J Cancer Res Clin Oncol (2004) 130: 417–422
DOI 10.1007/s00432-004-0552-0

ORIGINAL PAPER

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Randomized controlled trial of screening for hepatocellular carcinoma

Received: 25 September 2003 / Accepted: 28 January 2004 / Published online: 20 March 2004

Abstract *Purpose*: Screening for hepatocellular carcinoma (HCC) has been conducted for over 20 years, but there is no conclusive evidence that screening may reduce HCC mortality. The aim of this study was to assess the effect of screening on HCC mortality in people at increased risk. *Methods*: This study included 18,816 people, aged 35–59 years with hepatitis B virus infection or a history of chronic hepatitis in urban Shanghai, China. Participants were randomly allocated to a screening (9,373) or control (9,443) group. Controls received no screening and continued to use health-care facilities. Screening group participants were invited to have an AFP test and ultrasonography examination every 6 months. Screening was stopped in December 1997; by that time screening group participants had been offered five to ten times. All participants were followed up until December 1998. The primary outcome measure was HCC mortality. *Results*: The screened group completed 58.2 percent of the screening offered. When the screening group was compared to the control group, the number of HCC was 86 versus 67; subclinical HCC being 52 (60.5%) versus 0; small HCC 39 (45.3%) versus 0; resection achieved 40 (46.5%) versus 5 (7.5%); 1-, 3,-, and 5-year survival rate 65.9%, 52.6%, 46.4% versus 31.2%, 7.2%, 0, respectively. Thirty-two people died from HCC in the screened group versus 54 in the control group, and the HCC mortality rate was significantly lower in the screened group than in controls, being 83.2/100,000 and 131.5/100,000, respectively, with a mortality rate ratio of 0.63 (95%CI 0.41–0.98). *Conclusions*: Our finding indicated that biannual screening reduced HCC mortality by 37%.

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Keywords Hepatocellular carcinoma · Screening · Randomized controlled trial · Mortality

Introduction

Liver cancer is the third most common cause of death from cancer in the world, with an estimated 548,600 deaths in the year 2000 (Parkin et al. 2001). Since the 1990s, HCC has become the second cancer killer in China. Although progress has been made in the management of symptomatic HCC, there has been little overall reduction in HCC mortality during the past 30 years. Risk factors for HCC include hepatitis B and hepatitis C virus infections, dietary intake of aflatoxins, and drinking water contamination in the rural area (Yu 1995). In China, the hepatitis B virus is particularly prevalent, and vaccinating newborn babies against hepatitis B is anticipated to control the incidence of HCC in the future. However, early diagnosis before development of symptoms may also be helpful in the control of this disease.

The detection of alpha-fetoprotein (AFP) in the serum of an HCC patient by Tatarinov provided a new clue for the early detection and diagnosis of HCC (Tatarinov 1964). Screening for HCC has been conducted since the 1970s. However, there has been no direct evidence of the efficacy of screening in people at increased risk in reducing mortality from HCC.

From 1971 to 1976, nearly two million people were screened with AFP for HCC in Shanghai. Of 300 HCC patients detected, 134 were diagnosed as subclinical HCC. The 3-year survival rate of patients after resection in this group was 57.1%. The usefulness of an AFP screening was not widely accepted on the basis of results from Africa (Purves 1976). The screening modality has been changed from using AFP alone in people at average risk to the combination of AFP and ultrasonography in people at increased risk, since the 1980s (Purves 1976; Shanghai Coordinating Group for

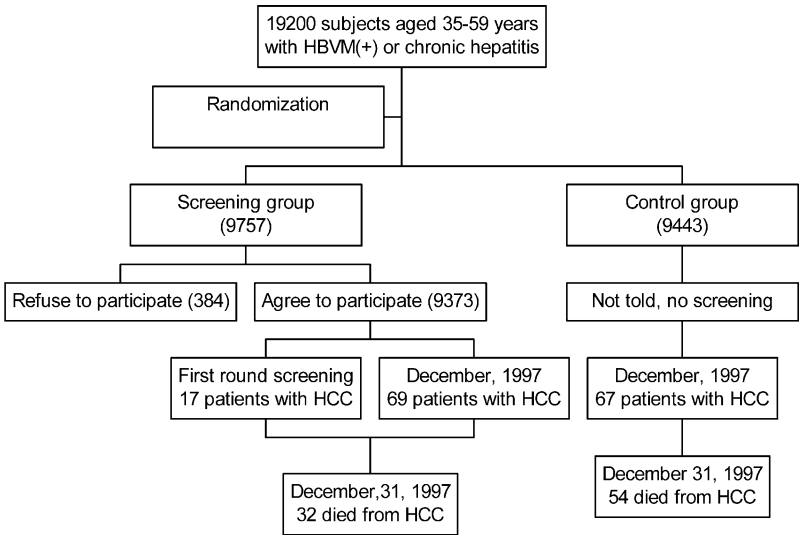

Fig. 1 Study profile

Research on Liver Cancer 1979; Mima et al. 1994; Izzo et al. 1998). It has been demonstrated that periodic screening results in a significant shift to an earlier stage, asymptomatic cancer at diagnosis (Shanghai Coordinating Group for Research on Liver Cancer 1979; McMahon and London 1991), and a significant increase in survival with HCC (Tang et al. 1980).

Since there were no randomized controlled trials of screening for HCC, nor adequate evidence of reduction of mortality, we conducted a randomized controlled trial to assess the effect of biannual screening with a combination of AFP and ultrasonography on HCC mortality in the people at increased risk in urban Shanghai, China.

Materials and methods

The Liver Cancer Institute of Fudan University has studied the secondary prevention of HCC since the 1970s. According to previous studies (Yang et al. 1987; Yang et al. 1988; Zhang et al. 1995), people aged 35 years to 59 years and with serum evidence of hepatitis B virus (HBV) infection or a history of chronic hepatitis have an increased risk for HCC (Zhang et al. 1995), and were eligible for the study. The serum evidence of HBV infection was defined as any of five markers of HBV (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) being detectable in serum, except for the condition when HBsAb is positive and the others are negative. We used an ELISA test to measure the antigens and antibodies of HBV. The HBV test kits were produced by Tianyuan Company, China. Before these kits were widely applied, we tested the agreement of results with these kits against those yielded by Abbot kits and calculated the kappa. The agreements of five HBV markers (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) were 97.5%, 95%, 95%, 90%, and 92.5%, respectively, and the kappas were 0.93, 0.80, 0.89, 0.71, and 0.85, respectively. A history of chronic hepatitis was defined as patients with abnormalities on serum biochemical tests lasting for 6 months or more. The most characteristic pattern is an elevation in both alanine and aspartate aminotransferase (ALT and AST), and also includes an elevation in serum bilirubin. In cooperation with the doctors (GP) in primary care centers, we selected more than 300 factories, enterprises, and schools in urban Shanghai. According to the medical records in the primary care centers, we excluded those with a known history of HCC, or other malignant diseases, or serious illness. Thus, 19,200 met the criteria of the program. These subjects were recruited into our program from January 1993 to December 1995. With a view to feasibility and potential bias of the study, simple cluster sampling was carried out. Every 'factor', 'enterprise', or 'school' was regarded as a unit. This ensured that all eligible members of the unit were allocated to the same group. These units were randomly allocated to a screening (9,757) or no screening (control, 9,443) group. In the screening group, 384 subjects refused to participate to the program (Fig. 1). Controls were identified but received no intervention, and continued to use health-care facilities as usual. This approach was judged to be ethical at the time of study design. The study was approved by Fudan Medical School Ethics Committee.

The screening group participants were invited by GPs to have a serum AFP test [ELISA, kits produced by Tianyuan, China (Yang et al. 1997)], and a screening ultrasonography examination every 6 months. The cut-off value of AFP was 20 μg/l. An abnormality detected by ultrasound was a solid lesion in the liver. Individuals who did not take the screening test had another chance later. Before the program initiation, laboratory technicians and ultrasound doctors from primary care centers were trained in Zhong Shan Hospital of Fudan University.

In order to minimize the false positive rate, a repeat test was sent to individuals with a positive AFP test or abnormal screening ultrasound. Only those individuals with positive results at the retest were offered diagnostic evaluation at the institute. The diagnostic protocol included a history and physical examination, liver function tests, AFP (radioimmunoassay, RIA), and an ultrasonography examination by a senior doctor. Computed tomography or magnetic resonance imaging was checked when necessary. The final diagnoses were reached by biopsy or long-term follow up. Some participants with positive screening tests went to other hospitals for the diagnostic evaluation. Detail information on the results of examinations was obtained from their medical records by their GPs. The validity of screening tests was reported elsewhere (Zhang and Yang 1999). When AFP and ultrasonography were used in parallel, the detection rate, false positive, and positive predictive values were 92%, 7.5%, and 3.0%, respectively.

Screening-group participants who were found to have HCC were treated and transferred to follow-up programs. Individuals with negative screening tests were invited to repeat screening every 6 months. We stopped screening in December 1997; by that time, all participants had been offered screening tests between five to ten times.

We obtained information on the development of HCC and death in screening-group participants and unscreened controls from the GPs in the factories, enterprises, and schools. Because of the requirements of the medical insurance system in Shanghai at

that time, all patients had to be registered in primary care centers before they were referred to other hospitals. We also cross-checked with the Shanghai Cancer Registry in early 1999 to confirm that no cases of HCC had been missed.

The staging systems such as TNM need surgical evaluation, but not all patients received surgical treatment in our program. We used the HCC staging system of China (Tang 1989). Three disease stages were differentiated: stage I (subclinical stage or early stage) refers to HCC patients without obvious cancer symptoms and signs; stage II (moderate stage) refers to those between stage I and stage III, i.e., patients with symptoms or signs of HCC, such as palpatable mass in the abdomen; stage III (late stage) refers to those HCC patients with obvious cachexia, jaundice, ascites or distant metastases. The diameter of a tumor less than 5 cm is empirically defined as small HCC.

Interval cases refers to those HCC patients who complied with screening, but were found to have liver cancer before the next screening. In fact, these patients were false negative. Non-responder patients referred to those HCC patients who did not comply with screening, but whose details were reported by their GPs, or who were found in the Shanghai Cancer Registry.

The primary outcome measure was mortality from HCC. Using the world standard population, the incidence and mortality of HCC were standardized. Rates of death from HCC in the screening and control groups were compared by a Poisson Model to calculate the confidence interval (CI). Cumulative survival was calculated by the life-table method from the date of diagnosis of HCC, censoring at the date of death or at 31 December 1998. Survival in the two groups was compared by the log-rank test. Proportions were compared by χ^2 test.

All analyses were on an intention-to-treat basis. The study was approved by the Shanghai Medical University Ethical Committee (currently merged withFudan University Ethical Committee).

Results

Randomization was effective in creating a balance between two groups in terms of age and sex (Table 1). The age and sex distributions of the groups did not change substantially among the study. However, most participants were younger than 50, and there were more men than women.

The screened group completed 58.2 percent of the screening offered (Fig. 2). Screening was carried out a minimum of one time, and the median was five times. More than 70 percent of the participants testing positive were examined at the Liver Cancer Institute of Fudan University.

During the study, 71 cases of HCC were detected by screening, three were interval cases, 12 were diagnosed in the non-responder group, and 67 were diagnosed in the control group. Since most participants in this program were younger than 50, the standardized incidence of HCC was 279.3 per 100,000 in the screening group, and 267.0 per 100,000 in the control group. The overall standardized incidence of HCC was 268.0 per 100,000. After the first round of screening, the incidences were similar in the screening and control group (Fig. 3). The distribution of the stages of HCC is shown in Table 2. There were no cases of subclinical HCC in the control group, whereas the proportion of stage III HCC was significantly higher in the control group than in the screening group. There were 39 small HCCs in the screened group, whereas there were none in the control group. Radical surgery was achieved in 40 (46.5%) patients in the screening group and only five (7.8%) patients in the control group (Table 3). In 52 subclinical HCCs, 37 patients (71.2%) were radically resected, and another two patients were treated by repeated percutaneous ethanol injection (PEI) because their tumors were less than 2 cm and they had severe liver cirrhosis.

Disease-specific survival of individuals with HCC is shown in Table 2. There was a significant survival advantage for HCC patients in the screening group over those in the control group ($P < 0.01$). No patients in the control group survived more than 5 years. The survival

Table 1 Age and sex of participants at initial screening

		Screening (9,373)	Control (9,443)
Sex			
	Male	5,869	5,979
	Female	3,504	3,464
Mean age		42	41
No. HBsAg+		6,071	6,027
No. HBsAg+ & history of hepatitis		2,508	2,644
No. history of hepatitis		794	772

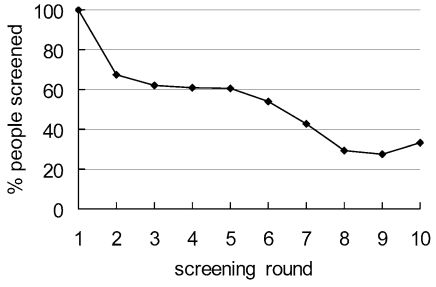

Fig. 2 Compliance during repeat screening

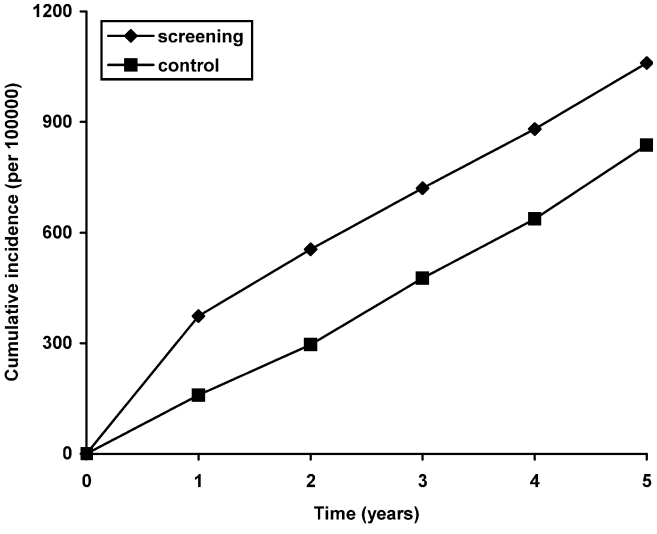

Fig. 3 Cumulative incidence of HCC in screening and control groups

Table 2 Stage distribution, treatment and survival of patients with HCC in the screened and control groups (*TACE* transcatheter arterial chemoembolization, *PEI* percutaneous ethanol injection)

	Screening group (86)	Control group (67)
Stage[a]		
Stage I	52(60.5%)	0(0%)
Stage II	12(13.9%)	25(37.3%)
Stage III	22(25.6%)	42(62.7%)
Small HCC	39(45.3%)	0
Treatment		
Resection	40(46.5%)	5(7.5%)
TACE/PEI	28(32.6%)	28(41.8%)
Conservative treatment	18(20.9%)	34(50.7%)
Survival (%)[b]		
1-year	65.9	31.2
2-year	59.9	7.2
3-year	52.6	7.2
4-year	52.6	0
5-year	46.4	0

[a] $\chi^2 = 61.41$, $p < 0.01$
[b] Log-rank $\chi^2 = 35.50$, $p < 0.01$

Table 3 Outcome of screening

	Screening group	Control group
Person-years in the study	38,444	41,077
HCC occurrence		
No. of cases	86	67
Total incidence(per 100,000)	223.7	163.1
Rate ratio (95% CI)	1.37(0.99, 1.89)	
Deaths from HCC		
No. of death	32	54
Total mortality(per 100,000)	83.2	131.5
Rate ratio (95% CI)	0.63(0.41, 0.98)	

rates of HCC in different stages are shown in Fig. 3. Subclinical cancers had the best prognosis, the 5-year survival reaching 67.8%, while this was only around 30% for stage II cancers, and 0% 5-year survival for stage III cancers. The survival rates of stage II and stage III cancers in the screened group and control were similar.

Vital status was determined for each study participant followed-up until the end of 1997. Up to December 1997, there were 153 HCCs, with 86 deaths from HCC among the 18,816 participants (Table 3). Although the total incidence of HCC was virtually identical in two groups, the total mortality rate from HCC was lower in the screened group (83.2 per 100,000) than in the control group (131.5 per 100,000). The rate ratio for mortality from HCC was 0.633 (95 percent confidence interval, 0.41–0.98). These results reveal a significant reduction in mortality at 5-year follow-up in the screened group compared to the control group (Fig. 4).

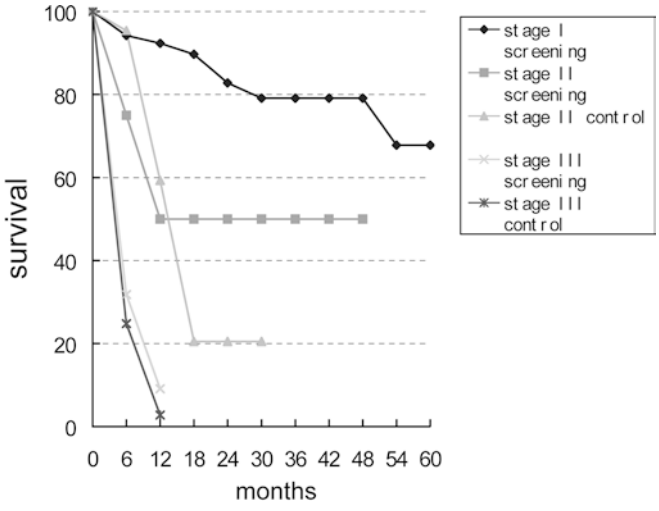

Fig. 4 Cumulative mortality from HCC in screening and control groups

Discussion

In this randomized controlled trial we found that after 5-year follow-up, screening by combined AFP testing and ultrasonography examination every 6 months led to a reduction of 37% in HCC mortality in individuals aged 35–59 years with HBV infection or a history of chronic hepatitis. The result was obtained with 58.2% compliance to screening. A greater reduction in mortality might be achieved with higher compliance to screening.

Since the 1970s, a number of screening programs have been reported, the results ranging from very optimistic to completely pessimistic (Purves 1976; Shanghai Coordinating Group for Research on Liver Cancer 1979; Yang et al. 1987; Sherman et al. 1995; Chen et al. 1997; McMahon et al. 2000). In 1990, a workshop on "screening for hepatocellular carcinoma" was held in Alaska to address the questions of whether screening should be routinely performed in high-risk populations. The questions included: can groups at high risk for development of HCC be identified? Can HCC be detected at an early stage? Is serum AFP elevated in hepatitis B surface antigen carriers with resectable HCC? What is the role of ultrasound in early detection of HCC? Can early detection of HCC lead to prolonged survival? (McMahon et al. 1991). We designed this randomized controlled study to answer these questions.

A high-risk population for HCC is mainly defined as serum evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. In this study, the incidence of HCC was 268.0/100,000 in all individuals, 359.5/100,000 in males, and 88.0/100,000 in females, while the incidence of HCC in the natural population in Shanghai was about 20/100,000. Beasley found that the annual incidence of HCC in HBsAg-positive male carriers in Taiwan was 495/100,000 (Yu 1995). Chen reported the incidence of HCC with HBsAg carriers is as high as 897.5/100,000 (Chen et al. 1982). In Qidong County, an epidemic area of HCC in China, the incidence was 38.1/100,000 in the natural population and 984.6/100,000 in a sub-population with a background of liver disease (Zhu et al. 1983).

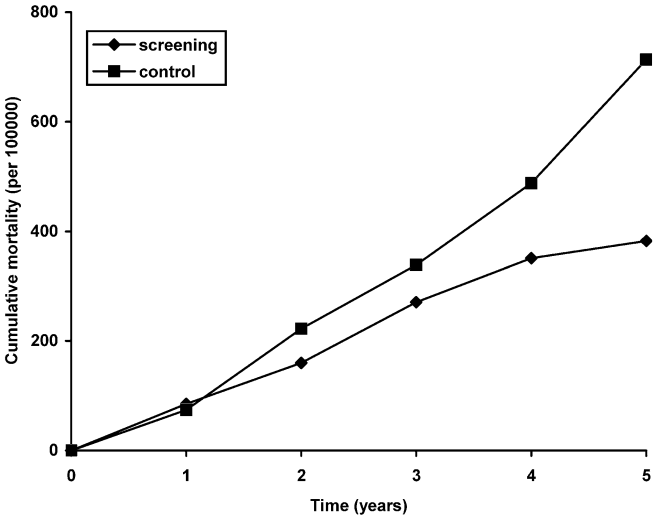

Fig. 5 Cumulative survival in different stages HCC patients

Cirrhosis is also a risk factor for HCC; however, more than 90% of cirrhoses are related to HBV infection in China. Thus, we did not regard cirrhosis as an inclusion criterion in this study. The incidence of HCC was higher in the screening group than in the control group which may be attributed to the lead-time of screening and over-diagnosis. From this program, the lead-time of screening was estimated at about 0.5 years (Yang et al. 1997). According to the rough incidence rates (223.7/100,000 vs 163.1/100,000), an over-diagnosis bias of screening seems to have existed in this study, but it is hard to estimate how many patients were over-diagnosed. Actually, the incidence rates in the two groups were similar after standardization.

In the workshop in Alaska, participants concluded that AFP is elevated in most HBsAg-positive carriers with resectable HCC (McMahon et al. 1991). In previous clinical trials, the detection rate using AFP was 60–70%. The sensitivity of AFP was confirmed at 69% in the present study (Zhang et al. 1999). In Japan, ultrasonography surveys have been proven effective in detecting small HCC (The Liver Cancer Study Group of Japan 1990). In the authors' institute, ultrasound has been used in addition to AFP screening since the 1980s, and has been proven to be useful in picking up HCC with negative AFP. However, the median tumor size detected by ultrasonography screening is generally bigger than that of tumors detected by AFP screening (Yang et al. 1989). In this study, ultrasonography was proven to be a useful screening method (Zhang and Yang 1999).

HCC patients at earlier stages were found significantly more often in the screened group versus the control. There were twice as many stage III cancers in the control group as in the screening group, being 22 (25.6%) vs 45 (62.9%). The detection of cancer before its development into a stage III cancer had a profound effect on mortality. No patients with stage III cancers survived more than 5 years, whereas for patients with cancer in the earlier stages, 5-year survival ranged from 68% for subclinical to 30.3% for stage II (Fig. 5). The results for cumulative survival from the time of diagnoses of HCCs were consistent with the view that earlier detection by screening results in improved survival. The survival rate was significantly higher in the patients with HCC in the screened group than in the control group ($P < 0.01$). These rates were similar to others as a number of screening programs have breported that cancers detected by screening were smaller and more amenable to potentially curative therapy (Izzo et al. 1998; Mima et al. 1994; Shanghai Coordinating Group for Research on Liver Cancer 1979; Sherman et al. 1995; Tang et al. 1980; Tang 1989; Yang et al. 1997). Based on a 16-year population-based study, McMahon et al. (McMahon et al. 2000) concluded that screening of HBsAg carriers with semiannual AFP was effective in detecting most HCC tumors at a resectable stage and significantly prolonged survival rates when compared with historical controls in this population. Although there were no randomized controlled trials of screening, and all results reported suffered from lead-time bias, it is clear that screening results in detecting small cancers in asymptomatic individuals, and the majority of them are treated with curative intent.

The results from a study conducted in Qidong County showed that screening can detect HCCs at an earlier stage; however, there was no advantage in reducing mortality from HCC (Chen et al. 1997). This might be attributed to insufficient early treatment being provided to HCC patients. Only 25% (25 of 100) subclinical HCCs detected by screening received proper treatment, and most patients gave up the treatment in that study (Zhang et al. 1994), whereas 75% subclinical HCCs received radical treatment in our study. This may be the most important reason for the profound difference between the two studies. Proper treatment is indispensable to HCC patients detected by screening. On the other hand, it is questionable whether to screen liver cancer in those with server liver cirrhosis.

In conclusion, biannual screening with combined AFP and ultrasound in individuals aged 35–59 years reduced HCC mortality after 5-year follow-up. Our findings suggest that consideration should be given to a program of screening using AFP and ultrasound to reduce HCC mortality in an increased risk population in the developed areas of China.

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