RESEARCH COMMUNICATION

Factors Associated with Attending the National Cancer Screening Program for Liver Cancer in Korea

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Abstract

Background and Aims: The National Cancer Screening Program (NCSP) for liver cancer was initiated in 2003 in Korea. The objective of this study was to evaluate the participation rate of the program and to provide preliminary information on its results based on data collected by the NCSP in 2009. Methods: The target population of the NCSP for liver cancer in 2009 was comprised of 373,590 adults aged ≥40 years at high risk for liver cancer. Participation rates and positivity rates were assessed in this population. Multivariate logistic regression analysis was performed to determine the factors associated with participation in the NCSP for liver cancer. Results: The overall participation rate was 37.9% and 1,126 participants were positive at screening. The highest participation rates were observed in women, those in their 60s, National Health Insurance beneficiaries, and individuals positive for hepatitis B surface antigen. Positivity rates for men, those in their 70s, Medical Aid Program recipients and individuals with liver cirrhosis were the highest in the respective categories of gender, age, health insurance type, and risk factor for liver cancer. Conclusions: The participation rates of the NCSP for liver cancer are still low, despite the fact that the program targets a high-risk group much smaller than the general population. Efforts to facilitate participation and to reduce disparities in liver cancer screening among Korean men and women are needed. These results provide essential data for evidence-based strategies for liver cancer control in Korea.

Key words: Liver cancer - screening - participation rate - positivity rate - factors - Korea

Asian Pacific J Cancer Prev, **13**, 731-736

Introduction

Liver cancer is the fifth most common cancer in men (16.0 per 100,000, 7.9% of the total cancer burden) and the seventh in women (6.0 per 100,000, 6.5% of the total cancer burden) worldwide (Ferlay et al., 2010). Because of its high fatality (overall ratio of mortality to incidence of 0.93), liver cancer is the third most common cause of cancer death worldwide (Ferlay et al., 2010). There are marked geographic variations in the incidence of liver cancer, with more than 80% of cases occurring in Asia and Africa (Boyle and Levin, 2008). Although the incidence of liver cancer in Korea has declined over the last decade, it is still the fourth most common cancer in Korean men (40.2 per 100,000) and the seventh most common cancer in Korean women (10.8 per 100,000) (Jung et al., 2010). Moreover, liver cancer is the second most common cause of cancer death in Korea (Ministry of Health & Welfare and National Cancer Center, 2010). The carcinogenic effect of chronic infection with hepatitis B and C viruses (HBV, HCV) in liver cancer development has been well demonstrated by epidemiological and experimental evidence (Boyle and Levin, 2008). There is a remarkably low incidence of liver cancer among healthy individuals that have no related risk factors. Therefore, liver cancer screening in patients at high risk for progression has the potential to significantly reduce morbidity and mortality. In China, a randomized controlled trial among individuals at high risk for liver cancer 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). In Japan, surveillance of patients with liver cirrhosis permitted the detection of much smaller hepatocellular carcinomas and significantly improved the 5-year survival rate (Ando et al., 2006).

Therefore, liver cancer surveillance or screening is widely practiced and generally recommended for certain high-risk groups. The combination of alpha-fetoprotein (AFP) and ultrasonography is commonly recommended

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for surveillance testing to detect liver cancer (Daniele et al., 2004). In Korea, the Hepatocellular Carcinoma Screening/Surveillance Recommendations were developed by the National Cancer Center and the Korean Association for the Study of the Liver in 2001 (Han and Park, 2002). It recommended AFP and ultrasonography testing every 6 months for individuals at high risk for liver cancer. Based on this recommendation, the nationwide liver cancer screening program was introduced in 2003 as part of the National Cancer Screening Program (NCSP). Currently, the NCSP provides liver cancer screening services free of charge to Medical Aid Program (MAP) recipients and National Health Insurance (NHI) beneficiaries in the lower 50% income bracket (Yoo, 2008). The NCSP provides AFP and ultrasonography testing for men and women 40 years of age or over with chronic HBV or HCV infection, liver cirrhosis, or chronic liver disease of any cause (Yoo, 2008). In the NCSP for liver cancer, the screening interval depends on an individual's health insurance type: MAP recipients are invited every 6 months; NHI beneficiaries are invited every 1-2 years, according to their NHI Corporation routine health check-up schedule.

Although, the NCSP for liver cancer has been in place since 2003, the participation rate remains low. According to the NCSP report, the participation rate for liver cancer screening was 32.7% in 2008 (Ministry of Health & Welfare and National Cancer Center, 2010). To maximize the benefits of liver cancer screening, a high level of participation and compliance is required. However, relatively little is known about the factors associated with participation in the NCSP for liver cancer. Therefore, the objectives of this study were to assess the participation rates of the NCSP for liver cancer and determine the factors associated with participation. Positivity rate according to risk factor for liver cancer was also examined.

Materials and Methods

The Study population

The major data source for this study was the NCSP database, which contains information on the MAP recipients and NHI beneficiaries invited to participate in the NCSP for liver cancer. The NCSP invites men and women aged 40 years and over at high risk for liver cancer. The NHI Corporation defined this high-risk group as individuals who had been tested or received medical care for HBV or HCV infection, chronic hepatitis, chronic liver disease, or liver cirrhosis within the past 2 years, using the computerized medical claims database. All those in the selected target population receive an invitation letter from the NHI Corporation at the beginning of the year.

The population for the current study was restricted to men and women who were invited for liver cancer screening through the NCSP between January 1, 2009 and December 31, 2009. In total, 381,960 eligible individuals were invited to liver cancer screening during this period. Excluded from the analysis were

Table1. Target Population and Number of Participants in the NCSP for Liver Cancer, Republic of Korea, 2009

	Target Population N (%)	Number of Participants N (%)	Participation rate % (95% CI)	OR[a] (95% CI)
Total	373,590 (100)	141,460 (100)	37.9 (37.7-38.0)	
Gender				
Male	223,501 (59.8)	78,160 (55.2)	35.0 (34.8-35.2)	1
Female	150,089 (40.2)	63,300 (44.8)	42.2 (41.9-42.4)	1.27 (1.25-1.29)
Age (years)				
40-49	122,651 (32.8)	41,802 (29.6)	34.1 (33.8-34.4)	1
50-59	130,152 (34.8)	51,945 (36.7)	39.9 (39.6-40.2)	1.31 (1.29-1.33)
60-69	76,440 (20.5)	34,254 (24.2)	44.8 (44.4-45.2)	1.64 (1.61-1.67)
≥70	44,347 (11.9)	13,459 (9.5)	30.4 (29.9-30.8)	0.96 (0.93-0.98)
Health insurance type				
MAP	91,872 (24.6)	25,963 (18.3)	28.3 (28.0-28.6)	1
NHI	281,718 (75.4)	115,497 (81.7)	41.0 (40.8-41.2)	1.61 (1.59-1.64)
Area of residence				
Rural	50,692 (13.6)	15,097 (10.7)	29.8 (29.4-30.2)	1
Urban	166,169 (44.5)	63,657 (45.0)	39.3 (38.1-38.5)	1.40 (1.37-1.44)
Metropolitan	156,729 (41.9)	62,706 (44.3)	40.0 (39.8-40.3)	1.47 (1.44-1.50)
Risk factor for liver cancer				
HBsAg+	88,694 (23.8)	40,013 (28.3)	45.1 (44.8-45.4)	1
Anti-HCV+	17,227 (4.6)	6,767 (4.8)	39.3 (38.6-40.0)	0.81 (0.79-0.84)
Chronic liver disease	133,841 (35.8)	54,721 (38.7)	40.9 (40.6-41.2)	0.85 (0.84-0.87)
Liver cirrhosis	86,836 (23.3)	24,819 (17.5)	28.6 (28.3-28.9)	0.56 (0.55-0.57)
Others	46,722 (12.5)	15,140 (10.7)	32.4 (32.0-32.8)	0.61 (0.60-0.63)

[a]OR, adjusted odds ratio; CI, confidence interval; MAP, Medical Aid Program; NHI, National Health Insurance; HBsAg, hepatitis B surface antigen; anti-HCV, antibodies against hepatitis C virus

Table 2. Previous Liver Cancer Screening among Participants of the NCSP for Liver Cancer, Republic of Korea, 2009

History of liver cancer screening	Total	Risk factor for liver cancer, N (%) HBsAg+	Anti-HCV+	Chronic liver disease	Liver cirrhosis	Other	p-value
Never	71,688 (50.7)	15,928 (39.8)	2,971 (43.9)	30,645 (56.0)	12,628 (50.9)	9,516 (62.8)	P<0.001
≤6 months	8,521 (6.0)	3,855 (9.6)	631 (9.3)	1,998 (3.6)	1,706 (6.9)	331 (2.2)	
7-12 months	22,332 (15.8)	8,957 (22.4)	1,245 (18.4)	6,895 (12.6)	3,652 (14.7)	1,583 (10.5)	
≥13 months	33,536 (23.7)	9,946 (24.9)	1,658 (24.5)	13,070 (23.9)	5,878 (23.7)	2,984 (19.7)	
Unknown	5,383 (3.8)	1,327 (3.3)	262 (3.9)	2,113 (3.9)	955 (3.8)	726 (4.8)	

HBsAg, hepatitis B surface antigen; anti-HCV, antibodies against hepatitis C virus

8,370 (2.2%) individuals with a previous diagnosis of liver cancer according to the Korean National Cancer Incidence database, which contains 95% of newly diagnosed malignancies in Korea (Won et al., 2009). Therefore, the current analysis was based on 373,590 individuals. This study was approved by the institutional review board of the National Cancer Center, Korea.

Data collection and measurement

The NCSP database includes information on the target population's gender, age, health insurance type (MAP or NHI), area of residence, and International Classification of Disease-10 (ICD-10) code. Based on the ICD-10 code, the individuals were classified into five groups: hepatitis B surface antigen (HBsAg)-positive (HBV carriers or those with chronic HBV infection), antibodies against HCV (anti-HCV)-positive (HCV carriers or those with chronic HCV infection), chronic liver disease, liver cirrhosis, and others. Cases that could not be assigned a category because of insufficient or unavailable information were classified as "others".

The NCSP database also has information on screening results and self-reported questionnaires of individuals who have participated in liver cancer screening. Overall screening results were reported in four categories (negative, benign, suspicious and other) based on AFP and ultrasonography results. In the analysis, a positive screening result was defined as an overall result of "suspicious". The self-reported questionnaire also assessed the history of liver cancer screening through questions on whether the participants had ever undergone liver cancer screening, and when they underwent their most recent screening (≤6 months, 7-12 months, ≥13 months ago). Information on family history of liver cancer was also collected, and included only immediate blood relatives (mother/father, sister/brother, daughter/son, half-sister/half-brother).

Statistical Analysis

Participation rates were analyzed by gender, age, health insurance type, area of residence, and risk factors for liver cancer. Multivariable logistic regression models were fit with generalized estimating equations to identify significant predictors of participation in the NCSP for liver cancer (participated versus not participated). We also analyzed the screening history of participants according to their risk factors for liver cancer.

Positivity rates for liver cancer screening were calculated from the proportion of positive cases among liver cancer screening participants in 2009. The adjusted odds ratio (aOR) was calculated for each subcategory of gender, age, health insurance type, area of residence, history of liver cancer screening and family history of liver cancer. All statistical analyses were conducted using SAS statistical software (version 9.1; SAS Institute Inc., Cary, North Carolina, USA).

Results

Characteristics of the study population and participation rates of the NCSP for liver cancer

The total target population invited for liver cancer screening in 2009 was 373,590 (Table 1). There were 223,501 (59.8%) men and 150,089 (40.2%) women. Individuals with chronic liver disease were the most frequent (35.8%), followed by HBsAg-positive individuals (23.8%), and those with liver cirrhosis (23.3%). Of the target population, 141,460 participants underwent liver cancer screening, yielding a participation rate of 37.9% (Table 1). Women were 1.27 times more likely to participate than men, and NHI beneficiaries were 1.61 times more likely to participate than MAP recipients. Individuals living in metropolitan areas were more likely to participate than those living in rural areas. Regarding risk factors for liver cancer, individuals with liver cirrhosis were less likely to participate (aOR=0.56; 95% CI=0.55-0.57) than HBsAg-positive individuals.

History of liver cancer screening

We analyzed history of liver cancer screening among participants, including both organized and opportunistic screening (Table 2). About half of the participants had no history of liver cancer screening. HBsAg-positive individuals showed the highest history of screening, followed by anti-HCV-positive individuals and those with liver cirrhosis. Overall only 6% of participants had undergone liver cancer screening within the past 6 months.

Positivity rates

Among the participants of liver cancer screening, 1,126 (0.80%) were positive (Table 3). The positivity rate for men (1.04%) was more than twice as high as that for women (0.49%). As age increased, positivity rates also

Table 3. Number of Participants and Number of Positive Cases in the NCSP for Liver Cancer, Republic of Korea, 2009

	Number of participants N (%)	Number of positive cases N (%)	Positivity rates % (95% CI)	OR[a] (95% CI)
Total	141,460 (100.0)	1,126 (100.0)	0.80 (0.75-0.84)	
Gender				
Male	78,160 (55.2)	815 (72.4)	1.04 (0.97-1.12)	1
Female	63,300 (44.8)	311 (27.6)	0.49 (0.44-0.55)	0.53 (0.46-0.60)
Age (years)				
40-49	41,802 (29.6)	216 (19.2)	0.52 (0.45-0.59)	1
50-59	51,945 (36.7)	430 (38.2)	0.83 (0.75-0.91)	1.69 (1.43-1.99)
60-69	34,254 (24.2)	343 (30.4)	1.00 (0.90-1.11)	2.14 (1.80-2.54)
≥70	13,459 (9.5)	137 (12.2)	1.02 (0.86-1.21)	2.51 (2.01-3.13)
Health insurance type				
MAP	25,963 (18.3)	228 (20.2)	0.88 (0.77-1.00)	1
NHI	115,497 (81.7)	898 (79.8)	0.78 (0.73-0.83)	0.90 (0.78-1.05)
Area of residence				
Rural	1,5097 (10.7)	112 (9.9)	0.74 (0.61-0.90)	1
Urban	63,657 (45.0)	493 (43.8)	0.77 (0.71-0.85)	1.18 (0.96-1.46)
Metropolitan	62,706 (44.3)	521 (46.3)	0.83 (0.76-0.91)	1.27 (1.04-1.57)
Risk factor for liver cancer				
HBsAg+	40,013 (28.3)	407 (36.2)	1.02 (0.92-1.12)	1
Anti-HCV+	6,767 (4.8)	74 (6.6)	1.09 (0.87-1.38)	0.99 (0.77-1.27)
Chronic liver disease	54,721 (38.7)	165 (14.6)	0.30 (0.26-0.35)	0.29 (0.24-0.34)
Liver cirrhosis	24,819 (17.5)	346 (20.7)	1.39 (1.25-1.55)	1.11 (0.96-1.30)
Others	15,140 (10.7)	134 (11.9)	0.89 (0.74-1.05)	0.85 (0.70-1.04)
History of liver cancer screening				
Never	71,688 (50.7)	497 (44.1)	0.69 (0.63-0.76)	1
≤6 months	8,521 (6.0)	100 (8.9)	1.17 (0.96-1.43)	1.40 (1.12-1.74)
7-12 months	22,332 (15.8)	200 (17.8)	0.90 (0.78-1.03)	1.14 (0.96-1.35)
≥13 months	33,536 (23.7)	302 (26.8)	0.90 (0.80-1.01)	1.22 (1.06-1.41)
Unknown	5,383 (3.8)	27 (2.4)	0.50 (0.34-0.74)	0.57 (0.37-0.88)
Family history of liver cancer				
No	121,336 (85.8)	921 (81.8)	0.76 (0.71-0.81)	1
Yes	11,879 (8.4)	135 (12.0)	1.14 (0.96-1.35)	1.44 (1.19-1.73)
Unknown	8,245 (5.8)	70 (6.2)	0.85 (0.67-1.08)	1.31 (1.00-1.72)

[a]OR, adjusted odds ratio; CI, confidence interval; MAP, Medical Aid Program; NHI, National Health Insurance; HBsAg, hepatitis B surface antigen; anti-HCV, antibodies against hepatitis C virus.

statistically significantly increased. Among categories of health insurance type, the positivity rate among MAP recipients (0.88%) was higher than among NHI recipients (0.78%). According to risk factors for liver cancer, the positivity rate was highest in individuals with liver cirrhosis (1.39%), followed by anti-HCV-positive (1.09%) and HBsAg-positive (1.02%) individuals. Among categories of area of residence, positivity rate was highest among individuals living in a metropolitan area; individuals who had undergone liver cancer screening within the past 6 months showed statistically significantly higher positivity rates than those who had never been screened before. Those who had a family history of liver cancer also showed statistically significantly higher positivity rates.

Discussion

Although several studies have reported on the effectiveness of liver cancer screening in high-risk groups (Chen et al., 2002; Zhang et al., 2004; Ando et al., 2006), the implementation of nationwide organized liver cancer screening programs is still controversial. At present, several Asian countries conduct liver cancer screening programs, but these are either opportunistic screening programs, or are regional instead of nationwide programs. In Korea, the liver cancer screening program was initiated in 2003 because liver cancer is the third most common cause of cancer death in the country after lung and stomach cancer. To our knowledge, the present study is the first, large population-based study reporting participation rate and positivity rate in the NCSP for liver cancer.

Overall in the present study, approximately 37.9% of those invited were screened in 2009. Despite the increasing trend in participation (from 15.8% in 2003 to 37.9% in 2009) (Lee et al., 2010) this rate is still low compared to the 58.2% participation in a Chinese scheme (Zhang et al., 2004). Furthermore, there is an apparent worldwide gap between the participation observed for liver cancer screening and other types of cancer screening. In the United Kingdom for example, where nationwide organized screening programs have been implemented, 73.7% of women aged 45-74 years underwent breast cancer screening by mammography in 2008-2009 (NHS Cancer Screening Programmes, 2010a), and 78.9% of women aged 25-64 years underwent cervical cancer screening by Pap smear in 2009-2010 (NHS Cancer Screening Programmes, 2010b). Although the target population for liver cancer screening in Korea is restricted to a smaller, high-risk population, the participation rate is still much lower than that for breast or cervical cancer screening, which targets the larger general population. There may be many reasons to explain why only about one-third of individuals participated in liver cancer screening in the present study. Low awareness of the existence of the program and the necessity for early detection of liver cancer among the high-risk population may be a factor. It is also possible that individuals at high risk for liver cancer routinely visit hospitals or clinics for health check-ups instead of utilizing the screening program. In the NCSP for liver cancer, screening is performed at a clinic or hospital that has been designated as a liver cancer screening unit, and those who are invited for screening should visit one of these designated liver cancer screening units instead of their usual care provider. The lack of a close relationship or continuous connection between a physician in a liver cancer screening unit and participants, which does exist between patients and their usual care provider, might have affected the low participation rate.

In the current study, women, individuals aged 60-69 years, and NHI beneficiaries were significantly more likely to participate in the NCSP for liver cancer. Specifically, individuals aged 70 years or over were less likely to participate than those aged 40-69 years. In the NCSP for liver cancer, there is no age limit for screening. All people in the target population receive an invitation letter from the NHI Corporation at the beginning of the year. Therefore, the lower participation rate among individuals aged 70 or over may be due to a hesitancy to follow the recommendation for liver cancer screening. Also, it may be more difficult for the elderly to understand the need to undergo liver cancer screening. MAP recipients were also less likely than NHI beneficiaries to participate in the NCSP for liver cancer, despite the fact that screening services are free of charge in the NCSP. Gaps in the participation rate between MAP recipients and NHI beneficiaries may reflect a decreased awareness among MAP recipients about the expected benefits of liver cancer screening. A previous study conducted in Korea reported that socioeconomic status is highly related to liver cancer incidence and mortality (Kim et al., 2008). Therefore, it is important to increase the participation of MAP recipients in liver cancer screening to decrease the burden of liver cancer in Korea.

The factors associated with liver cancer screening in the current study were similar to those found in other types of cancer screening (Farmer et al., 2008; Meissner et al., 2006). However, the target population of liver cancer screening does differ from that of other types of cancer screening, as liver cancer screening targets the high-risk population, i.e., patients with HBV or HCV infection, chronic hepatitis, chronic liver disease, or liver cirrhosis. The participation rate varied between individuals with different risk factors for liver cancer. Generally, compliance was better in individuals with liver cirrhosis than in asymptomatic HBV carriers (Benvegnu et al., 1994; Colombo et al., 1989; Kato et al., 1994; Oka et al., 1994). However, in the current study, individuals with liver cirrhosis were less likely to participate (aOR=0.56; 95% CI=0.55-0.57) than HBsAg-positive individuals. This may be partly explained by the fact that individuals with liver cirrhosis are more likely to use medical services than screening services, as liver cirrhosis is the highest stage of progression in terms of natural history of disease. As we analyzed only NCSP data, we could not consider liver cancer screening/surveillance occurring through private health examination or in the private medical sector.

An important issue related to the early detection of cancer is the extent to which patients continue to use screening services after an initial examination. In case of liver cancer screening, reported screening intervals vary from 3 to 12 months (Han and Park, 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, our study revealed relatively few participants that had undergone regular liver cancer screening. Among participants in 2009, only 6% had undergone liver cancer screening within the past 6 months, and 21.8 % within the past 12 months. Furthermore, individuals with liver cirrhosis were less likely to have undergone liver cancer screening within the framework of the NCSP for liver cancer, compared with HBsAg-positive or anti-HCV-positive individuals. Among those with liver cirrhosis, the proportion of MAP recipients was relatively high (data not shown), suggesting that people who do not undergo screening are generally from less affluent socioeconomic groups than those who do undergo screening. The consequence of this could be poorer health status among these less affluent groups, and a higher risk of disease. Therefore, active intervention that targets low-income liver cirrhosis patients may help increase the liver cancer screening rate.

In the current study, male gender and increasing age were also risk factors for screening positivity in those with chronic HBV or HCV infection, liver cirrhosis, or chronic liver disease. The positivity rate of liver cancer screening was higher in men (1.04%; 95% CI= 0.97-1.12) than women (0.49%; 95% CI=0.44-0.55), and as age increased, positivity rates for liver cancer screening also increased. According to risk factors for liver cancer, the positivity rate was highest in individuals with liver cirrhosis (1.39%) followed by anti-HCV-positive (1.09%), and HBsAg-positive (1.02%) individuals. Overall, liver cirrhosis of any etiology is the most important risk factor for liver cancer, as it represents the last stage before liver cancer (Sangiovanni et al., 2004).

Our study has several limitations. Although the NCSP for liver cancer is a nationwide population-based screening program, we may have missed some tests performed outside this framework, as the NCSP does not capture tests paid for privately, or conducted as a medical service unrelated to screening. Second, the NCSP database lacks details about why a patient did not undergo screening. We were unable to explore the influence of other important correlates, such as individual characteristics (e.g., education level, income, availability of transportation, or of screening facilities in the geographic area) and psychological factors (e.g., discomfort, concern about complications, or anxiety about the procedure) that might be involved in participation.

Despite these limitations, to the best of our knowledge, this is the first population-based study to provide a participation rate for liver cancer screening in the Republic of Korea. Indeed, the low participation rate of liver cancer screening in Korea revealed in this study is worrisome. The NCSP for liver cancer has been offered to the high-risk population since 2003, yet despite the reduced target population, the participation rate among these men and women is still disappointingly low; far lower than some screening programs geared toward the general population. This result underscores the urgent need for interventions to improve the participation rates of liver cancer screening. The findings of the study support the critical need for increasing efforts to raise awareness and provide more screening in the high-risk population.

Acknowledgement

This study was supported by a Grant-in-Aid for Cancer Research and Control from the National Cancer Center, Korea (Grant number: 1010200). The authors have no conflict of interest.

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