Trends in Epidemiology of Hepatitis B and Hepatocellular carcinoma in Asia

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Conflict of Interest

SHA has acted as an **advisor and investigator** for BMS, Gilead Sciences, MSD, AbbVie, Janssen, Assembly Biosciences, Arbutus Biopharma, GreenCross, Ildong, Yuhan and Samil Pharmaceuticals. SHA has received **unrestricted grant** from Gilead Sciences for the investigator initiated trials.

Sang Hoon Ahn is **the leader of the Korea HBV cohort study** from the Korea Centers for Disease Control (CDC) and Prevention, Ministry of Health and Welfare, Korea
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02 Epidemiology of HBV related HCC
03 Prevention of HBV and HCC
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01 Epidemiology of HBV infection

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Korean Mummy May Provide Clues To Combat Chronic Hepatitis B

- Hepatitis B virus discovered in the liver of the South Korean Handong mummy
  - 500-year-old child
  - First time HBV ever been found in a mummified body (HBV genotype C)

- Study of the genome of the 500-year-old virus under way
  - To see if there have been any significant changes to HBV over time

- Handong Mummy (above) is one of the mummies being excavated in South Korea

Molecular Epidemiology of HBV

- Most Asian patients have HBV genotype B & C (HBV genotype C >95% in Korea)

CHB Is a Major Global Health Problem

• An estimated 257 million people worldwide have CHB\(^1\)
  - 10% are aware of their diagnosis and 2% are currently on treatment

• 10th leading cause of death worldwide
  - In 2015, hepatitis B resulted in more than 800,000 deaths, mostly from complications, such as cirrhosis and HCC\(^1\)

  – In Asia-Pacific regions
  – Chronic HBV infection is common
  – One of three major causes of death in Asia and Pacific regions

Worldwide Deaths from Chronic Viral Hepatitis

Compared with Deaths from Tuberculosis, Human Immunodeficiency Virus (HIV) Infection, and Malaria

Data on deaths from 1990 to 2017 are from the Institute for Health Metrics and Evaluation as of November 14, 2018
Mortality by major communicable diseases, 2015:
- Global, South East Asia, Western Pacific

South East Asia has 30.5% of all global hepatitis-related deaths

The Western Pacific has 33.3% of all global hepatitis-related deaths

Asia: The Epicenter of Liver Disease

- Asia Pacific shoulders a significant proportion of the global disease burden of hepatitis B and hepatitis C.
- Approximately 340 million people living with chronic hepatitis B or C in Asia Pacific, which is 65% of the total number worldwide.

Kowdley et al., 2012; Patel et al., 2006.
Increasing Global Burden of Disease From Mortality and Morbidity Due to Hepatitis B

Changes in health measures from 2006 to 2016 resulting from CHB-associated cirrhosis and liver cancer


Over a 10-year period, from 2006 to 2016, the rates of mortality and productive life-years lost due to disability from cirrhosis and liver cancer caused by hepatitis B increased worldwide. GBD=Global Burden of Disease
Burden of Hepatitis B Complications in the Community

**Worldwide**
- 12 million cases attributed to hepatitis B
  - ~44% of cases attributable to HBV

**Africans**
- ~33% of cases attributable to HBV

**Asians**
- 600,000 cases attributed to hepatitis B
  - ~5× increased risk vs uninfected population

**Blacks (U.S.)**
- ~31× increased risk vs uninfected population

**Asians/Pacific Islanders (U.S.)**
- ~5× increased risk vs uninfected population

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*Estimate based on 2006 data.
High portion of HBV infection is undiagnosed and untreated

257 million infected individuals

8.6% (22 million) infected individuals diagnosed

0.7% (1.7 million) infected individuals treated

Undiagnosed and untreated patients have poor health outcomes and are at high-risk of transmitting the disease

Those who are diagnosed but untreated may be lost to follow-up. Healthcare engagement and regular monitoring of markers of HBV infection is needed

Educate ineligible patients on the importance of monitoring and initiating treatment once they become eligible

WHO Global Elimination Target of viral hepatitis by 2030

Data from WHO 2017 Global Hepatitis Report and 2016-2021 Global Health Sector Strategy

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### Table 1. Targets for the Primary Interventions Projected by the World Health Organization (WHO) to Eliminate Chronic Hepatitis by 2030.†

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Indicator</th>
<th>2015 Baseline</th>
<th>2020 Target</th>
<th>2030 Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV vaccination</td>
<td>% of infants with HEPB3 vaccination</td>
<td>84</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Prevention of maternal HBV transmission</td>
<td>% of infants with HBV vaccination ≤12 hr after birth</td>
<td>39</td>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td>Blood safety</td>
<td>% of donations screened with quality assurance</td>
<td>97</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Injection safety‡</td>
<td>% of unsafe injections</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Harm reduction§</td>
<td>No. of syringes or needles distributed/injection drug user/yr</td>
<td>27</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>HBV diagnosis</td>
<td>% of infected persons who receive a diagnosis</td>
<td>9</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>HCV diagnosis</td>
<td>% of infected persons who receive a diagnosis</td>
<td>20</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>HBV treatment¶</td>
<td>% of persons with diagnosed infection who are treated</td>
<td>8</td>
<td>—</td>
<td>80</td>
</tr>
<tr>
<td>HCV treatment¶</td>
<td>% of persons with diagnosed infection who are treated</td>
<td>7</td>
<td>—</td>
<td>80</td>
</tr>
</tbody>
</table>

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Global Elimination Target of Chronic hepatitis B


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**Figure 2.** World Health Organization (WHO) Goals for the Elimination of Hepatitis.

Estimates vary widely according to the input data and approximation methods used.\(^3\)
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Relationship between Incidence and Prevalence

Incidence

Prevalence

Mortality or Cure

Duration of disease
Cancer Incidences & Deaths Worldwide

Estimated number of incident cases

- Lung: 782,451
- Liver: 745,553
- Breast: 639,171
- Colorectum: 611,176
- Prostate: 589,414
- Stomach: 485,030
- Oesophagus: 479,992
- Bladder: 358,744
- Cervix uteri: 335,962
- NHL: 308,744

Estimated number of deaths

- Lung: 782,451
- Liver: 745,553
- Breast: 639,171
- Colorectum: 611,176
- Prostate: 589,414
- Stomach: 485,030
- Oesophagus: 479,992
- Pancreas: 358,744
- Cervix uteri: 335,962
- Leukemia: 2
Incidence of Liver Cancer Worldwide (Newly diagnosed HCC)

: > 70% occur in Asia, > 75% of them are infected with HBV

Regional mortality rates of HCC (per 100,000 persons) categorized by age-adjusted mortality rates

Annual mortality per region:
- Europe: 54,000
- USA: 19,000
- China–Korea–Japan: 390,000
Proportion of Incident Cancers in South Korea

New cases of liver cancer in 2014  **16,628**  M:F = 2.9:1

Korea Central Cancer Registry, Annual report of cancer statistics in Korea in 2014
Incidences of Primary Cancers

Crude incidence rate

- Thyroid
- Stomach
- Colon
- Lung
- Breast
- Liver
- Prostate

Age-standardized incidence rate
Deaths from Liver Disease and Liver Cancer

Death from Liver Disease

Death from Liver Cancer

*Korean National Health Insurance Service-National Sample Cohort database

Cancer Statistics

• **Crude (incidence) rate**
  • number of (new cancer) cases in a given population
  • helpful in determining the **cancer burden and specific needs for services** for a given population

• **Age-standardized (incidence) rate**
  • a **weighted average** of the age-specific (crude) rates, where the weights are the proportions of persons in the **corresponding age groups of a standard population**
  • **to make fairer comparisons** between groups with different age distributions

Death Rates Changes from 1999 to 2013

Crude Death Rate, per 100,000

Age-standardized Death Rate, per 100,000

Liver cancer in Korea
Liver disease in Korea
Global liver disease
Global liver cancer

Age-standardized Incidence of Liver Cancer (Males vs Females)

Age-standardized Incidence rates for males in liver cancer (per100,000).

Age-standardized Incidence rates for females in liver cancer (per 100,000)

Population in South Korea

2000
47,008,111

2014
50,746,659

Statistics Korea, Statistical Geographic Information Service
Age-standardized Incidence of Liver Cancer (Males vs Females)

Korea Central Cancer Registry, Annual report of cancer statistics in Korea in 2014
Trends in Primary Liver Cancer Survival

Korea Central Cancer Registry, Annual report of cancer statistics in Korea in 2014
Temporal Changes in Mean Age at Death

Liver cancer in Korea

Liver disease in Korea

Summary: Epidemiology of HCC

**Incidence**
- Number of incident cases and crude incidence rate
- Age-standardized incidence rate

**Prevalence**
- Number of prevalent cases and crude prevalence rate
- Age-standardized prevalence rate

**Survival**
- More likely to be caused by improvement of HBV-related HCC due to exponential use of antiviral agents

**Mortality**
- Mortality from liver disease
- Mortality from liver cancer
- Competing risk of mortality between liver disease and liver cancer
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CHB Is Associated With Severe Burden of Disease

of CHB patients will develop complications, including fibrosis, cirrhosis, and HCC, if left untreated

Percentages in the figure above are 5-year cumulative incidence rates. 

Patient is chronically infected if HBsAg+ for ≥6 months.


Prevention of HBV-related HCC

**Primary prevention**
- Hepatitis B vaccination

**Secondary prevention**
- Antiviral treatment (IFN, NUCs)
- Periodic surveillance (US,AFP)

**Tertiary prevention**
- Adjuvant antiviral treatment (IFN, NUCs)

Normal liver → HBV infection → Chronic hepatitis B → Cirrhosis → Early stage HCC → Curative resection → Postoperative status → HCC recurrence → Advanced stage HCC

*Seminars in Oncology 2015 Kim MN and Ahn SH*
HBV vaccination

• Encouraging trends in HBV incidence have resulted from large-scale neonatal vaccination efforts

• Worldwide, HBV prevalence among children <5 years (a surrogate of HBV incidence) has decreased from 4.7% in the pre-HBV vaccination era (1980s-2000s) to 1.3% in 2015.

• Improvements in vaccination coverage and subsequent decreases in childhood HBV infection have been specifically seen in South East Asia, Western Pacific, and the Eastern Mediterranean region.

• HBV vaccination coverage remains low in some regions, particularly in Africa, and coverage with the initial birth vaccination dose continues to lag (<40%).

Andrew M. Moon et al., Clin Gastroenterol Hepatol. 2019
Thirty-Year Outcomes of the National Hepatitis B Immunization Program in Taiwan

Chiang CJ et al., JAMA 2013,310(9):974-6
Experiences of Korea: Hepatitis B Management Policy in Korea

Goals

- Prevention of perinatal hepatitis B infection to reduce neonatal infection
- Reduce number of chronic hepatitis B patients
- Elimination of hepatitis B

<table>
<thead>
<tr>
<th>Prevention strategy</th>
<th>Goals</th>
<th>Program</th>
</tr>
</thead>
<tbody>
<tr>
<td>Universal vaccination for all neonates</td>
<td>Timely vaccination</td>
<td>National immunization program</td>
</tr>
<tr>
<td></td>
<td>Complete vaccination</td>
<td></td>
</tr>
<tr>
<td>Prevention of perinatal hepatitis B infection</td>
<td>Reduction of perinatal infection rate</td>
<td>Perinatal hepatitis B prevention program</td>
</tr>
<tr>
<td>Management of high risk groups</td>
<td>Increased vaccination rate in high risk group</td>
<td>Recommendation of vaccination in high risk group</td>
</tr>
</tbody>
</table>
Neonatal HBV vaccination in Korea

- **Initiation of national immunization program (NIP) from 1995**
  - Inclusion of hepatitis B vaccine in immunization table by Korean Pediatric Society at 1991: Policy to vaccinate all neonates
  - Reimbursement of full cost for neonatal vaccination from 1995
    - (Three doses; at birth and 1, 6 months after birth)

- **Complete vaccination rates (3rd dose vaccination) by NIP**

<table>
<thead>
<tr>
<th>Year</th>
<th>2008</th>
<th>2009</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rates (%)</td>
<td>92.9</td>
<td>98.1</td>
<td>98.7</td>
<td>99.0</td>
<td>99.4</td>
</tr>
</tbody>
</table>
Trends in the Prevalence of HBV Infection

- Plasma-derived HBV vaccine domestically licensed ('83)
- Use of recombinant HBV vaccine ('86)
- National Immunization Program for HBV introduced ('95)
- The Korean government launched HBV perinatal transmission prevention program ('02.7)

3.4% in Male
2.6% in Female

HBsAg-positive rates in Adults in Korea

- Although HBsAg positive rate is decreasing, it still remains at 3%. WHY?

Prevalence of HBV infection is still high in Adults over 30 years and will forward at least 20 years.
The goal of therapy for chronic HBV infection is to improve quality of life and survival of the infected person by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease.
Impact of antiviral therapy on mortality and transplantation

**FIG. 2.** Absolute number of deaths from liver disease and liver cancer, LTs, and patients taking antiviral agents for HBV from 1999 to 2013.
Is still a risk of liver-related events (cirrhotic complications and HCC) after long-term NA therapy?
• **Viral suppression/eradication in cirrhotics has favorable clinical outcomes**
  (Park, *Ahn SH*. JGH 2014)

1. Better survival (Van der Meer AJ et al. JAMA 2012)
3. Less need for liver transplantation (Van der Meer AJ et al. JAMA 2012)
4. Reduce, **but still be at**, the risk of HCC (*Ahn SH*. Clin Gastroenterol Hepatol. 2016)
Take Home Messages

• There has been progress in reducing mortality resulted from HBV infection, especially with universal HBV vaccination and effective antiviral treatment.

• However, despite declining prevalence in most Asian countries, HBV infection remains the primary cause of cirrhosis and HCC.

• HBV-related HCC is a leading cause of cancer-related death in the Asia-Pacific region. An estimated 70-80% of HCC cases worldwide occur in Asia.

• Incidence and mortality from HCC varies in different countries with different resources, particularly in Eastern Asia and Sub-saharan Africa.

• Despite a slowly decreasing trend in Age-standardized incidence rates (ASIRs) of HCC since 2000, total number of HCC cases has not been changed owing to aging and population growth.
Elimination of Hepatitis B and C by 2030
Establishment of Kwanghyewon (later Chejungwon)

1885

1904

1957

YONSEI University was born

Renamed “SEVERANCE Hospital”

1957

Opening of new SEVERANCE Hospital Building

2005

First JCI Accreditation in Korea Currently the 5th Approval in 2019

2007

Opening of YONSEI Cancer Center

2014

2018

Ranked No.1 in NCSI for 8 consecutive years

National Customer Satisfaction Index

History of Yonsei Univ., SEVERANCE Hospital (The First, The Best in Korea)
Shinchon Campus

CANCER CENTER
CARDIOVASCULAR HOSPITAL
CHILDREN’S HOSPITAL
REHABILITATION HOSPITAL
EYE & ENT HOSPITAL
COLLEGE OF MEDICINE

2,467 Beds
6,622 Employees
2,430,000 Outpatients
779,000 Inpatients
8 Da-Vinci Surgical Robot
APPRECIATE
YOUR KIND ATTENTION!

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