Liver and Stomach Cancer in Korean American
(Town Hall Meeting)

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It is well known that the incidences and mortality rates of stomach cancer and liver cancer in Korean Americans are higher than general U.S. population. In this meeting, there will be 6 expert presentations regarding this topic mainly to confirm these well-known scientific fact. The epidemiologic study performed by Dr. Eunjung Lee using 1988-2012 California Cancer Registry data showed Korean Americans had about 5 times greater incidence of stomach cancer than non-Hispanic whites and twice that of Japanese Americans. The mortality rate of stomach cancer in U.S. is twice as high as that of Koreans living in South Korea. It is quite likely that this difference in stomach cancer mortality rate is due to early detection of the disease through regular screening endoscopies followed by effective treatments, including delicate surgeries with and without adjuvant treatments, in patients living in South Korea.

The incidence and mortality rate for liver cancers in Korean Americans show the similar trends compared to general U.S. population. This implies that we will be able to save many lives of Korean Americans if we adopt similar screening programs to make early diagnoses of these illnesses and implement effect treatments as Koreans living in South Korea. Unfortunately, U.S. government does not recognize the need to screen Korean Americans/Asian Americans for these illnesses to effectively reduce mortalities from these illnesses. Furthermore, the practicing U.S. physicians and Korean-Americans may not be aware of these statistics fully.

The purpose of this Town Hall meeting is to gather opinions from the audience how to avoid unnecessary Korean American death from these illnesses by effectively implementing population screening, early diagnosis and adequate treatments. The Town Hall meeting is open to any constructive and realistic ideas on how effectively promote the physician/community education, research and political campaigns on healthcare disparity in Korean Americans.

The ultimate goal of the meeting is to make U.S. government and Health Insurance Industry to adopt screening strategies for stomach cancers, and liver cancers in high risk Asian immigrant populations such as Korean Americans. The established practice of lung cancer screening in the US provides a precedent for targeted screening of asymptomatic high risk population to effectively decrease mortality rate in the selected population. I think it is timely to consider insurance coverage for stomach cancer and liver cancer screening for high-risk populations such

as Korean Americans and other high risk Asian Americans. The Town Hall meeting will welcome any suggestions toward achieving this goal.

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Persistent Risk for Hepatocellular carcinoma in patients with successful viral replication with anti-HBV therapy: A need for HBV cure.

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During the past 20 years, with the antiviral drugs, mainly the nucleos(t)ide analogues, for Hepatitis B virus (HBV), we have witnessed successful viral suppression as well as the delay and prevention of progressive liver disease leading to cirrhosis and hepatocellular carcinoma (HCC). Reduced incidence of HCC with antiviral treatment has been well documented with lamivudine, entecavir and tenofovir

Prevention of recurrent HCC was reported by numerous investigators following initial tumor ablation when patients received combined antiviral treatment.

However, we are observing a persistent risk for HCC in patients who have maintained successful suppression of viral replication with undetectable serum HBV DNA and normal liver function. The longest duration of treatment was 18 years before the HCC was detected.

In addition, among patients who are on antiviral therapy and post first tumor ablation, some developed subsequent new HCC or recurrent HCC several years after the first HCC. Continued antiviral therapy and additional tumor ablation have been successful.

The persistent risk for new and recurrent HCC among patients with successful control of HBV is attributed to the incomplete control of HBV, namely due to the presence of cccDNA in the host's hepatocytes. While we are able to achieve a functional cure, a complete cure that is able to eliminate the cccDNA has not yet been possible. Therefore, even though HBV is not actively replicating, cccDNA remains in the nucleus of the hepatocytes and continues hepatocarcinogenic processes including HBV and host DNA integration.

There is a need for the drugs that can eradicate the virus. Due to the complexity of HBV replication, It has not been easy, potential strategies include preventing the entry of the virus by blocking the receptor of hepatocytes, preventing the replication of new HBV DNA from the pregenomic RNA (successful with currently available nucleos(t)ide analogues), enhancing the host innate immunity (such as small molecule agonists of toll-like receptors), developing a therapeutic vaccine engineered to activate an HBV-specific T cell immune response, and directly targeting cccDNA, in addition to other strategies. Recent development of potential HBV cure drugs was recently presented by Levrero et al. and Block et al.

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Epidemiology and Immunopathology of Chronic Hepatitis B and Liver Cancer

Richard S. Hann, M.D.

During the past decades, the influx of immigrants from hepatitis B virus (HBV) endemic regions has brought significant changes in the prevalence of chronic hepatitis B and liver cancer in the United States.

The prevalence of HBV carriers in the general U.S. population was 0.2% while that of Asian Americans was reported to be 5-15% in 1994 and 10.5% in 2004. It has been well documented that chronic infection with HBV leads to chronic hepatitis B, liver cirrhosis and hepatocellular carcinoma (HCC).

In Asia, the primary mode of transmission of HBV is perinatal infection of infants born to the infected mothers, and the majority of chronic hepatitis B carriers in Asia were infected either at birth or during early childhood.

As of 2000, Asian Americans constitute 4.2% of the U.S. population. Even though Asian Americans represent less than 5% of the total population, they contribute significantly higher carrier rates, causing a major public health problems.

As of 2017, we have screened over 30,000 Korean Americans and detected about 3,000 carriers of HBV, The great majority of these carriers has been followed up at the Thomas Jefferson University Hospital in Philadelphia by Dr. Hie-Won Hann.

As shown in our survey, primary HBV infection in susceptible host can be either symptomatic or asymptomatic. The latter is more common than the former, especially in young subjects.

HBV carriers with persistent HBV infection may be symptomatic or asymptomatic. This group is classified as having chronic hepatitis B. Cirrhosis develops in about 20% of this group. The resulting hepatic insufficiency and portal hypertension would ensue.

In persistent HBV infection, HBsAg remains in the blood and virus production continues. However, levels of viremia are generally lower than during primary infection. High titers of HBV in the blood are often indicated by the continued presence of HBeAg.

At least 70 to 85% of subjects with anti-HBe antibodies have detectable viral DNA in the circulation, in the range of 10^3 to 10^5 molecules per milliliter, and sometimes higher, which is significant amount. Considering the short half-life of HBV virions (approx. one day), such levels can be sustained only by ongoing viral replication. Therefore, anyone who has a positive test for HBsAg should be presumed to have significant level of ongoing viral replication, the notion which might have implications on the possible carcinogenesis in those subjects with low antibody titers.

In 1965, Baruch Blumberg et al. identified an antigen in the serum from patients with leukemia, leprosy, and hepatitis, and named it Australia Antigen (Au). In 1968, Alfred Prince et al. established that Australia Antigen is identical with serum hepatitis antigen. The antigen thus identified is called hepatitis B surface antigen (HBsAg).

These findings led to the discovery of hepatitis B virus, which is double stranded DNA virus of 40-42 nm in diameter with an outer lipoprotein envelope which contains three envelope glycoproteins (or surface antigens). Within the envelope is the viral nucleocapsid, or core. The core contains the viral genome, a covalently closed circular DNA (cccDNA), and a polymerase.

The HBV genome has 4 long open reading frames. The preS-S region encodes the 3 surface antigens. They are the most abundant proteins, S antigen (HBsAg), the L protein (preS1) and M protein (preS2).

The PreC-C region encodes hepatitis B core antigen (HBcAg) and hepatitis B e antigen (HBeAg). The P coding region is specific for the viral polymerase, which is involved in DNA synthesis and RNA encapsidation.

The X open reading frame encodes the viral X protein (HBx) which modulates host-cell signal transduction and can affect host and viral gene expression.

The pathogenesis of hepatitis is not completely elucidated. However, it is now thought that host immune responses to viral antigens displayed on the infected hepatocytes are the principal determinants of hepatocellular damage. The immune response involve both major-histocompatibility complex (MHC) class II-restricted CD4 helper T cells and MHC class I-restricted CD8 cytotoxic T lymphocytes.

In addition, much of the injury is due to secondary antigen-nonspecific inflammatory responses that are set in motion by the response of the cytotoxic T lymphocytes. The cytotoxic by-products (cytokines) that render much of the damage are tumor necrosis factor (TNF), interferon ɣ (IFN-ɣ), free radicals, and notably proteases.

Chronic hepatitis B increased the risk of developing HCC by 100 times higher than the non-carrier. The higher the viral DNA in the circulation, the higher the risk of HCC. And those subjects with cirrhosis show also higher risk. Thus, the chronic carriers of HBV should be monitored very closely by the physicians, which issues will be dealt with by the next speaker.

Chronic hepatitis B in Korean Americans: Poor linkage to care

Hepatitis B virus (HBV) is a leading cause of chronic liver diseases, causing cirrhosis and hepatocellular carcinoma. Approximately 240 million people in the world are chronically infected with HBV, and it is expected that up to quarter of infected persons may develop serious complications of the infection. In the United States alone, about 2 million people are infected with HBV, of whom half are Asian-Americans. As Asians and other minority groups such as Pacific islanders and African immigrants are affected disproportionately, CHB has risen as a serious health disparity issue in the United States. A majority of these infected individuals may not be aware of their infection, and more importantly, those aware of their infections are not accessing care. For instance, it is believed that only 10 % of the individuals in the United States who could benefit from antiviral treatment are currently receiving it.

Numerous barriers can impede healthcare access in the Asian-American population. Language, finance and other socio-cultural factors are all important in determining one's behavior and decision-making with respect to accessing care. In addition, providers and healthcare systems that can accommodate the needs of the community are crucial in delivering adequate care in a culturally and linguistically competent manner in these minority populations. During the past few decades, a number of large-scale community-based hepatitis B initiatives have demonstrated the efficacy of campaigns to reach out to and educate and screen the communities at risk. These community outreach programs can potentially overcome many of the barriers to reduce the large burden of disease, thereby achieving positive outcomes.

Successful hepatitis B LTC in the community setting involves full mobilization of resources, including health care professionals who can provide culturally competent health care. Partnering with community organizations and fostering both medical and non-medical personnel are also essential to developing strategies to tailor community- based HBV screening and improving LTC in high risk populations.

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Epidemiology of Stomach Cancer Disparity in Korean Americans

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Stomach cancer incidence shows substantial racial-ethnic disparity in the United States (US), with Korean Americans experiencing by far the highest incidence. Our group used the 1988-2012 California Cancer Registry data and reported stomach cancer incidence rates by racial-ethnic groups, sex, and tumor characteristics.

Although the stomach cancer incidence rates in Korean Americans were only 40% (for men) and 50% (for women) of the rates in South Korea, Korean Americans had about 5 times greater incidence than non-Hispanic whites and twice that of Japanese Americans. Tumor characteristics with respect to subsite and histology showed difference by ethnicity and sex: the proportion of cardia stomach cancer was highest among non-Hispanic white men and lowest among Korean American men and women, and the intestinal type histology was more frequent among men than in women for all racial-ethnic groups. The stomach cancer incidence in Korean Americans has declined during recent years, for both cardia- and non-cardia sites and for both intestinal- and diffuse-type histology. Korean Americans were diagnosed at an earlier stage than other Californians. However, the proportion with localized disease in Korean Americans (43% in 2006-2012) was much smaller than those in South Korea (57%) and Japan (55%), where population-based screening is available.

The unfavorable stage distribution in Korean Americans compared to South Koreans or Japanese indicate that additional prevention and screening strategies need to be implemented targeting high risk immigrant populations such as Korean Americans. Lung cancer screening in the US provides a precedent for targeted screening of asymptomatic high risk populations. It is timely to consider insurance coverage of stomach cancer screening for high-risk populations such as Korean Americans and other high risk Asian Americans.

Reference article: Lee et al. *Cancer Epidemiol Biomarkers Prev* 2017; 26(4):587.

We intellectual leadership together has the obligation to reduce the unacceptably high rate of stomach cancer deaths in Korean Americans.

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The biostatistics on stomach cancer survivals (5-year survival, or the chance of living 5 years after diagnosis) released yearly for the past ~10 years by the governments of the US and Korea respectively have steadily shown that it is ~30% in the US and ~70% in Korea, with the survival in Japan practically as good as that in Korea. In other words, the most patients with stomach cancer die in the US, while the most survive in Korea and Japan. However, the stomach cancer is very rare in the US overall with it not included in fourteen most common cancers in the US, and the US overall effort or attention toward stomach cancer is generally poor understandably; but it is one of the most common lethal cancers in Korea with it being at the top of the list for male population with female population not much lagging behind.

Now, what about us Korean Americans: We are not Koreans in Korea, neither mainstream Americans in the US. The problem is this; the chance of acquiring stomach cancer is as high as Koreans in Korea unlike main stream Americans, but the chance of dying of stomach cancer once acquired is as high as main stream Americans unlike Koreans in Korea. The reason for Koreans in Korea surviving better than Koreans in the US is that the most adults in Korea over age of 40 (now approaching 70%) is undergoing stomach endoscopy (esophago-gastro-duodenoscopy, or EGD) every 1-2 years without any stomach symptom (screening endoscopy) mandated by Korean government at nominal cost, while almost none in the US. This screening stomach endoscopy allows early detection of stomach cancer while it is curable. If stomach endoscopy is performed after there already is symptom from stomach cancer (diagnostic endoscopy), it is already too late to cure in most cases leading to deaths. The most recent statistics this year shows that EGD q 2 years has cut down stomach cancer deaths by 81%.

There are two barriers for us to break here. Our US government insurance system (Center for Medicare and Medicaid Services, CMS) currently does not cover screening stomach endoscopy, and it will costs average $3,500 out-of-pocket, and we need to have them cover it (just like screening mammogram which currently is covered). We also need to enlighten Korean American population to seek the screening stomach endoscopy.

NIH Funding Opportunities for Research on Minority Health and Health Disparities

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Abstract:

The National Institutes of Health (NIH) define:

- "Minority Health" as distinctive health characteristics and attributes of the minority racial and/or ethnic groups in the U.S.; and
- "Health Disparity" as a health difference that adversely affects disadvantaged populations, based on one or more of the health outcomes.

Health disparity populations include racial/ethnic minorities (African American or Black, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Latino or Hispanic), low socioeconomic status (SES), sexual and gender minorities, underserved rural populations, and/or others subject to discrimination who have poorer health outcomes attributed to being socially disadvantaged.

Over 80% of the NIH budget is used to fund projects carried out by the extramural research community. In fiscal year 2017, the NIH made awards with approximately $3.2 billion (9% of the NIH's total budget) and $300 million for supporting research on health disparities and chronic liver disease & cirrhosis, respectively. During this presentation, the following information will be provided and discussed:

- NIH extramural research funding mechanisms;
- Funding Opportunity Announcements and Notices;
- NIH grant application, peer review, and award process;
- RePORT: A searchable database of the NIH-funded biomedical research projects;
- NIH funding opportunities for research on minority health and health disparities; and
- Useful web links to the NIH Office of Extramural Research.

Gastric and Liver Cancer - Current State of Care in Korea

Yang, Jong In

Data about gastric and liver cancer in Korea may contribute to the care of Korean American patients because racial disparities may exist in cancer incidence, mortality, and therapeutic responses. Gastric cancer was the most commonly diagnosed cancer and the fourth cause of cancer deaths, and liver cancer was the sixth commonly diagnosed cancer and the second cause of cancer deaths in Korea in 2015. It may be fortunate that there exist efficient screening methods for these two clinically significant cancers in Korea. Gastric cancer can be screened by upper endoscopy or upper gastrointestinal series, and liver cancer can be screened by abdominal ultrasonography. Korean National Cancer Screening Program has provided screening for gastric cancer in individuals 40 years and older by biennial using upper endoscopy or upper gastrointestinal series since 1999. Korean National Cancer Screening Program has also provided liver cancer surveillance in high risk subjects with liver cirrhosis or chronic viral hepatitis by checking abdominal US and serum alphafetoprotein level every six months since 2016. I will summarize and present recent data about screening and care of gastric and liver cancer in Korea.