Status of Primary Liver Cancer Found through Routine Health Check-up

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INTRODUCTION

According to many guidelines, surveillance for liver cancer is strongly recommended in high-risk subjects to improve prognosis by early diagnosis (1-4). Hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection and heavy alcohol consumption are representative risk factors for liver cancer (3). As Korea has been an endemic area of HBV, liver cancer also has been a major public health problem in Korea (5). Actually in 2011, liver cancer was ranked as the second most common cause of cancer mortality in Korea (6). Therefore, surveillance for liver cancer in high-risk subjects for liver cancer may be important in view of improving not only personal health but also public health in Korea (5, 7). Since 2001, in order to reduce the clinical burden of liver cancer through early diagnosis and treatment, the Ministry of Health and Welfare, Republic of Korea Government has recommended the regular surveillance of subjects older than 40 yr who are at a high risk for liver cancer (8).

Routine health check-ups are performed on people in Korea for the purpose of primary prevention or secondary prevention of major public health problems such as cancers or cardiovascular disease. Therefore, a routine health check-up may be a good chance not only to perform essential surveillance activities but also to detect liver cancer in the early stage. The purpose of this study was to study the characteristics of liver cancers found during routine health check-ups and their previous surveillance status in one health check-up specialized center which exists as a part of a major tertiary hospital in Korea.

MATERIALS AND METHODS

Study subjects
A total of 91,219 subjects (48,122 males and 43,097 females) received a routine health check-up which included abdominal ultrasonography (USG) or computed tomography (CT) at the Seoul National University Hospital Healthcare System Gangnam Center (Seoul, Korea) between October, 2003 and August, 2011. Among these 91,219 subjects, those who were diagnosed with liver cancer for the first time during a routine health check-up or during a surveillance which had started after a routine health check-up were the final subjects for this study. After excluding the 17 subjects with a previous history of liver cancer, the subjects who were diagnosed with liver cancer for the first time during a routine health check-up or during a surveillance which had started after a routine health check-up were the final subjects for this study.

Methods
Each subject answered a questionnaire, underwent anthropometric assessment, and had laboratory tests and a radiologic study of abdominal USG or CT done on the same health check-up day. Data about age, gender, cigarette smoking, amount of...
alcohol intake, family history of cancer, and general symptoms about weakness, weight loss or dyspepsia were collected from the questionnaire. Body mass index (BMI) was calculated by dividing the weight in kilograms by square of the height in meters. Laboratory tests included serum hepatitis B surface antigen (HBsAg), an antibody to hepatitis C virus (anti-HCV) and alpha-fetoprotein (αFP). Blood samples were collected from each subject before 10 a.m. after an overnight fast. All biochemical analyses of blood samples were performed in the same quality-controlled laboratory and done according to standard laboratory methods. Abdominal magnetic resonance imaging (MRI) or USG guided liver biopsy were performed on a separate day if needed diagnostically. A heavy alcohol consumer was defined as a person who consumed more than 80 g of alcohol per drinking session and drank more than 5 times a week for more than 10 yr (9). All USG, CT and MRI were assessed by radiologists. Liver cirrhosis was assessed by surface nodularities of a liver, regenerating nodules in a liver and/or an accompanied hypersplenism. Liver cancer was diagnosed according to the Practice Guidelines for Management of Hepatocellular Carcinoma (2009) (10). Nodular tumor was divided into single nodular or multinodular type by the number of tumor nodules. Infiltrative tumor was diagnosed if more than 50% of a tumor margin showed infiltrative and irregular invasion into adjacent liver tissues. Primary liver cancer found during a routine health check-up was treated by surgery, percutaneous ethanol injection, radiofrequency ablation or transarterial chemoembolization at the main tertiary Seoul National University Hospital (11-13).

## Statistical analysis

The data were expressed as the mean ± standard deviation. However, for data which did not follow standard normal distribution, data were expressed as median and range. Intergroup differences in continuous variables were explored by using Kruskal-Wallis test or Student’s t-test. Intergroup differences in frequency variables were explored by using chi-square test or Fisher’s exact test. SAS 9.2 version (SAS Institute, Cary, NC, USA) was used for the statistical analysis. A two-tailed P value that was less than 0.05 was regarded to be statistically significant.

## Ethics statement

The study protocol was approved by the institutional review board of Seoul National University Hospital (IRB No. 1201-021-392). Informed consent was waived by the board due to retrospective study without any harm to each study subject.

## RESULTS

A total of 34 subjects were diagnosed with primary liver cancer for the first time through a routine health check-up during a period of 8 yr. Only 11.8% of liver cancer subjects had been under previous surveillance (Table 1). Of the liver cancers, 82.4% were detected at a health check-up, and 17.6% were detected by surveillance which had been started after the initial health check-up. Liver cirrhosis was found in 76.5% of the liver cancer subjects. HBsAg was the most commonly found underlying risk factor for liver cancer in our study (55.8%), followed by anti-HCV (17.7%).

### Table 1. Baseline characteristics, tumor marker and gross tumor type according to risk factors for primary liver cancer in detected cases in this study

| Risk factors for liver cancer | HBsAg+ | Anti-HCV+ | Alcoholic | Not viral or alcoholic | Total |
|-----------------------------|--------|-----------|-----------|-----------------------|-------|
| Total number                | 19 (55.8%) | 6 (17.7%) | 3 (8.8%) | 6 (17.7%) | 34 (100%) |
| Male                        | 17 (50.0%) | 3 (8.8%) | 3 (8.8%) | 6 (17.7%) | 29 (85.3%) |
| Female                      | 2 (5.9%) | 3 (8.3%) | 0 (0%) | 0 (0%) | 5 (14.7%) |
| Age                         | 54.5 ± 8.5 | 64.3 ± 10.9 | 62.7 ± 9.3 | 66.2 ± 8.7 | 59.0 ± 10.1 |
| Previous surveillance*      | 1 (5.3%) | 2 (33.3%) | 0 (0%) | 1 (16.7%) | 4 (11.8%) |
| Tumor found                 | 14 (73.7%) | 5 (83.3%) | 3 (100%) | 6 (100%) | 28 (82.4%) |
| At health check-up*         | 12 (66.7%) | 4 (66.7%) | 2 (66.7%) | 2 (66.7%) | 20 (58.8%) |
| At a surveillance after health check-up* | 2 (33.3%) | 1 (16.7%) | 0 (0%) | 0 (0%) | 3 (8.8%) |
| Diabetes*                   | 8 (42.1%) | 3 (50.0%) | 2 (66.7%) | 3 (50.0%) | 16 (47.1%) |
| Current smoker*             | 13 (68.4%) | 2 (33.3%) | 2 (66.7%) | 5 (83.3%) | 22 (64.7%) |
| Body mass index (kg/m²)     | 24.8 ± 2.9 | 24.9 ± 6.0 | 27.0 ± 3.2 | 24.4 ± 2.1 | 24.9 ± 3.5 |
| Family history of any cancer* | 7 (36.8%) | 2 (33.3%) | 0 (0%) | 2 (33.3%) | 11 (32.4%) |
| Family history of primary liver cancer* | 4 (21.1%) | 1 (16.7%) | 0 (0%) | 0 (0%) | 5 (14.7%) |
| General symptom*            | 6 (31.6%) | 3 (50.0%) | 1 (33.3%) | 2 (33.3%) | 12 (35.3%) |
| Alpha-fetoprotein (ng/mL)*  | < 20    | 9 (47.4%) | 1 (16.7%) | 2 (66.7%) | 4 (66.6%) | 16 (47.0%) |
|                            | 20-400  | 5 (26.3%) | 2 (33.3%) | 1 (33.3%) | 1 (16.7%) | 9 (26.5%) |
|                            | ≥ 400   | 5 (26.3%) | 3 (50.0%) | 0 (0%) | 1 (16.7%) | 9 (26.5%) |
| Tumor type*                 | Single nodular | 13 (68.4%) | 1 (16.7%) | 1 (33.3%) | 2 (33.3%) | 17 (50.0%) |
|                            | Multinodular | 3 (15.8%) | 1 (16.7%) | 2 (66.7%) | 2 (33.3%) | 8 (23.5%) |
|                            | Infiltrative | 3 (15.8%) | 4 (66.6%) | 0 (0%) | 2 (33.3%) | 9 (26.5%) |
| Underlying liver cirrhosis* | 15 (79.0%) | 4 (66.6%) | 3 (100%) | 4 (66.6%) | 26 (76.5%) |

*Percent in each risk factor group.
and heavy alcohol consumption (8.8%). However, 17.7% of the liver cancer subjects did not have any evidence of HBsAg, anti-HCV or heavy alcohol consumption. Mean age was significantly younger in subjects with HBsAg than in those without HBsAg ($P = 0.028$). Male was about 6 times more common than female. Of the liver cancer subjects, 47.1% had diabetes, and 64.7% were current smokers. Family history of liver cancer was positive in 21.1% of subjects with HBsAg and 16.7% of subjects with anti-HCV. Among 34 liver cancers, 1 intrahepatic cholangiocarcinoma was confirmed by biopsy in a subject with HBV.

Gross tumor type was significantly different between subjects with HBsAg and those with anti-HCV (Fig. 1). Nodular tumor was more common than infiltrative tumor in subjects with HBsAg, but infiltrative tumor was more common in subjects with anti-HCV. General weakness, weight loss or dyspepsia was significantly more common in subjects with infiltrative tumor than in those with nodular tumor (Table 2). Serum αFP level was significantly higher in subjects with infiltrative tumor than in those with nodular tumor. Metastasis was observed only in 5 subjects with infiltrative tumor, 4 lung metastasis and 1 lymph node metastasis. Surgery was the most common method of treatment for single nodular liver cancer, but transarterial chemoembolization was used for multinodular or infiltrative liver cancer (Fig. 2).

**DISCUSSION**

Our study showed that a low proportion of the liver cancer subjects had been under previous surveillance for primary liver cancer. Moreover, even though HBV is the most common risk factor in Korea, only 5.3% of HBV positive liver cancer subjects were under surveillance. This result may suggest that the actual surveillance rate may be low in spite of the recommendations by the Korean government since 2001 that regular surveillance of high risk subjects for liver cancer who are older than 40 yr be performed (8). As regular surveillance can improve the morbidity and prognosis of liver cancer, more efforts to enroll subjects at high risk for liver cancer into regular surveillance programs may be needed (14).

A routine health check-up may provide a good chance to detect liver cancer and start surveillance for liver cancer. In our study, 82.4% of the liver cancers were found during a health check-up.
check-up and 17.6% of the liver cancers were found by surveil-
ance which had been started after a health check-up because
the HBsAg or anti-HCV was found to be positive.

In regards to the major risk factor for liver cancer found in
our study, HBsAg was the most common factor, followed by an-
ti-HCV and heavy alcohol consumption. The proportion of Hb-
sAg-positive subjects was similar to the previously reported
worldwide proportion of 50%-55%, but the proportion of anti-
HCV positive subjects was less than the previously reported
worldwide proportion of 25%-30% (15). The proportion of anti-
HCV in liver cancer subjects in Korea may not have changed for
20 yr when comparing the present data to that (17.0%) publish-
ed 20 yr ago (16). Considering the previous report that HCV-re-
lated hepatocellular carcinoma represents 70% of all primary
liver cancers in Japan, the underlying cause of primary liver
can vary quite considerably among geographically near
countries such as Japan and Korea (16, 17). The liver cancer was
accompanied by liver cirrhosis in 76.5% of the subjects with liv-
er cancer, which was a rate similar to the 73.3% figure quoted in
a previous report in Korea (18). Of the liver cancer subjects, 64.7%
were current smokers in our study. As smoking is known to in-
crease the risk of liver cancer, smoking might contribute to the
development of liver cancers (19). In our study, 47.1% of the
subjects had diabetes. As diabetes is also recognized as a pre-
disposing factor for liver cancer, diabetes might also have con-
tributed to the development of liver cancer in our subjects (20-
22). Our subjects’ mean BMI was 24.9 ± 3.5, which was near 25,
the cutoff value for being overweight (23). Adequate weight
control may be needed in subjects with risk factors for liver can-
cer because obesity has been shown to have an association with
liver cancer (24, 25).

The proportion of subjects without HBsAg, anti-HCV, and
heavy alcohol consumption was 17.7%, which is comparable to
the figure of 17.6% published 20 yr ago in Korea but is slightly
higher than that of 8%-15% in Japan (16, 17). These results sug-
gest that any liver mass found by chance at USG or CT should
be thoroughly evaluated even in a subject without positive test
results for HBV or HCV, or who does not have heavy alcohol
consumption. Among subjects without HBsAg, anti-HCV, and
heavy alcohol consumption, 83.3% were smokers and 16.7%
were obese in our study. Nonalcoholic steatohepatitis was found
in 10% of liver cancer subjects without HBV and HCV in Japan
(17). Smoking, nonalcoholic steatohepatitis, aflatoxin or other
carcinogenic causes may also be an associated underlying risk
factor in these subjects without HBsAg, anti-HCV, or heavy al-
cohol consumption (26).

Male sex was 5.8 times more common than female in our
study. This male predominance coincides with the finding in
previous reports (3). Mean age was 59.0 ± 10.1 yr. Mean ages
were significantly different according to associated risk factors
for liver cancer. Mean age of subjects with HBsAg was 54.5 ± 8.5
yr but that of subjects with anti-HCV was 64.3 ± 10.9 yr, which
also coincides with the findings in a previous report (16). Pro-
portion of intrahepatic cholangiocarcinoma may be compara-
table to a previous study in Japan that reported 95% of primary
liver cancers were hepatocellular carcinoma (17).

The general symptoms of weakness, fatigue or dyspepsia were
more frequently found in subjects with infiltrative tumor than
in those with nodular tumor in our study. Newly occurring gen-
eral symptoms of weakness, fatigue or dyspepsia in a high-risk
subject for liver cancer need attention because these symp-
toms may come from a newly developed liver cancer (18).

aFP level was higher in subjects with infiltrative liver cancer
than in those with nodular liver cancer. This finding is in con-
cordance with the previous report that aFP reflects tumor activ-
ity in hepatocellular carcinoma (27).

A routine health check-up may be a good opportunity to de-
tect liver cancer in an early stage. Single nodular liver cancer
was found in 50% of the subjects in our study. On the other hand,
the proportion of single nodular cancer among all liver cancers
detected was previously reported to be 32.0% and 37.3% in each
of two different tertiary hospitals in Korea (18, 28). The reason
for this difference in the proportion of single nodular cancer
may have two possibilities. First, liver cancers detected at tertia-
ry hospitals were found in subjects with already known high-
risk factors for liver cancer by surveillance. Second, liver can-
cers detected in a routine health check-up are found at a very
early stage and this phenomenon may reflect the real effect of
screening for liver cancer in a primary care setting. This may be
important because detecting a liver cancer in an early or at a
single nodule stage can lead to curative treatment. Surgical re-
section or local ablative therapy has been regarded as a curative
therapy (29). A total of 44.0% of our liver cancer subjects recei-
ved curative therapy: 26.5% of subjects received surgical resec-
tion and 17.6% of subjects received local ablative therapy. This
may be higher than the 12.4% of subjects who were reported to
be curatively treated in a previous report (18). Moreover, con-
sidering that transarterial chemoembolization can be a curative
treatment if the embolization is compact, the actual proportion
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tion and 17.6% of subjects received local ablative therapy. This
may be higher than the 12.4% of subjects who were reported to
be curatively treated in a previous report (18). Moreover, con-
sidering that transarterial chemoembolization can be a curative
treatment if the embolization is compact, the actual proportion
of single nodular liver cancer were completely treated by transar-
terial chemoembolization only or consecutive surgery.

Our study has the limitation of not representing the whole
Korean population because the subjects in our study visited the
center voluntarily for a routine health check-up. There may be
some selection bias in our study because a person with high
risks for liver cancer may get their liver evaluated in a liver-spe-
cific clinic than in a routine health check-up center. Our study
may also have the limitation of being a retrospective study.

In summary, a routine health check-up may provide 3 im-
portant opportunities for detection of liver cancer. The first is
the opportunity to detect a liver cancer at a very early stage. The second is the opportunity to start surveillance in high-risk subjects for liver cancer. The third is the opportunity to detect a liver cancer in subjects without the representative risk factors of chronic viral hepatitis or heavy alcohol consumption.

**DISCLOSURE**

The authors have no conflicts of interest to disclose.

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