Community-Based Mass Ultrasonographic Screening of Hepatocellular Carcinoma among Thrombocytopenic Adults

Sheng-Nan Lu,[1] Jing-Houng Wang,[1] Pao-Fei Chen,[1] Hung-Da Tung,[1,2] Po-Lin Tseng,[1] Chao-Hung Hung,[1] Kwong-Ming Kee,[1] Chien-Hung Chen,[1] Kuo-Chin Chang,[1] Chuan-Mo Lee,[1] Chi-Sin Changchien, Yao-Der Chen,[3] Lin-San Tsai,[3] and Tony Hsiu-Hsi Chen[4]

[1]Division of Hepato-Gastroenterology, Department of Internal Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan, [2]Division of Gastroenterology, Department of Internal Medicine, Chi Mei Hospital Liuying Branch, Tainan, Taiwan; [3]Tainan County Health Bureau, Tainan, Taiwan, and [4]Institute of Preventive Medicine, National Taiwan University School of Public Health, Taipei, Taiwan

Abstract

Thrombocytopenia has been reported as a valid surrogate for liver cirrhosis and could be used to identify groups at high risk of hepatocellular carcinoma (HCC) for ultrasonographic (US) screening. We designed this two-stage community-based screening for HCC. In 2004, subjects (ages ≥40 years) were invited to undergo comprehensive health examinations, with 17,551 men (ages 63.0 ± 11.5 years) and 39,151 women (ages 59.9 ± 11.7 years) participating. Subjects with platelet counts <150 × 10^9/L or α-fetoprotein (AFP) >20 ng/mL were enrolled for the second-stage US screening; 3,242 subjects (5.7%; male/female, 1,415/1,827; age 66 ± 10 years) were candidates for US screening and 2,983 (92.2%) responded. Of 137 suspected cases, 124 (90.5%) complied with referral for confirmation and 72 (58.1%) were confirmed to be HCC cases (male/female, 41/31; age 68.1 ± 8.8 years). Screening with AFP, thrombocytopenia, or both could identify 0.64% (*n* = 364), 5.33% (*n* = 3,205), and 5.7% (*n* = 3,242) of the high-risk subjects from the population, estimated to include 50.5%, 54.5%, and 71.3% of all HCC cases. Among confirmed patients, tumor diameters were <3 cm for the 27 (37.5%) patients and 3 to 5 cm for the 23 (31.9%) patients. Only 5 (6.9%) patients' conditions were too advanced to be actively treated. This study enrolled only 5.7% of the participants for US, which cover 64.7% to 71.3% of the HCC cases. Most (93%) of the detected cases were caught early enough to undergo effective treatment modalities. This HCC screening protocol should be feasible, economical, and effective. (Cancer Epidemiol Biomarkers Prev 2008;17(7):1813–21)

Introduction

In 2000, 414,900 men (rank 3 of male cancer death; age-adjusted mortality 13.6/10^5) and 191,000 women (rank 6; 6.4/10^5) died of liver cancer, including hepatocellular carcinoma (HCC; ref. 1). Taiwan is one of prevalent areas of liver cancer. It was the first cause of cancer death of men (40.5/10^5) and the second of women (15.0/10^5) in 2006 (2). Cancer screening is useful in that early diagnosis and prompt treatment improve the survival rates for some cancers. HCC (3) have encouraged us to attempt even earlier detection of such tumors. Benefits of HCC screening have been documented by cohort studies (4) and randomized control trials (5). Regular follow-up or surveillance of high-risk subjects for early detection of HCC has become commonplace in hospitals, especially in areas with a prevalence of chronic hepatitis B virus (HBV; ref. 6) or hepatitis C virus (HCV; ref. 7) infections. Hospital-based surveillance of patients resulted in increased early detection of HCC and improved patient survival rates (8). Although some community-based HCC screening projects have been reported previously (5, 9-13), it has not been routine. In earlier community-based screenings, subjects with elevated α-fetoprotein (AFP) were referred to hospitals for further examination after an entire community had been screened for AFP (9-11). It is relatively easy to collect blood samples in the traditional or filter paper methods and send them back to the AFP laboratory (10, 11). However, AFP alone is neither sensitive nor specific enough to detect HCC (12, 14). Therefore, AFP alone should not be recommended for screening unless ultrasonography (US) is not available (15). A combination of AFP and US is the most acceptable screening tool for HCC documented thus far (14, 16). Regrettably, it would be impossible to perform US for the entire population of any community, so a two-stage community-based HCC screening program, in which US is limited only to high-risk groups, seems more feasible. The first screening identifies the high-risk group among the larger population, and the second-stage US screening is used only for the high-risk group. A

Received 10/30/07; revised 4/11/08; accepted 4/24/08.

Grant support: Chang Gung Memorial Hospital CMRP 8032 and National Science Council, Republic of China NSC 91-2314-B-182A-177 (S-N. Lu).

Requests for reprints: Sheng-Nan Lu, Division of Hepato-Gastroenterology, Department of Internal Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, 123 Ta Pei Road, Niao Sung 833, Kaohsiung, Taiwan, Republic of China. Phone: 886-7-7317123, ext. 8301; Fax: 886-7-7322402. E-mail: juten@ms17.hinet.net

doi:10.1158/1055-9965.EPI-07-2746

community-based HCC screening program has been conducted in Taiwan since 1991. Serum hepatitis B surface antigen (HBsAg), anti-HCV antibody, aspartate aminotransferase, alanine aminotransferase, AFP, and a family history of HCC were selected as markers for identifying members of the high-risk group (4, 12, 17, 18). Although ≥90% of HCC cases in each community were covered by inclusion criteria of first-stage screening, ~30% of the participants were identified as belonging to the high-risk group for second-stage US screening (4, 12), and performing US on up to 30% of a community's adult population would be a heavy load. Because most HBV- and/or HCV-related HCC occur together with cirrhotic liver parenchyma (19), limited HCC screening on cirrhotic patients might therefore be cost-effective. Our pilot studies suggested that thrombocytopenia (platelet counts $<150 \times 10^9$/L) is a valid surrogate for liver cirrhosis and can be used to identify high-risk candidates for US HCC screening in dual HBV- and HCV-endemic areas (20). Based on these findings, this study's HCC mass screening was conducted in a HCC-endemic county that has not been screened before.

Materials and Methods

As shown in Fig. 1, the study area was Tainan County in southern Taiwan. Of the 31 townships, 15 have high HCC mortality rates (male $>50/10^5$; ref. 2). The population of Tainan County is ~1,105,000, of which 475,957 residents (43.1 %) are ≥40 years old. Focusing on the population ages ≥40 years, the countywide prevalence of anti-HCV antibody and HBsAg were 10.2% and 10.9%, respectively (21).

During April and November 2004, the Tainan County Health Bureau conducted a countywide community health screening in 216 different locations. All residents ages ≥40 years were invited by mail, telephone, and media to undergo a comprehensive health examination. Blood samples were obtained for measurements of HBsAg, anti-HCV, and AFP levels (ELISA, General Biological), biochemical tests (Hitachi 747 auto-analyzer, Hitachi), and complete blood counts (Sysmex SE9000 analyzer, Sysmex UK). A total of 17,551 males and 39,151 females eligible for the health examination were enrolled. The mean age of these 56,702 subjects was 63.0 ± 11.5 years for males and 59.9 ± 11.7 years for females (20). Subjects with thrombocytopenia (platelet count $<150 \times 10^9$/L) or elevated AFP (>20 ng/mL) were defined as candidates for the high-risk group and were enrolled for second-stage US screening. US was done in their communities 1 week after blood tests by nine experienced hepatologists of a medical center using a hand-carried US apparatus with a 5 to 2 MHz convex probe (Titan, SonoSite). Once suspected hepatic focal lesions were found, the subjects were referred to medical centers for further confirmation and treatment. Medical records were abstracted from referral medical centers. Diagnostic criteria of HCC were based on pathology/cytology, a combination of AFP >400 ng/mL and a positive arterial image, or arterial images of at least two modalities (22). Study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Taiwan. Each participant provided informed written consent.

For estimating the sensitivity of the first screening, our previous hospital-based study of 4,042 HCC cases was cited as a reference. In the reference, prevalence of thrombocytopenia was 42% in HBsAg(+)/anti-HCV(-) HCC cases, 63% in HBsAg(-)/anti-HCV(+) cases, 50% in HBsAg(+)/anti-HCV(+) cases, and 30% in HBsAg(-)/anti-HCV(-) cases (20).

For evaluating the validity of this screening, we linked our file with the National Cancer Registration Database to find HCC cases, who were reported before the end of 2005, among our whole study population. There is National Cancer Registration System in Taiwan. All hospitals that have ≥50 beds should report the newly diagnostic cancer cases to this system. These hospitals covered most but not all incident cases of malignancy. Not only pathologically proven cases but also clinical

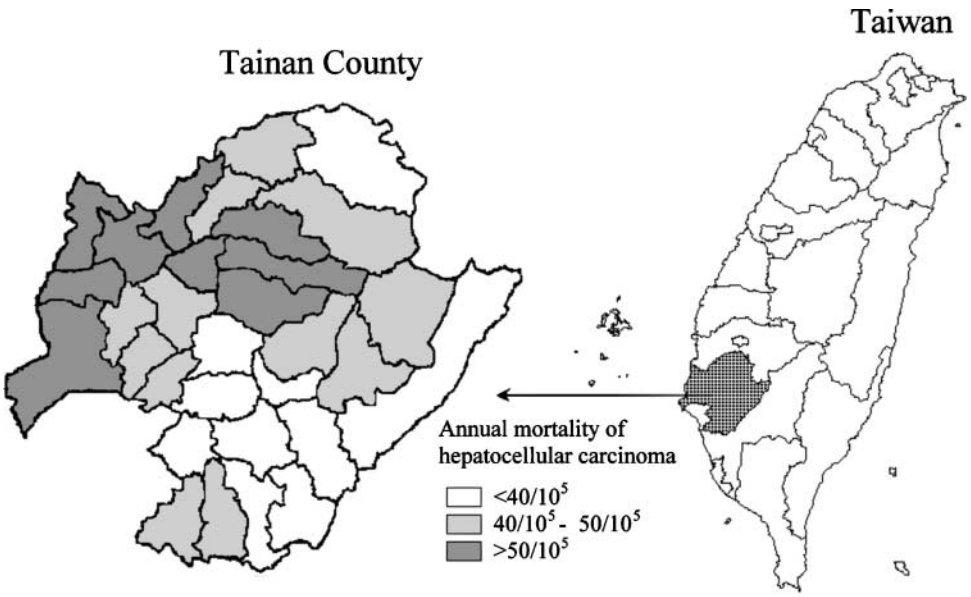

Figure 1. *Right,* Tainan county, located in southern Taiwan, comprised 31 townships; *left,* male mortality rates for HCC were $>40/10^5$ in 21 townships.

Table 1. High-risk subjects' distribution and response rates to US by risk factors and viral etiology in the community-based screening for HCC in Tainan, Taiwan, 2004

	High-risk subjects, *n* (%)	Responder to US, *n* (%)
Total	3,242 (100)	2,983 (92.2)
Risk factors		
Platelet count $<150 \times 10^9$/L	2,928 (90.3)	2,697 (92.1)
AFP >20 ng/mL	87 (2.9)	67 (77.0)
Both	227 (7.0)	219 (79.1)
Viral etiology		
HBsAg(+) alone	465 (14.3)	440 (94.6)
Anti-HCV(+) alone	1,291 (39.8)	1,151 (89.2)
Both	123 (3.8)	106 (86.2)
Neither	1,363 (42.1)	1,286 (94.4)

diagnosed cases should be reported. International Classification of Diseases Codes 9th edition (ICD9) was used in this registration system. All the primary liver cancer (ICD9=155) would be included in our analysis. In Taiwan, >90% of primary liver cancers are HCC (23). Because the screening ended at the end of 2004, the analysis was divided into three periods: (I) during screening (from April to December 2004), (II) within 6 months after screening (from January to June 2005), and (III) between 6 and 12 after screening (from July to December 2005).

The continuous variables were described by mean ± SD. Categorical variables were presented by percentage. The difference between groups was determined by χ^2 test, and the trend was examined by χ^2 test for a linear trend. The α level was set at 0.05. Diagnostic validity was expressed by sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV).

Results

A total 3,242 (5.7%) residents (male/female, 1,415/1,827; ages 66 ± 10 years) meeting the criteria for ''high risk,'' including 2,928 (90.3%) with thrombocytopenia, 87 (2.7%) with AFP elevation, and 273 (7.0%) with both, were enrolled for US screening. Of these, 465 (14.3%) were positive for HBsAg, 1,291 (39.8%) were positive for anti-HCV, and 123 (3.8%) were positive for both and the remaining 1,363 (42.1%) were neither (Table 1).

Figure 2 is the flowchart of this screening. A total of 2,983 (92.0%) underwent US examination. In addition to 42 known HCC cases, 137 suspected cases of HCC were referred to medical centers for confirmation; 124 (90.5%) cases complied with referrals and 72 patients (58.1%; PPV of second-stage US screening) were confirmed as cases of HCC. Overall PPV of first-stage screening was 2.41% (72 of 2,983). Table 2 shows the number and percentage of confirmed HCC cases in groups by screening markers and viral etiology. Subjects with AFP elevation alone had the highest PPV (25.4%, 17 of 67, 1 in 4 cases), subjects with thrombocytopenia alone had the lowest (0.78%, 21 of 2,697, 1 in 128 cases), and 15.5% (34 of 219, 1 in 6 cases) of the subjects had both AFP elevation and thrombocytopenia. The PPV increased from cases without HBV or HCV infection (0.47%, 6 of 1,286, 1 in 214 cases), with HBsAg alone (3.18%, 14 of 440, 1 in 31 cases), and with anti-HCV alone (4.09%, 47 of 1,151, 1 in 24 cases) to dual infection (4.72%, 5 of 106, 1 in 21cases; $P < 0.001$, χ^2 test for linear trends). The PPV of cases with HBV and/or HCV infection (3.89%, 66 of 1,697, 1 in 26) was significantly higher than that of without (0.47%, 6 of 1,286, 1 in 214 cases; $P < 0.001$). Three of 6 detected non-B, non-C HCC cases had normal AFP levels. Using thrombocytopenia as the only marker of first-stage screening, 23.6% (17 of 72) of the HCC cases would have failed to have been detected, whereas using AFP alone would have failed to detect 29.2% (21 of 72). As mentioned in Materials and Methods, our previous hospital-based study was cited as a reference (20). As shown in Table 3, we estimated that there should be 101 HCC cases among the entire population of participants. Using AFP > 20 ng/mL as the only marker for the first screening, 0.64% (364 of 56,702) of the population would be identified as belonging to the high-risk group, of which 50.5% (51 of 101, sensitivity) might be determined to be cases of HCC. Using thrombocytopenia, 5.33% (3,205 of 56,702) would be placed in the high-risk group, with a sensitivity of HCC detection should be 55.5% (55 of 101). Using a combination AFP > 20 ng/mL and thrombocytopenia as first-stage screening markers, 5.7% (3,242 of 56,702) of the population should be identified as members of high-risk group, and the estimated sensitivity should be 71.3% (72 of 101).

As shown in Table 4, there should be 119 HCC cases that have been diagnosed as HCC in whole screening population during this period. Besides 72 confirmed HCC cases, 17 subjects among low-risk group and another 30 from high-risk group have been registered as cases of HCC before the end of 2005. The incidence of primary liver cancer in the high-risk group (102 of $3,242 = 3,146/10^5$) is 100 times higher than that in the low-risk group (17 of $53,460 = 32/10^5$; $P < 0.001$). Among 259 nonresponders to second-stage US, 7 were registered as cases of HCC during screening period and another 3 were reported within 1 year. Eight of the 10 were with AFP levels >20 ng/mL. Among 2,804 subjects negative for second-stage US screening, 15 were registered to be cases of HCC within 1 year after screening. None was registered during screening period and 11 were diagnosed between 6 and 12 months after screening. All of them were with low platelet counts and 6 of them were also with high AFP level. Another 5 US-positive cases were reported as cases of primary liver cancer by the National Cancer Registration Database, and 3 of them were registered during screening period. These 5 cases should be defined as true positive HCC cases in the second-stage screening. The total number of true positive should be 77 (Table 5). As summarized in Table 6, the sensitivity, specificity, accuracy, PPV, and NPV of first screening were 85.7%, 94.5%, 94.4%, 3.15%, and 99.97%, respectively. Those of the whole two-stage screening were 64.7%, 99.9%, 99.8%, 56.2%, and 99.9%, respectively. Limited to the high-risk group selected by first-stage screen, those of second-stage US screening were 75.5%, 98.1%, 97.4%, 56.2%, and 99.2%. Ten of the 25 false-negative cases were US nonresponders.

The 72 confirmed cases, 41 men and 31 women, were ages 68.1 ± 8.8 years. Their largest tumor diameters were ≤3 cm in 27 (37.5%) cases, between 3 and 5 cm in 23

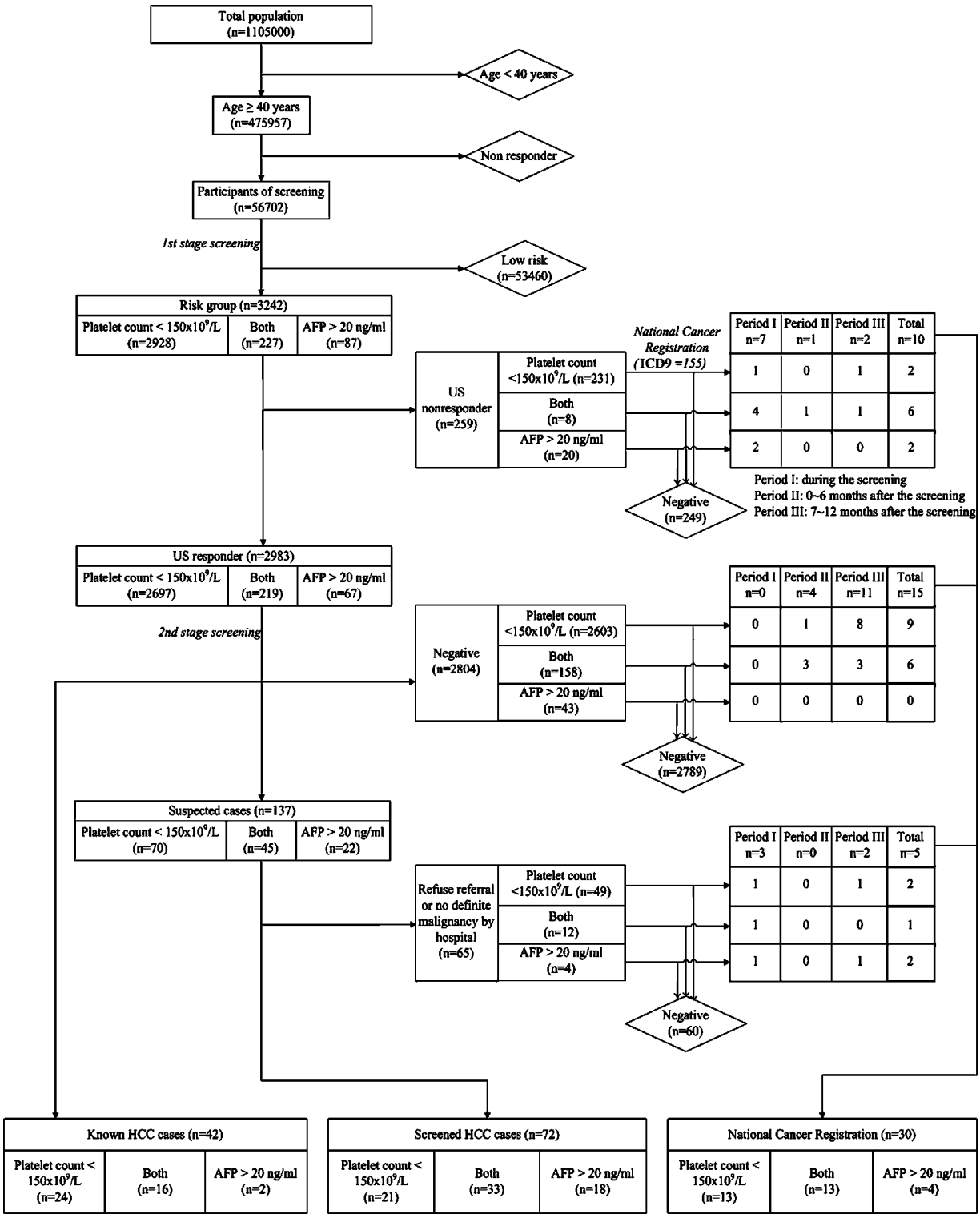

Figure 2. Flowchart of the community-based screening for HCC conducted in Tainan, Taiwan, 2004.

(31.9%) cases, and ≥5 cm in 22 (29.2%) cases. Only 5 (6.9%) cases had progressed beyond the intermediate stage of Barcelona Clinic Liver Cancer staging system and were recommended to receive conservative treatment only (17). Of 53 cases treated by modern medicine, initial treatment modalities were surgical resection in 13 cases, local ablation in 8 cases, and transcatheter arterial embolization in the remaining 32 cases.

Table 2. Distributions of responders by risk factors and viral etiology and confirmed HCC cases found in each group

Risk factors	Viral etiology	HBsAg(+), *n* (%)	Anti-HCV(+), *n* (%)	Both, *n* (%)	Neither, *n* (%)	Total, *n* (%)
Platelet count <150 × 10^9/L	Received US	390 (13.1)	961 (32.2)	87 (2.92)	1,259 (42.2)	2,697 (90.4)
	Confirmed	3 (0.77)	13 (1.35)	2 (2.29)	3 (0.24)	21 (0.78)
AFP >20 ng/mL	Received US	18 (0.60)	34 (1.14)	4 (0.13)	11 (0.37)	67 (2.25)
	Confirmed	6 (33.3)	7 (20.6)	2 (50.0)	2 (18.2)	17 (25.4)
Both	Received US	32 (1.07)	156 (5.23)	15 (0.50)	16 (0.54)	219 (7.34)
	Confirmed	5 (15.6)	27 (18.0)	1 (6.67)	1 (6.25)	34 (15.5)
Total	Received US	440 (14.8)	1,151 (38.6)	106 (3.55)	1,286 (43.1)	2,983 (100.0)
	Confirmed	14 (3.18)	47 (4.09)	5 (4.72)	6 (0.47)	72 (2.41)
Platelet + both	Received US	422	1,117	102	1,275	2,916
	Confirmed	8 (1.90)	40 (3.58)	3 (2.94)	4 (0.31)	55 (1.89)
AFP + both	Received US	50	190	19	27	286
	Confirmed	11 (22.0)	34 (17.9)	3 (15.8)	3 (11.1)	51 (17.8)

Discussion

Although there were several reasons of thrombocytopenia, the major reason should be chronic hepatitis C infection especially in HCV-endemic area. In a published article using the same population of this study, the village- and township-specific rates of thrombocytopenia are significantly correlated to their rates of anti-HCV. It concluded that excess rates of thrombocytopenia than general population should be due to high prevalence of chronic HCV infection (21). A pilot study showed that thrombocytopenia is an effective surrogate of liver cirrhosis in HCV-endemic area but not in low HCV prevalent areas (20). In this study, the over all prevalence of anti-HCV was as high as 10.2%. Thrombocytopenia can be used as a screening marker. The aim of first-stage screening in a two-stage screening design is identification of high-risk groups. Our pilot studies reported only ~50% of HCC cases can be detected by such means (20). Although the recommendation 4 in American Association for the Study of Liver Diseases HCC practice guideline wrote ''AFP alone should not be used for screening unless ultrasound is not available (level II) (15),'' Trevisani et al. reported that the best discriminating AFP value was 16 ng/mL. A value of 20 ng/mL (above which investigations for HCC are recommended) had equivalent sensitivity (60.0 versus 62.4%) and specificity (90.6 versus 89.4%; ref. 24). To increase the sensitivity of mass screening, serum AFP was added as a another screening marker.

To understand the validity of cancer screening, the number of false negative should be estimated or identified. In the article, we designed two approaches to elucidate this issue. Firstly, we cited distributions by viral etiology of HCC cases in a nearby medical center. Under the assumption of different rates of thrombocytopenia in groups of different viral etiology, the numbers of false-negative cases in each group were estimated. Based on the estimation, there should be 101 HCC cases and 72 were detected in this screening with a sensitivity of 71.3%. The criticism of this design is that the distributions of viral etiology between hospital and community might different. Because the viral etiology of HCC is with geography difference (25), large sample size in the nearby hospital might minimize the bias. Secondly, we linked our file with National Cancer Registration Database to find registered cases of liver cancer (ICD9=155) within 1 year after screening as the false-negative cases. The results of data linkage showed that there should be 119 cases of liver cancer and 77 were detected in the screening with a sensitivity of 64.7%. Although there were still some limitations of this design, such as incomplete registration of National Cancer Registration Database, inclusion cases of primary liver cancer other than HCC, and misclassification of some newly developed true-negative cases as false negative, it is the most reliable and available information. The estimations of these two quite different designs were compatible. This newly designed mass HCC screening showed that only 5.7% of participants could be defined as members of the HCC high-risk group and had a high coverage or sensitivity rate of 64.7% to 71.3% of all HCC cases. This screening design is therefore feasible and sensitive.

The sensitivity (64.7%) of the two-stage screening, estimated according to National Cancer Registration Database, seems unsatisfied. There were 25 HCC cases in the high-risk group not detected by second-stage US screening (false-negative). Ten of the 25 false-negative

Table 3. Estimation of HCC detection rates using platelet count, AFP, or both as the tool of risk group identification

Viral etiology	(1)*	(2)	(3) = (2) ÷ (1)	(4)		(6) = (3) - (5)
	% Thrombocytopenia in HCC cases	Cases included by thrombocytopenia	Estimated HCC cases	Cases included by AFP	Cases included by thrombocytopenia or AFP	Estimated undetected cases
B	42	8	19	11	14	5 (26.3)
C	63	40	63	34	47	16 (25.4)
B + C	50	3	6	3	5	1 (16.7)
NBNC	30	4	13	3	6	7 (53.8)
Total, *n* (%)		55 (54.5)	101 (100)	51 (50.5)	72 (71.3)	29 (28.7)

*Ref. 20.

Table 4. Numbers of subjects and cases of primary liver cancer in variant screen status

Status of two-staged HCC screening	No. subjects	No. cases
Total screening cases	56,702	119
(1) Low-risk group by first-stage screening	53,460	17
High-risk group	3,242	102
(2) Nonresponder to US	259	10
Responder to US	2,983	92
(3) Negative US results	2,804	15
Known HCC cases	42	42
Suspected cases	137	77
(4) Refuse referral	13	3
Refer for confirmation	124	74
(5) No definite malignancy by hospital	52	2
Confirmed HCC cases	72	72

cases were nonresponders of the second-stage US screening. Eight of the 10 were with AFP levels >20 ng/mL and 6 of the 8 cases were reported during screening period. It means that some subjects skipped US screening, and visited hospital for further study, once AFP elevation were informed. In this study, the response rate of subjects with high AFP was only 78.6% (286 of 364). Their high absent rate resulted in lower sensitivity of this screening. US technique is operator dependent. Among 2,804 subjects with negative results of second-stage US screening, 15 were reported to been cases of HCC within 1 year after screening. None was reported during screening period, and 11 were diagnosed between 6 and 12 months after screening. All of them were with low platelet counts and 6 of them were also with high AFP level. Some of the 15 HCC cases should be newly developed after screening rather than lost by the previous US screening. Inclusion of these cases might overestimate the case number of false-negative and decrease the sensitivity of this screening. Based on the above two points of view, the sensitivity (64.7%) of this screening design should be underestimated.

In this large-scale study, a total of 56,702 adults ages ≥40 years were screened and 72 detected cases were confirmed as HCC. The prevalence of HCC was $127/10^5$ or 3 to 5 times higher than the annual incidence or mortality in Taiwan as a whole (2). This high prevalence rate may result from more asymptomatic HCC cases being detected earlier. Only 5 (6.9%) of 72 confirmed cases were beyond the intermediate Barcelona Clinic Liver Cancer stage (13) and were recommended to receive conservative treatment only. More than half (n = 37; 51.4%) were detected in the very early or early stages and detected early enough to have a chance for effective treatment.

The mean age of detected cases was 68.1 years, and most of the confirmed cases (52 of 72; 72%) in the current study were positive to anti-HCV. The mean ages of HCV-related HCC patients in Taiwan is 65.1 years (25). A study from the United States showed that the median age of HCC patients at diagnosis is 74 years, and most patients (91%) were >65 years (26). Of Japanese HCC patients, ~80% were anti-HCV positive and were >60 years old (16). An Italian study concluded that elderly patients (≥70 years old) with HCC have a worse prognosis compared with nonelderly patients. Such a difference seems to be a consequence of undertreatment (27). On the other hand, a Japanese study reported that an advanced stage of HCC, not advanced age, influenced the survival rates of these elderly patients (≥80 years old; ref. 28). Therefore, older high-risk cases should be screened and older HCC cases should be treated in the same manner as nonelderly patients. As mentioned earlier, the other factor was a platelet count of $<100 \times 10^9$/L. Thrombocytopenia, indicating advanced liver cancer, has been reported to be a poor prognostic factor of curative treatments, such as resection (29), radiofrequency ablation (30), and percutaneous ethanol injection therapy (31). Besides the HCC itself, hepatic failure is another major cause of death among HCC patients. HCC screening can detect early HCC but not early liver cancer. This indicates that medical care for the complications of liver cancer might improve patients' survival rates. Antiviral treatment for cases with chronic HBV (32, 33) and HCV (34) infections decreased their incidence of HCC and hepatic failure. Marked AFP elevation (>400 ng/mL) correlated with poor differentiation and extended invasion (35). It has also been one of the poor prognostic factors in the Cancer of the Liver Italian Program score (36) and several analyses of the survival rates for resection (37), radiofrequency ablation (38), and transcatheter arterial

Table 5. Cases of primary liver cancer found from National Cancer Registration Database by status of second-stage screening, periods and screening markers

Status of second-stage screening	n	Period*			
		I	II	III	Total cases
(2) Nonresponder to US	259	7 (1, 4, 2) †	1 (0, 1, 0)	2 (1, 1, 0)	10 (2, 6, 2)
(3) Negative US results	2,804	0	4 (1, 3, 0)	11 (8, 3, 0)	15 (9, 6, 0)
(4) Refuse referral	13	2 (0, 1, 1)	0	1 (0, 0, 1)	3 (0, 1, 2)
(5) No definite malignancy by hospital	52	1 (1, 0, 0)	0	1 (1, 0, 0)	2 (2, 0, 0)
Total	3,128	10	5	15	30
Platelet count $<150 \times 10^9$/L		2	1	10	13
AFP >20 ng/mL		3	0	1	4
Both		5	4	4	13

*Period I, during the screening (from April to December 2004); period II: within 6 months after the screening (from January to June 2005); and period III: between 7 and 12 months after the screening (from July to December 2005).

† Number of cases with platelet count $<150 \times 10^9$/L, number of cases with platelet count $<150 \times 10^9$/L and AFP >20 ng/mL, number of cases with AFP >20 ng/mL.

Table 6. Validity of first-stage screening, second-stage screening, and the whole two-stage screening based on National Cancer Registration Database

	First-stage screening liver cancer			Second-stage screening liver cancer			Two-stage screening liver cancer		
	(+)	(-)	Total	(+)	(-)	Total	(+)	(-)	Total
Screening (+)	102	3,140	3,242	77	60	137	77	60	137
Screening (-)	17	53,443	53,460	25	3,080	3,105	42	56,523	56,565
Total	119	56,583	56,702	102	3,140	3,242	119	56,583	56,702
Sensitivity	102/119 = 85.7%			77/102 = 75.5%			77/119 = 64.7%		
Specificity	53,443/56,583 = 94.5%			3,080/3,140 = 98.1%			56,523/56,583 = 99.9%		
Accuracy	53,545/56,702 = 94.4%			3,157/3,242 = 97.4%			56,600/56,702 = 99.8%		
PPV	102/3,242 = 3.15%			77/137 = 56.2%			77/137 = 56.2%		
NPV	53,443/53,460 = 99.97%			3,080/3,105 = 99.2%			56,523/56,565 = 99.9%		

embolization (39). In the present study, we used platelet count (<150 × 10^9/L) and AFP level (>20 ng/mL) as screening markers. The screen levels of screening were not so severe than those from the previously mentioned reports of poor prognoses, such as platelet count <100 × 10^9/L or AFP level >400 ng/mL.

Abdominal ultrasound as a surveillance tool has shown a sensitivity of 71% to 73%, a specificity of 93%, and a PPV of 14% to 73% in some studies (14). It is a well-documented tool for HCC screening (15, 16). The rates are similar to those of this study. Due to cost-benefit considerations, it is impossible to conduct a US screening on the entire population of any community. As a result, the two-stage HCC screening design has tried to limit US screening to members of the high-risk group only. However, there still remains the controversy of ''Who should be defined as being in the high-risk group for HCC and should be screened by US?'' Table 7 shows four community-based two-stage HCC screenings with different designs. Cost of screening tools, sensitivity of the screening tests, and PPV of the high-risk group are all important issues. In the earliest study (model 1), the subjects with elevated AFP were referred to a hospital for further examination after the entire community's screening for AFP (11). Although it is easy to collect blood samples in community, AFP alone should not be recommended for screening (15). The other community-based HCC screening program (model 2) has been conducted in seven townships in Taiwan since 1991. Six markers, including HBsAg, anti-HCV, aspartate aminotransferase, alanine aminotransferase, AFP, and a family history of HCC, were selected as the first-stage markers for high-risk group identification (4, 12, 17, 18). Although the sensitivity of the first screening markers should be ≥90%, ~30% of all participants should be enrolled in second-stage US screening. Unfortunately, the high cost of screening tools in the first stage and the heavy load of second-stage US are two limitations of this design. Thrombocytopenia was the only marker for first-stage screening, and AFP and US were employed as tools for the second-stage screening (20), creating what an economical version of our previous design (model 3). However, the sensitivity is only ~50%. The current design used thrombocytopenia and AFP as markers for first-stage screening (model 4). Shifting AFP from the second stage (model 3) to the first stage (model 4) increased sensitivity to an estimated 71.3% but also increased the cost of the new design. Only 5.7% of the participants were enrolled in the second-stage US. The six-marker design (model 2) had higher sensitivity but also a higher cost, so for budget and feasibility considerations, the present design should be a reasonable alternative. Another issue is postscreening surveillance of the high-risk group. Surveillance is recommended for patients with chronic HBV and HCV infections (15). Model 2 provides the information on HBsAg, anti-HCV,

Table 7. Comparison among four two-stage community-based HCC screenings

References*	Model 1 (9)*	Model 2 (10, 2, 15)*	Model 3 (19)*	Model 4
First author	Wu JC	Chen CJ, 1995	Lu SN	Current study
Year published	1988	Chen TH, 2002 Yang HI, 2002	2006	
Sample size of screening	1,894	Male/female: 12,026/1,800	(Low) † 1,694, (High) † 4,616	56,702
Screening makers in first stage	AFP	HBsAg, anti-HCV, AFP, aspartate aminotransferase, alanine aminotransferase, family history	Platelet	(A), (P), (B) ‡
% High-risk subjects identified from population	1%	Male/female: 30.9%/34.6%	(Low) 6.1%, (High)17.9%	(A) 0.64%, (P) 5.33%, (B) 5.70%
Estimated sensitivity for HCC detection	Not available	>90%	48%	(A) 50.5%, (P) 54.5%, (B) 71.3%
Second-stage Screening tools	US in hospital	US in community	US, AFP in community	US in community
PPV of first-stage marker(s)	21%	Not available	(Low) 0%, (High) 4.27%	17.8%, 1.89%, 2.41%
Surveillance program for high-risk group	Nil	Cirrhosis every 3 mo, others every 6 mo	Nil	Limited to HBsAg(+), anti-HCV(+), or cirrhosis

*(9), Wu JC, Liver 1988; (10), Chen CJ, J Formosan Med Assoc 1995; (2), Chen THH, Int J Cancer 2002; (15), Yang HI, NEJM 2002; (18), Lu SN, Cancer 2006.
†(Low) and (High), low and high prevalence areas of hepatitis C and hepatocellular carcinoma.
‡(A), AFP alone; (P), platelet count alone; (Both), combination of both AFP and platelet count.

and US diagnosis of liver parenchyma after the first cross-sectional screening, which is essential for long-term surveillance. In the present study (model 4), >40% of the subjects in the high-risk group were negative for HBsAg and anti-HCV. In the second-stage US screening, thrombocytopenic subjects without chronic HBV and HCV infection were proven to have lower risk for HCC. We therefore recommend that HBsAg and anti-HCV should be checked among the high risk identified by the current design and that high-risk subjects who are either HBsAg or anti-HCV positive should be enrolled into the surveillance program.

Response rates influence results, but this is inevitable in any community-based study. This comprehensive screening, which included not only liver tests but also lipids, sugars, chest X-rays, and bone marrow density, should have helped minimize selection bias. Large numbers (n = 56,702) of participants from every part of the study area increased the representativeness of the study population. A total of 2,983 (92.0%) identified high-risk cases responded to US, and 124 (90.5%) suspected cases complied with referrals for further confirmation. Although the PPV may have been underestimated, such high response rates may have limited the negative influence.

For obvious high-risk groups, well-documented screening tools, and good treatment results of early-stage cases, HCC should be screened for in either a hospital-based or a community-based design in high endemic areas. Multiple factors, such as budget, manpower, validity, and feasibility, should be considered in the design of the screening methods. In this study, we present a new design of mass HCC screening, discussing its effectiveness and limitations. This economical design enrolled only 5.7% of participants for US and could detect 64.7% to 71.3% of all HCC cases early enough for them to be successfully treated. Screening for HCC using the current design should prove to be economical and effective and should be applied to those communities with a high prevalence of HCC, especially those areas with limited budgets, and seldom or never been screened before.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank all 31 primary health-care centers in the study area for cooperation.

References

1. Shibuya K, Mathers CD, Boschi-Pinto C, Lopez AD, Murray CJ. Global and regional estimates of cancer mortality and incidence by site. II. Results for the global burden of disease 2000. BMC Cancer 2002;2:37.
2. Department of Health, Taiwan. National Health Insurance. Cause of death statistics. Available from: http://www.bhp.doh.gov.tw/BHP/index.jsp. [cited 2007 Mar 10].
3. Omata M, Tateishi R, Yoshida H, Shiina S. Treatment of hepatocellular carcinoma by percutaneous tumor ablation methods: ethanol injection therapy and radiofrequency ablation. Gastroenterology 2004;127:S159–66.
4. Chen TH, Chen CJ, Yen MF, et al. Ultrasound screening and risk factors for death from hepatocellular carcinoma in a high risk group in Taiwan. Int J Cancer 2002;98:257–61.
5. Zhan BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130:417–22.
6. Liaw YF, Tai DI, Chu CM, et al. Early detection of hepatocellular carcinoma in patients with chronic type B hepatitis. A prospective study. Gastroenterology 1986;90:263–7.
7. Caturelli E, Bartolucci F, Biasini E, et al. Diagnosis of liver nodules observed in chronic liver disease patients during ultrasound screening for early detection of hepatocellular carcinoma. Am J Gastroenterol 2002;97:397–405.
8. Toyoda H, Kumada T, Kiriyama S, et al. Impact of surveillance on survival of patients with initial hepatocellular carcinoma: a study from Japan. Clin Gastroenterol Hepatol 2006;4:1170–6.
9. Tang ZY. Screening and early treatment of primary liver cancer—with special reference to the east part of China. Ann Acad Med Singapore 1980;9:234–9.
10. McMahon BJ, Bulkow L, Harpster A, et al. Screening for hepatocellular carcinoma in Alaska natives infected with chronic hepatitis B: a 16-year population-based study. Hepatology 2000;32:842–6.
11. Wu JC, Lee SD, Hsiao KJ, et al. Mass screening of primary hepatocellular carcinoma by α-fetoprotein in a rural area of Taiwan—a dried blood spot method. Liver 1988;8:100–4.
12. Chen CJ, Lu SN, You SL, et al. Community-based hepatocellular carcinoma screening in seven townships in Taiwan. J Formos Med Assoc 1995;94:s94–102.
13. Mima S, Sekiya C, Kanagawa H, et al. Mass screening for hepatocellular carcinoma: experience in Hokkaido, Japan. J Gastroenterol Hepatol 1994;9:361–5.
14. Daniele B, Bencivenga A, Megna AS, Tinessa V. α-Fetoprotein and ultrasonography screening for hepatocellular carcinoma. Gastroenterology 2004;127:S108–12.
15. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–36.
16. Okita K. Clinical aspects of hepatocellular carcinoma in Japan. Intern Med 2006;45:229–33.
17. Yang HI, Lu SN, Liaw YF, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002;347:168–74.
18. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B DNA level. JAMA 2006;295:65–73.
19. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004;127:S35–50.
20. Lu SN, Wang JH, Liu SL, et al. Thrombocytopenia as a surrogate for cirrhosis and a marker for the identification of patients at high-risk for hepatocellular carcinoma. Cancer 2006;107:2212–22.
21. Tsai MC, Kee KM, Chen YD, et al. Excess mortality of hepatocellular carcinoma and morbidity of liver cirrhosis and hepatitis in HCV-endemic areas in an HBV-endemic country—geographic variations among 502 villages in southern Taiwan. J Gastroenterol Hepatol 2007;22:92–8.
22. Bruix J, Sherman M, Llovet JM, et al.; EASL Panel of Experts on HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421–30.
23. Yu MW, Tsai SF, Hsu KH, et al. Epidemiologic characteristics of malignant neoplasms in Taiwan. II. Liver cancer. J Natl Public Health Assoc Taiwan 1998;8:125–38.
24. Trevisani F, D'Intino PE, Morselli-Labate AM, et al. Serum α-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status. J Hepatol 2001;34:570–5.
25. Lu SN, Su WW, Yang SS, et al. Secular trends and geographic variations of hepatitis B virus and hepatitis C virus-associated hepatocellular carcinoma in Taiwan. Int J Cancer 2006;119:1946–52.
26. El-Serag HB, Siegel AB, Davila JA, et al. Treatment and outcomes of treating of hepatocellular carcinoma among Medicare recipients in the United States: a population-based study. J Hepatol 2006;44:158–66.
27. Pignata S, Gallo C, Daniele B, et al.; CLIP Investigators. Characteristics at presentation and outcome of hepatocellular carcinoma (HCC) in the elderly. A study of the Cancer of the Liver Italian Program (CLIP). Crit Rev Oncol Hematol 2006;59:243–9.
28. Dohmen K, Shirahama M, Shigematsu H, Irie K, Ishibashi H. Optimal treatment strategy for elderly patients with hepatocellular carcinoma. J Gastroenterol Hepatol 2004;19:859–65.
29. Kaneko K, Shirai Y, Wakai T, Yokoyama N, Akazawa K, Hatakeyama K. Low preoperative platelet counts predict a high mortality after partial hepatectomy in patients with hepatocellular carcinoma. World J Gastroenterol 2005;11:5888–92.

30. Camma C, Di Marco V, Orlando A, et al.; Unita Interdipartimentale Neoplasie Epatiche (UINE) Group. Treatment of hepatocellular carcinoma in compensated cirrhosis with radio-frequency thermal ablation (RFTA): a prospective study. J Hepatol 2005;42:535–40.
31. Pompili M, Rapaccini GL, Covino M, et al. Prognostic factors for survival in patients with compensated cirrhosis and small hepatocellular carcinoma after percutaneous ethanol injection therapy. Cancer 2001;92:126–35.
32. Liaw YF, Sung JJ, Chow WC, et al.; Cirrhosis Asian Lamivudine Multicentre Study Group. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521–31.
33. Lin SM, Yu ML, Lee CM, et al. Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. J Hepatol 2007;46:45–52.
34. Yu ML, Lin SM, Chuang WL, et al. A sustained virological response to interferon or interferon/ribavirin reduces hepatocellular carcinoma and improves survival in chronic hepatitis C: a nationwide, multicentre study in Taiwan. Antivir Ther 2006;11:985–94.
35. Peng SY, Chen WJ, Lai PL, Jeng YM, Sheu JC, Hsu HC. High α-fetoprotein level correlates with high stage, early recurrence and poor prognosis of hepatocellular carcinoma: significance of hepatitis virus infection, age, p53 and β-catenin mutations. Int J Cancer 2004;112:44–50.
36. The Cancer of the Liver Italian Program (CLIP) investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. Hepatology 1998;28:751–5.
37. Kaibori M, Matsui Y, Yanagida H, Yokoigawa N, Kwon AH, Kamiyama Y. Positive status of α-fetoprotein and des-γ-carboxy prothrombin: important prognostic factor for recurrent hepatocellular carcinoma. World J Surg 2004;28:702–7.
38. Choi D, Lim HK, Rhim H, et al. Percutaneous radiofrequency ablation for early-stage hepatocellular carcinoma as a first-line treatment: long-term results and prognostic factors in a large single-institution series. Eur Radiol 2007;17:684–92.
39. Reichman TW, Bahramipour P, Barone A, et al. Hepatitis status, Child-Pugh classification, and serum AFP levels predict survival in patients treated with transarterial embolization for unresectable hepatocellular carcinoma. J Gastrointest Surg 2005;9:638–45.

Community-Based Mass Ultrasonographic Screening of Hepatocellular Carcinoma among Thrombocytopenic Adults

Sheng-Nan Lu, Jing-Houng Wang, Pao-Fei Chen, et al.

Cancer Epidemiol Biomarkers Prev 2008;17:1813-1821.