dead	99	15%		100%	70	11%		100%
HCC			42	42%			31	44%
Other liver dis			16	16%			12	17%
Other cancers			17	17%			9	13%
Other diseases			20	20%			14	20%
Unknown causes			4	4%			4	6%
Missing	10	2%			6	1%		
5-years Cumulative Mortality (95% CI)		8% (5.9-10%)				6% (4.3-8.3%)		
Cumulative incidence of HCC	74	11%			58	9%		
Screening detected	65			88%				
Not screening detected	9				58			

rationale for the present projects against hepatitis C and HCC is as follows; although there is no direct evidence that screening for HCV among the general population reduces the risk for HCC, there is good evidence that antiviral treatment with IFN with or without ribavirin will reduce the risk for HCC among patients with chronic hepatitis C (Tanaka et al., 2001). More than half of the HCV carriers detected through blood donation were diagnosed as having chronic hepatitis by the subsequent workup. Follow-up studies of HCV carriers detected through blood donation indicate that the risk for HCC is very high; cumulative risk for 40-74 year olds reached 21.6% for males and 8.7% for females (Tanaka et al., 2004). This risk seems rather higher than that observed in the US. It might be caused by longer duration of HCV carrier state and/or longer life expectancy among Japanese, since most Japanese HCV carriers exhibited no risky behaviors like drug abuse as in the US. Most Japanese HCV carriers have been infected through inadequate medical or non-medical procedures in the past. New infection of HCV is extremely rare among the Japanese general population at present (Tanaka et al., 1998).

Future Directions for Prevention of Liver Cancer in the World

Future directions for liver cancer prevention should be pointed out in conclusion. These are; 1) prevention of new HBV infections, including thorough HBV vaccination programs, especially in high risk areas, 2) prevention of new HCV infections, 3) identification of HCV-infected persons in order to control HCV-related chronic liver disease, using antiviral treatment to prevent progression of chronic liver disease (rather than relying on early detection of liver cancer), and counseling of both infected and uninfected persons, as well as providing referral for medical evaluation and treatment, 4) surveillance and research to evaluate the effectiveness of preventive activities.

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