RESEARCH COMMUNICATION

Liver Cancer Screening in Korea: A Report on the 2008 National Cancer Screening Programme

Eun-Ha Lee, Mi Ah Han, Hoo-Yeon Lee, Jae Kwan Jun*, Kui Son Choi, Eun-Cheol Park

Abstract

Background: The Korean National Cancer Screening Programme (NCSP) for liver cancer was initiated in 2003. The objective of this study was to evaluate participation in the NCSP and provide essential evidence associated with the screening of Korean adults at high risk for liver cancer. Methods: Liver cancer screening was conducted in two stages. During the first, the fraction of the population at high risk for liver cancer was identified through detection of the hepatitis B virus surface antigen (HBsAg) and hepatitis C virus antibodies (anti-HCV Ab). During the second stage, this high-risk population was kept under surveillance to detect liver cancers as quickly as possible, and screening participation rates and recall rates were assessed. We estimated the 95% confidence intervals (CIs) for all outcome measures. Results: In the first stage, 2.57% (95% CI, 2.47-2.67) of Medical Aid Programme (MAP) recipients tested positive for HBsAg and 3.70% (95% CI, 3.25-4.15) tested positive for anti-HCV Ab. The total target population for liver cancer screening in 2008 included 433,822 adults over 40 years of age. Of them, 141,381 (32.6%) participated in the NCSP for liver cancer. Participation rates were 34.9% for National Health Insurance (NHI) recipients and 25.2% for MAP recipients. Among participants, 1,139 individuals exhibited a positive screening result (recall rate = 0.81%). Conclusions: Our findings demonstrate the current status of liver cancer screening in Korea. They provide evidence for implementing an organised liver cancer screening programme among high-risk groups.

Keywords: Liver cancer - mass screening - Korea

Asian Pacific J Cancer Prev, **11**, 1305-1310

Introduction

In 2008, an estimated 747,000 new cases of primary liver cancer were diagnosed world-wide and 695,000 people died in the advanced stages of this disease, identifying liver cancer as a major global public health concern. However, marked geographic variation is observed in the incidence of liver cancer, with the highest estimated incidence in Eastern Asia (35.5 cases per 100,000 people). Within Eastern Asia, the number of cases per 100,000 population range from 37.4 in China, 40.6 in Thailand, and 52.0 in Chinese Taipei to 116.6 cases per 100,000 in Mongolia. These values are striking in comparison with those from United States (7.0), Canada (5.2), and the United Kingdom (3.8). In Korea, the liver cancer incidence in men was 38.7 per 100,000 (IARC, 2008). Although the incidence of liver cancer in Korea has declined over the last decade, it remains the fourth most common cancer in Korean men and the sixth most common cancer in Korean women (Jung et al., 2010). Liver cancer is the second most common cause of cancer death in Korea, with a mortality rate of 22.9 per 100,000 in 2008. Although the 5-year relative survival rate of liver cancer increased from 10.7% in 1993-1995 to 21.7% in 2003-2007, survival remains much lower than with other cancers. For example, the survival rates for gastric, colorectal, cervical, and breast cancer were 61.2, 68.7, 80.5, and 89.5%, respectively, for the period of 2003 to 2007 (Ministry of Health and Welfare, 2009).

Those at high risk for liver cancer include patients with background chronic hepatic disease, such as chronic hepatitis, as determined through serological evidence of infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), or liver cirrhosis (Stuver et al., 2008). There is a remarkably low incidence among healthy individuals with none of the risk factors for liver cancer. Surveillance tests commonly used for the detection of liver cancer are ultrasonography (US) of the liver and measurement of α-fetoprotein (AFP) levels in serum. Compared with any single test, the combination of AFP and US increases both the sensitivity and specificity of liver cancer detection (Daniele et al., 2004). For this reason, routine screening using both US and AFP is recommended for individuals with liver cirrhosis (Bruix et al., 2001).

A randomised controlled trial in China reported that the mortality rate from primary liver cancer was significantly lower in the screened group (83.2 per 100,000) than in the control group (131.5 per 100,000; Zhang et al., 2004).

*National Cancer Control Institute, National Cancer Center, Goyang, Korea. *For correspondence : jkjun@ncc.re.kr*

Additionally, a cohort study in Taiwan reported a non-significant 41% reduction in hepatocellular carcinoma-related mortality in screening participants versus non-participants (Chen et al., 2002). In Japan, surveillance of cirrhotic patients permitted the detection of much smaller hepatocellular carcinomas and significantly prolonged the 5-year survival rate (Ando et al., 2006).

A cost-utility evaluation of screening programmes conducted under variable medical circumstances estimated that the incremental cost-effectiveness ratio for such programmes ranged from $26,000 to $55,000 per gain of one quality-adjusted life year (QALY), with a mean gain in life expectancy ranging from 3 to 9 months (Nouso et al., 2008). In Japan, Mima et al. (1994) found that the cost per tumor detected using combined US and AFP methodology every 6 months was approximately $25,000, whereas researchers in Switzerland estimated the cost of surveillance per year of life saved to be between $26,000 and $55,000 (Sarasin et al., 1996). These estimates are generally within the range considered to be “acceptable” . However, in Italy, Bolondi et al., (2001) estimated the cost per year of life saved to be $112,996, an amount greatly exceeding the $55,000 typical cut-off point.

In 1996, the Korean government established a long-term Cancer Control Programme, and in 1999, the National Cancer Screening Programme (NCSP) was introduced to provide screening services for low-income participants. The initial target cancers were stomach, breast, and cervical cancer; however, after the Korean Association for the Study of the Liver (KASL) and the National Cancer Centre (NCC) cooperatively developed and released their “Hepatocellular Carcinoma Screening/Surveillance Recommendations” in 2001 (Han and Park, 2002), screening programmes for liver cancer were implemented in 2003. Currently the NCSP targets five common cancers in Korea: stomach, breast, cervical, liver, and colorectal cancers.

The liver cancer screening program consists of two stages. The first was performed to identify that fraction of the population deemed to be at high risk for liver cancer, while the second stage focused on maintaining these high-risk individuals under surveillance. The target population for liver cancer screening included all individuals 40 years and older, within which there was a high-risk group of patients with liver cirrhosis, carriers of HBV or HCV, or HBV- or HCV-induced chronic hepatitis. Two methods were used to identify individuals at high risk for liver cancer. First, individuals in the high-risk group were identified using computerised medical records, including workplace health check-up records held by the National Health Insurance Corporation (NHIC). Second, serological analyses to identify individuals at high-risk of liver cancer were conducted only for Medical Aid Programme (MAP) recipients for whom the statuses of surface antigen of HBV (HBsAg) and HCV antibody (Anti-HCV Ab) were unknown (Figure 1).

In the present study, we aimed to provide preliminary information on the results of the 2008 NCSP for liver cancer.

Subjects and Methods

The target population for liver cancer screening in the 2008 NCSP consisted of 433,822 adults born before December 31,1968 (i.e., aged 40 years or over, with a mean age of 55.5±10.4 years). The target population was composed of 60% men and 40% women; according to health insurance type, the study included 103,901 MAP recipients and 329,921 National Health Insurance (NHI) recipients.

From January 1, 2008 to December 31, 2008, certified screening units collected the data and entered them into a web-based database system managed by the NHIC. We used all 2008 data that had been entered as of December 31, 2009. During the data collection phase, HBsAg and anti-HCV Ab titers were measured by quantitative or qualitative tests, depending on the screening unit in which data were collected. We classified these test results as negative or positive. If the HBsAg test result was positive, the anti-HCV Ab test was omitted, and such subjects were included in the target population for liver cancer screening regardless of alanine aminotransferase (ALT) results. When ALT levels were 46 mg/dL or greater, we defined the result as an “elevated” ALT level. In patients showing a negative HBsAg result, but an elevated ALT level, anti-HCV Ab testing was conducted. If the patient’s anti-HCV

<table>
<tr><th rowspan="2">Target population</th><th colspan="2">Liver Cancer Screening Programme</th></tr>
<tr><th>1st stage : Identifying the high-risk group</th><th>2nd stage : Surveillance of the high-risk group</th></tr>
<tr><td>Lower 50% of NHI beneficiaries</td><td>Screening using computerised medical records, including workplace health check-up records stored by the National Health Insurance Corporation</td><td rowspan="2">Active surveillance using US and serum AFP testing</td></tr>
<tr><td>MAP beneficiaries</td><td>Screening using blood tests
1. ALT
2. HBsAg test
3. Anti-HCV Ab test [1]</td></tr>
</table>

Figure 1. Target Population and Screening Methods for the Detection of Liver Cancer, as Established within the National Cancer Screening Programme (NCSP) in Korea. AFP, alpha-fetoprotein; ALT, alanine aminotransferase; Anti-HCV Ab, hepatitis C virus antibody; HBsAg, hepatitis B virus surface antigen; MAP, Medical Aid Programme; NHI, National Health Insurance; US, ultrasonography; [1]Anti-HCV Ab test was also conducted among participants with a negative HBsAg test, but an elevated ALT level (ALT ≥ 46 mg/dL)

Table 1. Target Populations and Number of Participants During the First Stage Screening to Identify the High-Risk Group for Liver Cancer Among Medical Aid Programme (MAP) Recipients and Their Outcomes in 2008

	HBsAg and ALT test [1]				Anti-HCV Ab test [2]		
	Target population (n)	No. of participants (n)	HBsAg positive rate (%) (95% CI)	Elevated ALT [3] (%) (95% CI)	Target population (n)	No. of participants (n)	Anti-HCV Ab positive rate (%) (95% CI)
Total	710,801	100,419	2.57 (2.47-2.67)	7.30 (7.14-7.46)	6,862	6,303	3.70 (3.25-4.15)
Gender							
Male	282,134	35,109	2.73 (2.56-2.90)	11.47(11.13-11.80)	3,689	3,457	3.71 (3.10-4.32)
Female	428,667	65,310	2.49 (2.37-2.60)	5.06 (4.89-5.23)	3,173	2,846	3.69 (3.03-4.34)
Age group							
40-49	194,402	25,352	3.83 (3.59-4.06)	9.26 (8.90-9.61)	2,163	1,991	2.64 (1.96-3.31)
50-59	137,643	19,846	3.17 (2.93-3.42)	10.33 (9.91-10.75)	1,926	1,743	2.60 (1.89-3.31)
60-69	128,022	23,651	2.16 (1.98-2.35)	7.25 (6.92-7.58)	1,606	1,459	4.30 (3.30-5.29)
70+	250,734	31,570	1.49 (1.36-1.62)	3.86 (3.65-4.07)	1,167	1,110	6.68 (5.25-8.12)

ALT, alanine aminotransferase; Anti-HCV Ab, hepatitis C virus antibody; CI, confidence interval; HBsAg, hepatitis B virus surface antigen; [1]The subjects were screened using serologic tests for hepatitis, HBsAg, and ALT level to identify the high-risk group; [2]Anti-HCV Ab testing was limited to individuals with a negative HBsAg result, but an elevated serum ALT level (ALT ≥ 46 mg/dL); [3]Elevated ALT is defined as ≥ 46 mg/dL

Ab result was positive, he or she was included in the target population for liver cancer screening. A positive result for serological tests aimed at identifying individuals at high risk of liver cancer were defined as a positive HBsAg or anti-HCV Ab result, as well as elevated ALT levels.

Liver cancer screening at 6-month intervals is recommended for high-risk individuals. Accordingly, individuals were able to participate twice a year; however, for the purposes of this study, we counted repeat participants only once in the calculation of the participation rate. In total, 471 repeat visits were excluded; the repeat participants were 236 MAP beneficiaries and 235 NHI beneficiaries.

US and AFP results were collected, integrated, and classified for each patient as "negative," "benign," "needing further evaluation," "suspicious of cancer," or "confirmed liver cancer patient." The category "confirmed liver cancer patients" was defined as patients whose medical histories included diagnosis and treatment of liver cancer before screening. Patients falling within the categories "needing further evaluation" and "suspicious of cancer" were identified as recall cases.

Positive rates for serological analyses were calculated from the proportion of positive cases among all participants subjected to serological tests. We calculated the participation rate for liver cancer screening by dividing the number of participants by the high-risk population. Recall rates for liver cancer screening were defined as the proportion of recall cases among the cancer-screened participants. The 95% confidence intervals (CIs) were calculated for all outcome variables.

Results

During the first stage of this liver cancer screening programme, high-risk individuals were identified among MAP recipients. The target population included 710,801 MAP recipients, and among them, 100,419 underwent serological analyses (14.1% participation rate). For men, the target population included 282,134 individuals, and 35,109 (12.4%) of these subjects participated in serological testing. For women, the target population included 428,667 individuals, and 65,310 (15.2%) of these subjects participated in serological testing. Individuals in their 60s demonstrated the highest rates of participation (18.5%) for serological testing (Table 1).

Among MAP beneficiaries, the positive rate for HBsAg was 2.57% (95% CI, 2.47-2.67). Subjects in their 40s showed the highest mean positive rate 3.83% (95% CI, 3.59-4.06). As age increased, the rate of positive HBsAg results decreased, with individuals in their 50s, 60s, and 70s exhibiting rates of 3.17% (95% CI, 2.93-3.42), 2.16% (95% CI, 1.98-2.35), and 1.49% (95% CI, 1.36-1.62), respectively. Regarding anti-HCV testing, 3.70% (95% CI, 3.25-4.15) of all participants showed positive results, and subjects in their 70s and older showed the highest positive rate among age groups 6.68% (95% CI, 5.25-8.12, Figure 2).

The target population for liver cancer screening in the 2008 NCSP included a total of 433,822 individuals, including 3,205 high-risk individuals identified from serological analyses. Among the total target population, 146,550 (34.0%) were deemed at high risk of liver cancer, because of liver cirrhosis, whereas 92,149 (21.4%) were included as HBV carriers, 22,350 (5.2%) as HCV carriers, and 390,912 (90.8%) as chronic hepatitis patients. In total, only 141,381 individuals (32.6%) participated in the liver cancer screening programme. The screening participants

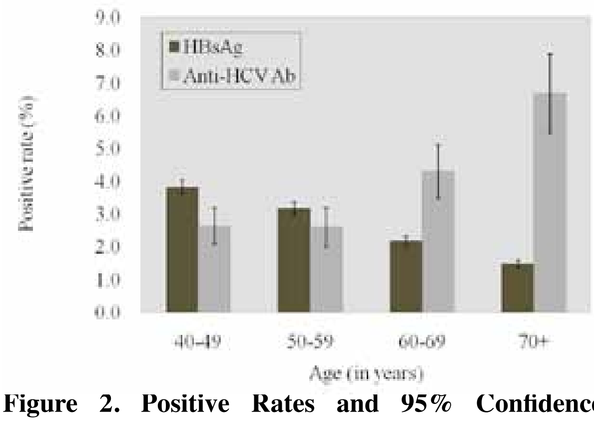

Figure 2. Positive Rates and 95% Confidence Intervals for HBsAg and Anti-HCV Antibody Tests. Anti-HCV Ab, hepatitis C virus antibody; HBsAg, hepatitis B virus surface antigen

Table 2. Target Population and Number of Participants in the 2008 National Cancer Screening Programme and their Screening Results

	Target population (n)	No. of participants (n)	Participation rate (%)	No. of positive cases (n) [1]	Recall rate (%)	(95% CI)
Total	433,822	141,381	32.6	1,139	0.81	(0.76-0.86)
Health insurance type						
MAP	103,901	26,135	25.2	282	1.08	(0.95-1.21)
NHI	329,921	115,246	34.9	857	0.74	(0.69-0.79)
Gender						
Male	258,371	76,640	29.7	776	1.01	(0.94-1.08)
Female	175,451	64,741	36.9	363	0.56	(0.50-0.62)
Age group						
40-49	143,265	40,482	28.6	208	0.51	(0.44-0.58)
50-59	147,567	51,639	36.5	391	0.76	(0.69-0.83)
60-69	91,416	35,702	25.3	369	1.03	(0.93-1.13)
70+	51,574	13,558	9.6	171	1.26	(1.07-1.45)

CI, confidence interval; MAP, Medical Aid Programme; NHI, National Health Insurance; [1]Individuals without available screening results were excluded (n = 49);

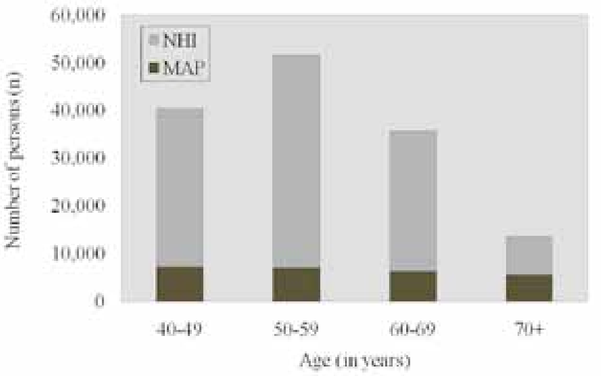

Figure 3. Number of Participants in the 2008 National Cancer Screening Programme According to Age Group and Health Insurance Type. MAP, Medical Aid Programme; NHI, National Health Insurance

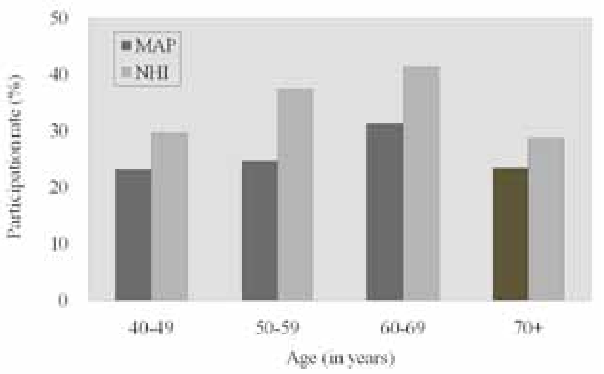

Figure 4. Participation Rates in the 2008 National Cancer Screening Programme According to Age Group and Health Insurance Type. MAP, Medical Aid Programme; NHI, National Health Insurance

included 115,246 NHI recipients (81.5%) and 26,135 MAP recipients (18.5%). Participants in their 50s showed the highest participation rate (36.5%). Participation rates for women (36.9%) were higher than those for men (29.7%; Figure 3, Table 2).

According to NCSP data, the liver cancer screening participation rate was 32.6% in 2008 (95% CI, 32.5-32.7). NHI recipients made up 34.9% (95% CI, 34.8-35.1) of participants, while MAP recipients made up 25.2% (95% CI, 24.9-25.4). Regardless of health insurance type, individuals in their 60s showed the highest participation rates (41.3% (95% CI, 40.9-41.6) for NHI recipients; 31.2% (95% CI, 30.6-31.9) for MAP recipients). NHI beneficiaries in their 70s or older showed the lowest participation rate of 28.8% (95% CI, 28.3-29.3), while MAP beneficiaries in their 40s or older all demonstrated participation rates lower than 30%, with rates of 23.0% (95% CI, 22.6-23.5), 24.7% (95% CI, 24.2-25.2), and 23.3% (95% CI, 22.8-23.9), respectively (Figure 4). Women showed higher liver cancer screening participation rates than men (37.0% (95% CI, 36.8-37.3) vs. 29.8% (95% CI, 29.6-29.9), respectively; data not shown).

We excluded 49 participants from calculations of positive rates for liver cancer because their liver cancer results were unavailable. Among the 141,322 known liver cancer screening results, 1,139 were positive (0.81% (95% CI, 0.76-0.86)). The recall rate was higher among MAP recipients (1.08% (95% CI, 0.95-1.21)) than among NHI recipients (0.74% (95% CI, 0.69-0.79)), and the positive rate for men was about twice as high as that for women (1.01% (95% CI, 0.94-1.08) vs. 0.56% (95% CI, 0.50-0.62), respectively). As age increased, positive rates for liver cancer screening also increased (Table 2).

Discussion

Although several studies have reported on the effectiveness of liver cancer screening for high-risk groups (Chen et al., 2002; Zhang et al., 2004; Ando et al., 2006), the implementation of a nationwide organised screening programme for liver cancer is still controversial. Nevertheless, because liver cancer is the third leading cause of death in Korea, after lung and stomach cancer, a nationwide liver cancer screening programme was implemented in 2003, Several Asian countries also conduct liver cancer screening programmes, but these are opportunistic screening or regionally restricted, rather than nationwide programmes.

Because of the high prevalence of HBV infection and related liver problems in Korea, the Korean government has made major efforts to reduce the burden of these problems. In 1983, a vaccine against HBV was first introduced in Korea, and was initially recommended to government employees, soldiers, and students on a voluntary basis. In 1995, a national vaccination programme for infants and children was launched, followed by a 2002 national vaccination programme directed at HBV-infected mothers to prevent vertical transmission to neonates (Yoo, 2008; Chae et al., 2009; Juon et al., 2009). Liver cancer screening was later implemented in 2003 as a secondary preventative measure.

The NCSP results showed a participation rate of 32.6% in 2008. Compared to the 58.2% participation in a Chinese scheme (Zhang et al., 2004), participation in the Korean NCSP is low. Because the target population for liver cancer screening is a high-risk population rather than a general population, it is imperative to increase participation in screening programmes. Reported screening intervals vary from 3 to 12 months (Han et al., 2002). However, there is no study that directly addresses the question of how frequently screening should be performed. Although the NCSP recommends a screening interval of 6 months, which is based on tumor doubling time, we observed relatively few biannual participants.

Despite the increasing trend in general participation (from 15.8% in 2003 to 32.6% in 2008), participation remains higher among NHI recipients (34.9%) than among MAP recipients (25.2%; National Cancer Information Centre, 2010). Because socioeconomic status is associated with liver cancer incidence and mortality, individuals with lower socioeconomic status may be at higher risk of liver cancer (Kim et al., 2008). The results reported here signal a strong need to increase liver cancer screening participation among MAP recipients.

The successful implementation of screening programmes is dependent on effective, standardised recall procedures, as well as resources for confirmatory diagnoses and cancer treatment. Although two Chinese randomised controlled trials reported increased detection rates of smaller sized cancers, the effectiveness of these two trials in reducing mortality is controversial; the main reason for the difference in mortality reduction may be attributable to the different treatment strategies in the two regions (Chen et al., 2003; Zhang et al., 2004). In Korea, the Korean Liver Cancer Study Group (KLCSG) and NCC established "Practice Guidelines for the Management of Hepatocellular Carcinoma" in 2003 and a revised version was announced in 2009 (Korean Liver Cancer Study Group and National Cancer Centre, 2009). As a result of these guidelines, the national liver cancer screening programme in Korea may achieve better results in future.

Despite a lack of evidence regarding the effectiveness of nationwide screening programmes for liver cancer, a nationwide programme was implemented in Korea in 2003. Although there are several problems with this programme, including low compliance and disparities in participation according to socioeconomic status, our results indicate that the NCSP will help to decrease the burden of liver cancer in Korea. Our results provide evidence for implementing an organised liver cancer screening programme among high-risk groups.

References

Ando E, Kuromatsu R, Tanaka M, et al (2006). Surveillance program for early detection of hepatocellular carcinoma in Japan: results of specialized department of liver disease. *J Clin Gastroenterol*, **40**, 942-8.

Bolondi L, Sofia S, Siringo S, et al (2001). Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. *Gut*, **48**, 251-9.

Bruix J, Sherman M, Llovet JM, et al (2001). Clinical management of hepatocellular carcinoma. Conclusions of the barcelona-2000 EASL conference. European association for the Study of the Liver. *J Hepatol*, **35**, 421-30.

Chae HB, Kim JH, Kim JK, et al (2009). Current status of liver diseases in Korea: Hepatitis B. *Korean J Hepatol*, **15**, S13-24.

Chen JG, Parkin DM, Chen QG, et al (2003). Screening for liver cancer: results of a randomised controlled trial in Qidong, China. *J Med Screen*, **10**, 204-9.

Chen TH, Chen CJ, Yen MF, et al (2002). Ultrasound screening and risk factors for death from hepatocellular carcinoma in a high risk group in Taiwan. *Int J Cancer*, **98**, 257-61.

Han KH, Park JW (2002). The usefulness and current status of the screening program for early diagnosis of hepatocellular carcinoma. *J Korean Med Assoc*, **45**, 972-80.

International Agency for Research on Cancer (IARC) Web site. Available at: http://globocan.iarc.fr/. Accessed August 6, 2010.

Jung KW, Park S, Kong HJ, et al (2010). Cancer Statistics in Korea: Incidence, mortality and survival in 2006-2007. *J Korean Med Sci*, **25**, 1113-21.

Juon HS, Choi KS, Park EC, et al (2009). Hepatitis B vaccinations among Koreans: results from 2005 Korea national cancer screening survey. *BMC Infect Dis*, **9**, 185.

Kim CW, Lee SY, Moon OR (2008). Inequalities in cancer incidence and mortality across income groups and policy implications in South Korea. *Public Health*, **122**, 229-36.

Korean Liver Cancer Study Group and National Cancer Centre (2009). Practice guidelines for management of hepatocellular carcinoma 2009. *Korean J Hepatol*, **15**, 391-423.

Mima S, Sekiya C, Kanagawa H, et al (1994). Mass screening for hepatocellular carcinoma: experience in Hokkaido, Japan. *J Gastroenterol Hepatol*, **9**, 361-5.

Ministry of Health and Welfare. Annual report of cancer incidence (2007), cancer prevalence (2007) and survival (1993-2007) in Korea. Seoul: Ministry of Health and Welfare; 2009.

National Cancer Information Centre (NCIC). Cancer Facts & Figures 2010. Available at: http://www.cancer.go.kr/cms/data/edudata/1391947_1619.html. Accessed on September 6, 2010.

Nouso K, Tanaka H, Uematsu S, et al (2008). Cost-effectiveness of the surveillance program of hepatocellular carcinoma depends on the medical circumstances. *J Gastroenterol Hepatol*, **23**, 437-44.

Sarasin FP, Giostra E, Hadengue A (1996). Cost-effectiveness of screening for detection of small hepatocellular carcinoma in western patients with child-pugh a cirrhosis. *Am J Med*, **101**, 422-34.

Stuver S, Trichopoulos D (2008). Cancer of the liver and biliary tract. In: 'Textbook of cancer epidemiology', Eds Adami HO, Hunter D, Trichopoulos D. Oxford University Press, New York 308-32.

Ward E, Jemal A, Cokkinides V, et al (2004). Cancer disparities by race/ethnicity and socioeconomic status. *CA Cancer J Clin*, **54**, 78-93.

Yang HI, Lu SN, You SL, et al (2002). Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med*, **347**, 168-74.

Yoo KY (2008). Cancer control activities in the Republic of Korea. *Jpn J Clin Oncol*, **38**, 327-33.

Yuen MF, Lai CL (2003). Screening for hepatocellular carcinoma: Survival benefit and cost-effectiveness. *Ann Oncol*, **14**, 1463-7.

Zhang BH, Yang BH, Tang ZY (2004). Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol*, **130**, 417-22.

Zhou XD, Tang ZY, Yang BH, et al (2000). Hepatocellular carcinoma: the role of screening. *Asian Pac J Cancer Prev*, **1**, 121-6.