Title: TRENDS OF LIVER CANCER AND ITS MAJOR RISK FACTORS IN KOREA

Authors: Eun-young Lee*, Tran Thi Xuan Mai*, Yoonjung Chang, Moran Ki

Institute: Department of Cancer Control and Policy, Graduate School of Cancer Science and Policy, National Cancer Center, Republic of Korea

*First author

Correspondence: Moran Ki, MD, PhD

Institute: Department of Cancer Control and Policy, Graduate School of Cancer Science and Policy, National Cancer Center, Republic of Korea

Tel: +82-31-920-2736

Email: moranki@naver.com
Abstract

To understand the great difference of incidence in liver cancer between male and female in South Korea, one of the countries of high incidence of liver cancer, the trends of major three risk factors, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and alcoholic liver cirrhosis were analyzed. Incidence of liver cancer was obtained from Cancer Registration Statistics in National Cancer Center of Korea. HBsAg seropositivity was based on Korea National Health and Nutrition Examination Survey in 2011. For HCV infection and alcoholic liver cirrhosis, we used disease statistics from Health Insurance Review and Assessment Service, Korea. The prevalences of these risk factors were observed and compared with the incidence of liver cancer. In the incidence of liver cancer, male continuously showed 3 to 4 times higher level than female from 1999 to 2011. By age the gap of incidence between male and female increased with age increasing and male in 50s showed 5 times higher incidence than female in 50s. HBsAg seropositivity decreased generally from 1998 to 2011, the prevalence of HCV infection was 96.2 and 90.3 per 100,000 persons in female and male, respectively in 2013. The prevalence of HCV from 2009 to 2013 showed no significant difference. Regarding alcoholic liver cirrhosis, the annual average prevalence from 2009 to 2013 was 77.22 and 8.90 per 100,000 persons in male and female, respectively; the prevalence of male was average 8.7 times higher than that of female. By age, male prevalence rapidly increased with age increasing. Male in 60s peaked with 19.2 times higher prevalence than female in 60s. Regarding the higher incidence of liver cancer in male, this research found that the incidence pattern of alcoholic liver cirrhosis, one of its major risk factors, showed similarity in its remarkable difference by gender.

Key message

한국의 간암 발생 추세에서 나타나는 큰 남녀차이와 관련하여 간암의 주요 위험요소로 평가되는 만성 간염, 음주, 간경변과 관련한 B형간염, C형간염, 알코올성 간경변의 유병률 추세를 살펴본 결과 알코올성 간경변의 유병률 추세에서 간암 발생에서와 유사한 큰 남녀차이가 발견되었다.
Introduction

Liver cancer characteristics; incidence, prevalence and mortality

Liver cancer is the one of the most common cancers and the second most common cause of death from cancer worldwide [1], especially in Asia and Africa countries [2]. There is a significant difference in the incidence of liver cancer between male and female in the world. The 5-year prevalence of liver cancer for both sexes is 3.7% [2]. Overall, the burden of liver cancer is in developing countries, which covered almost 85% of the cases. [1, 3]

Korea is a high endemic area of chronic hepatitis B virus infection, which is one of the major risk factors for liver cancer [3, 4]. For men, liver cancer accounted for 18.3% of cancer deaths in 2011 and 10.2% for women. In spite of having an increasing trend over the last two decades, the five-year relative survival of liver cancer in Korea was still among the lowest ones with only 26.7% from 2006-2010 [4]. According to the GLOBOCAN 2012, the incidence of liver cancer in Korea is the 6th highest in the world and the 4th highest among Asian countries.

Major risk factors of liver cancer in Korea

In Korean national cancer screening program, people with HBV, HCV, and liver cirrhosis are categorized as high risk group for development of liver cancer and they are main targets of the liver cancer screening program [5]. Another risk factor, which is generally pointed out, is excessive alcohol consumption. According to national cancer information center of Korea, among those with liver cancer, 74% were caused by HBV, 9% and 7% of them were attributable to HCV infection and harmful alcohol consumption, respectively.

This research aimed to compare the trends of infections with HBV and HCV, and alcoholic liver cirrhosis in Korea for recent years to understand the great difference by sex in the incidence of liver cancer in Korea.
Methods

1. Incidence of Liver cancer in Korea

Annual incidence of liver cancer in Korea was observed by sex from 1999 to 2011 based on the data from the Korea Central Cancer Registry. [6]

Age-specific incidence of liver cancer in Korea was based on age-specific crude incidence of liver cancer, which is categorized as C22 (malignant neoplasm of liver and intrahepatic bile ducts) according to Korean Standard Classification of Diseases (KCD), by sex in 2011 from cancer registry statistics in the Statistics Korea (KOSTAT). [7]

2. Risk factors

2.1 Hepatitis B Virus (HBV)

HbsAg seropositivity means percentage of individuals who have tested positive to HBsAg. HbsAg seropositivity from 1998 to 2011 and age-specific HBsAg seropositivity in 2011 were based on the data from Korean National Health and Nutrition Examination Survey (KNHANES), 2011 [8]. In this data, the surveyed population was over 10 years old and it was age-standardized based on estimated population in 2005.

2.2 Hepatitis C Virus (HCV)

Prevalence of HCV infection from 2009 to 2013 came out based on the data of patient number of HCV infection available in Health Insurance Review and Assessment Service (HIRA) [9], Korea and on the data of population registered as residents available in Ministry of Security and Public Administration (MOSPA) [10]. Number of patients with HCV infection includes both the number of acute and chronic HCV infection, which are categorized as B171 and B182, respectively, according to KCD. Then the patient number was divided by population for each year.

For the age-specific prevalence, year of 2011 was chosen considering that other factor’s age-specific data was observed in 2011. Number of patient with HCV infection including both acute and chronic in 2011 from HIRA was divided by population by age in 2011 from MOSPA.
2.3 Alcoholic liver cirrhosis

Prevalence of alcoholic liver cirrhosis from 2009 to 2013 was based on the data of number of patient with alcoholic liver cirrhosis, which is categorized as K703 according to KCD, from HIRA and also on the data of population registered as residents for each year from MOSPA. \[9, 10\] Then the number of patients with alcoholic liver cirrhosis was divided by population for each year by sex.

For the age-specific prevalence in 2011, the number of patients with alcoholic liver cirrhosis was divided by population number for each age group.
Results

1. Incidence of Liver cancer by year in Korea
Male continuously showed 3 to 4 times higher level than female. In 2011, male and female incidences were 35.6 and 10.3 per 100,000 persons, respectively. Both incidences showed slow decrease. (Figure 1)

Figure 2 illustrates the age-specific incidence of liver cancer by sex in Korea. Both of male and female showed increase with age increasing but male showed more rapid increase. The biggest gap between male and female appeared in those in 50s with 223.2 and 44.5 per 100,000 in male and female, respectively. Male incidence was 5 times higher than that of female. (Figure 2)

2. RISK FACTORS:

2.1 HBV
For HBsAg seropositivity, both male and female showed a downward trend overall. Male HBsAg seropositivity was slightly higher than that of female generally. Average annual seropositivity was 3.94% and 3.13% in male and female, respectively. This is known to be because of national vaccination program since 1995. Also from 2002 hepatitis B perinatal transmission prevention program started in Korea. (Figure 3)

Generally, male seropositivity was slightly higher than that of female. However, in the age groups of those under 20 years old and over 70 years old, female seropositivity was higher than male one. In the age group of those in 50s, male seropositivity was around two times higher than that of female. (Figure 4)

2.2 HCV infection
Average annual prevalences were 93 and 89 per 100,000 in male and female, respectively. There were slight decrease and increase by year. (Figure 5)

The prevalence of HCV infection by age showed similar trend in both sexes. It increased with age increasing and it peaked at those in 60s both in male and female. (Figure 6)
2.3 Alcoholic liver cirrhosis

The prevalence of alcoholic liver cirrhosis showed constant increase by year in both sexes. However male prevalence was continuously much higher than female’s. Male prevalence was around 10 times higher than that of female in 2009 and around 8 times higher than that of female in 2013. On average, annual male prevalence was 8.7 times higher than that of female. (Figure 7)

In age-specific prevalence, female prevalence stayed under 20 per 100,000 persons in all age groups and it peaked at 50s. However, male prevalence increased rapidly with age increasing and it peaked at those in 60s with highest prevalence of 268.3 per 100,000 persons. Then it decreased but the rate was still much higher than that of female. In those in 60s, male prevalence was 19 times higher than that of female in same age. (Figure 8)

Discussion

Trend of liver cancer incidence in Korea and some other countries

The trend of age-specific incidence of liver cancer in Korean male is similar to some other Asian countries including China, Japan, Philippines, Singapore and Thailand. This feature increases gradually with higher age-groups and therefore, the age-group >80 possesses the highest incidence. Furthermore, in China and Japan, the gap in the incidence of liver cancer between male and female became more apparent with increasing age. [2]

This study figures out that the incidence of liver cancer in Korea shows a modest decrease in both genders from 1999 to 2011. According to GLOBOCAN 2012, Singapore and China has the same trend in liver cancer incidence as Korea’s. In European countries, this feature for male has remained stable for a long period from 1975 until now and for female, it has a light increase. Incidence of liver cancer in the US has an opposite trend compared with Korea. In the US, recent statistics demonstrates that liver cancer has gradually increased in both genders. [11]

This study also found that there is a significant gap in the incidence rate of liver cancer between male and female in Korea. Other Asian countries with high incidence of liver cancer also share the similar patterns. The incidence sex ratio (male:female)
is over three times in some countries including Viet Nam (3.6), Thailand (3.1), China (3.1) and Japan (3.1). Male has higher liver cancer rate than female in almost all population, and the sex ratio usually fluctuates between 2:1 and 4:1 [12].

Risk factors of liver cancer in Korea

Hepatitis B virus infection

HBV infection has been considered as main risk factor in the development of liver cancer in Korea. HBsAg seropositivity showed decreasing trend from 1998 to 2011 overall because of national vaccination program. Liver cancer caused by HBV infection is expected to decrease considering the effect of HBV vaccination [13]. As for children under 10 years old, their HBsAg seropositivity remarkably decreased to 0.2% in 2007 [14]. The difference of the average annual HBsAg seporositivity from 1998 to 2011 between male and female was 0.81%p.

Hepatitis C virus infection

For HCV, there is no vaccination yet and the volume of incidence is not relatively higher, however, more than 80% of those infected with HCV are likely to proceed into chronic HCV infection and then it can be advanced into liver cancer to some extent. For the cumulative incidence which proceeds from liver cirrhosis to liver cancer, it is
higher in HCV infection than in HBV infection and with time, the rate of burden for liver cancer development came out to be higher due to HCV than due to HBV. [15] In the prevalence of HCV infection by year and by age, both sexes showed similar trend.

**Alcoholic liver cirrhosis**

Korea is one of the countries with high alcohol-consumption and as of 2010, the index of Korean men's prevalence of alcohol use disorders and alcohol dependence was 10.3%, Korean women's was 2.2% and average of WHO western pacific region was 4.6%. In the same year, total alcohol per capita consumption was 37.6 liters in Korean men and 11.5 liters in Korean women. For the prevalence of heavy episodic drinking in Korea, there was a marked difference between men and women as 12.1% for men and 0.1% for women. [16]

In the proportion of causes for liver cirrhosis in Korea, HBV accounts for 64.9% and alcohol use accounts for 18.6%. According to an epidemiological survey, the prevalence of alcoholic liver disease correlated with per capita alcohol consumption and the risk of alcoholic hepatitis and liver cirrhosis increased with increase of alcohol consumption [17].

In this research, there was similarity between incidence of liver cancer and prevalence of alcoholic liver cirrhosis. Both of them showed big difference between male and female and male showed much higher rate than female. The difference in alcohol consumption between men and women might have led to big gap of incidence of liver cancer between men and women to some extent. To decrease the quantity of drinking of nationals, Ministry of Health of Korea is studying several measures including regulating liquor advertising and drinking places. [18]

Previous studies found significant associations between heavy alcohol consumption and risk of hepatocellular carcinoma in HBV and HCV patients. One research from Taiwan concluded that excessive alcohol consumption dramatically increased the risk of hepatocellular carcinoma in HBV-related cirrhotic patients. [19] Similar result was found in research conducted in US population, which stated that moderate and excessive alcohol consumption increased the risk of liver-related mortality in HCV patients. [20]
Limitations of data

Our study has some limitations. First, secondary data was used in this study. However, the similarity found in this study between incidence of liver cancer and incidence of alcoholic liver cirrhosis can suggest a hint that alcohol might have been playing a role in it to some extent. Further studies in direct way are needed for clear verification.

For the patient number of HCV and alcoholic liver cirrhosis, disease statistics was based on Health Insurance Review and Assessment Service (HIRA), Korea. The disease statistics was collected on the basis of details of medical care expenses requested from hospitals and clinics. Because of classification of main diseases, secondary cases were not included in this data and patients who did not visit hospital also were not included.

Another limitation of our study is that we only pay attention to the main three risk factors of liver cancer in Korea. However, there are some other potential matters that may cause the gender disparity in the incidence of hepatocellular carcinoma. One controversial suggestion is the attribution of tobacco consumption. Further studies on the causes of gender disparity in hepatocellular carcinoma are needed.

Conclusion

Most noticeable characteristic in incidence of liver cancer in Korea is that male continuously showed much higher incidence than female. In this research the similarity was found in the incidence of alcoholic liver cirrhosis among main risk factors of liver cancer in Korea. It opens the possibility that harmful use of alcohol of male might have led to much higher incidence of liver cancer of them. Further study is needed for the verification.
References

14. Jung C-w. 10-year of Hepatitis B Perinatal Transmission Prevention Program. Korea centers for Diseae Control and Prevention
17. Chae HB. Alcoholic Liver Disease. Department of Internal Medicine, Chungbuk National University of Medicine and Medical Research
20. Z. M. Younossi LZ, M. Stepanova, C. Venkatesan. Moderate, excessive or heavy alcohol consumption each is significantly associated with increased mortality in patients with chronic hepatitis C. Alimentary Pharmacology and Therapeutics 2013;37:703-709.
Figure 1. Age-standardized Incidence of Liver Cancer in Korea by year from 1999 to 2011

*Standard population: Korean population in 2000

Source: The Korea Central Cancer Registry.[6]
Figure 2. Age-specific crude Incidence of Liver Cancer in Korea by gender in 2011

Source: Cancer Registry Statistics in The Statistics Korea (KOSTAT) [7]
Figure 3. Trend of HBsAg seropositivity in Korea 1998-2011

Source: Korea Health Statistics 2011: Korea National Health and Nutrition Examination Survey [8]

Note: HBsAg seropositivity: Percentage of individuals who have tested positive to HBsAg (those who are 10 years old and over)
Figure 4. Age-specific HBsAg seropositivity in Korea in 2011

Source: Korea Health Statistics 2011: Korea National Health and Nutrition Examination Survey [8]
Figure 5. Trend of prevalence of HCV infection in Korea from 2009 to 2013

Source: Health Insurance Review & Assessment Service, Ministry of Security and Public Administration [9,10]
Figure 6. Age-specific prevalence of HCV infection by age in Korea in 2011

Source: Health Insurance Review & Assessment Service, Ministry of Security and Public Administration [9,10]
Figure 7. Trend of prevalence of alcoholic liver cirrhosis in Korea from 2009 to 2013

Source: Health Insurance Review & Assessment Service, Ministry of Security and Public Administration [9,10]
Figure 8. Age–specific prevalence of alcoholic liver cirrhosis in Korea in 2011

*Source: Health Insurance Review & Assessment Service, Ministry of Security and Public Administration [9,10]*