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TOPIC HIGHLIGHT

2015 Advances in Hepatitis B Virus

Hepatitis B among Asian Americans: Prevalence, progress, and prospects for control

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Abstract

After tobacco use, chronic hepatitis B (CHB) viral infections are the most important cause of cancer globally in that 1 out of 3 individuals have been infected with the hepatitis B virus (HBV). Though infection rates are low (< 1%) in the United States, Asian Americans who comprise about 6% of the population experience about 60% of the CHB burden. This paper reviews the magnitude of hepatitis B (HBV) burden among Asian Americans and the progress being made to mitigate this burden, primarily through localized, community-based efforts to increase screening and vaccination among Asian American children, adolescents, and adults. This review brings to light that despite the numerous community-based screening efforts, a vast majority of Asian Americans have not been screened and that vaccination efforts, particularly for adults, are sub-optimal. Greater efforts to integrate screenings by providers within existing healthcare systems are urged. Evidence-based strategies are offered to implement CDC's three major recommendations to control and prevent hepatitis B through targeted screening and enhanced vaccination efforts.

Key words: Hepatitis B; Asian Americans; Chronic hepatitis B; Vaccination

Core tip: Hepatitis B viral infections disproportionately affect Asian Americans. Untreated, hepatitis B viral infections can lead to hepatocellular carcinoma that is almost universally fatal. Unfortunately, a vast majority of Asian Americans have not been screened. To reduce the HBV burden, screening both in community and clinical settings must be accelerated; and both physicians and patients must see the need for testing. Based on test results, those who screen positive must be referred to appropriate care and those without

natural immunity, recommended for vaccination.

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INTRODUCTION

Worldwide, two billion people (1 in 3) have been infected with the hepatitis B virus (HBV), making HBV one of the most common and serious infections in the world[1]. Based on this magnitude, the HBV, in its chronic form leading to hepatocellular carcinoma (HCC), are the most important cause of cancer globally after tobacco use[2]. Unless detected and treated early, HBV-induced HCC is a highly fatal form of primary liver cancer[3-6]. More than 75% of liver cancers are attributed to HBV infections[7,8], and of the 40 million individuals chronically infected with HBV, unless medical intervention occurs, 15% to 25% will progress to HCC[9]. Although the overall prevalence of chronic HBV (CHB) infection is low in the United States (< 1%), increasing immigration from hepatitis B endemic areas (where the hepatitis B surface antigen prevalence is ⩾ 2%), such as East Asia, Pacific Islands, and parts of Africa and Eastern Europe[10], have led to rising health disparities among these groups, with immigrants now having the same risk of CHB as their country of birth[5,11,12].

In the United States, Americans of Asian ancestry (otherwise known as Asian Americans), comprise less than 6% of the United States population, however, represent the highest and most disproportionate (approximately 58%)[6], burden for HBV-linked HCC[6,13-17]. Per 100000, Asian Americans experience the highest incidence for cancers of the liver and intrahepatic bile (male: 21.2 *vs* 8.9 for Whites; female: 8.0 *vs* 3.0 White) and mortality rates (male: 14.5 *vs* 7.3 for Whites; female: 6.0 *vs* 3.0 for Whites)[17]. Most dramatically, the hepatitis B seroprevalence rate among foreign-born Asian/Pacific Islander women of childbearing ages was 8.9% compared to 0.08% for non-Hispanic White mothers for a disparity rate of 110:1[18]. Since 2000, Asian Americans experienced a 51% increase in population, the highest growth rate of any racial/ethnic group[19]. By the year 2050 there will be 33.4 million Asian Americans living in the country representing a 213% population increase compared to a 49% increase for the rest of the Nation[20]. At the same time, the highest increases in liver cancer cases in the United States are expected among Hispanics, Asians, and Pacific Islanders[21]. Thus, addressing liver cancer is a very relevant and significant arena for impacting cancer health disparities with great importance for the United States population. To set the context for this paper, we first present important and relevant characteristics of Asian American populations based on the United States Census data.

According to the Office of Budget Management, "Asian" refers to "a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, South Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam"[22]. This categorization represents at least 32 subgroups and over 100 spoken languages and dialects[23]. Asian Americans are the fastest growing racial group (between 2000 and 2010 the Asian populations experienced a 46% increase) and it is estimated that in 2013, 19.4 million Asian Americans resided in the United States[24]. In terms of demographics, Asian Americans are the only racial population in the United States with a bimodal distribution for major demographic risk factors related to health outcomes: education, income, insurance status, and age[25]. While the median household income for all Asian Americans is $72472; across ethnic groups, the median income ranges from $48249 for Hmong Americans to $98562 for Asian Indians. The median age for Asian Americans is 36.3 and that ranges from 22.2 years of age for Hmong Americans to 49.1 years of age for Japanese Americans. The poverty rate for the Asian alone category is 12.7%, and is as low as 8% for Japanese Americans to as high as 26.3% for Hmong Americans. As an aggregate, 14.6% of Asian Americans do not have health insurance, with 24.2% of Korean Americans and 6.9% of Japanese Americans living without coverage. In terms of education, 86.2% of Asian Americans have their high school diploma (compared to 86.4% of the United States population); however that number ranges from 64.8% for Cambodian Americans to 95.1% for Japanese Americans[26]. These stark and alarming differences between the Asian groups are masked by the aggregated data; for Asian Americans these differences create devastating disparities in cancer outcome. Asian Americans have one of the lowest cancer screening rates[27] and are the least represented ethnic population in cancer control research studies and targeted intervention programs by the United States Federal government[28].

LITERATURE RESEARCH

The objectives of this review are to: (1) focus on the six Asian American populations with the largest numbers who may be chronically infected with HBV (see Table 1 below)[6], *i.e.*, those of Cambodian, Chinese, Filipino, Hmong/Laotian, Korean, Vietnamese ancestry and the limitations of these data based on PubMed papers published since 2000; (2) highlight the progress to reduce the burden of HBV among Asian Americans;

Table 1 Chronic hepatitis B prevalence rate of foreign-born with chronic hepatitis B living in the United States for selected Asian Countries[6]

Country	Chronic hepatitis B prevalence rate (%)
Laos (home to the Hmong)	13.61
Vietnam	12.48
China	12.25
Cambodia	10.27
Philippines	7.36
Thailand (home to the Hmong)	5.97
South Korea	5.26

and (3) recommend public health-oriented measures for mitigating the HBV burden among Asian Americans. For the first objective, we conducted PubMed searches in April 2015 for "Hepatitis B prevalence among Asian Americans" supplemented by papers that the authors were aware of. For the second objective, we chose to focus on progress exemplified by: (1) Federally-funded, randomized controlled, community-based interventions to increase HBV screenings and those listed on ClinicalTrials.gov; (2) results of increasing HBV vaccination efforts in PubMed-retrieved publications from 2001-April 2015; and (3) linkage to care for HBV-infected Asian Americans. For (2) and (3) we conducted PubMed searches for "Increasing HBV vaccinations among Asian Americans" and "Linkage to care for HBV positive Asian Americans", and supplemented the results with articles that the authors were aware of. The two activities of increasing HBV vaccinations and linkage to care for HBV positive patients are in accordance with the latest American Association for the Study of Liver Diseases guidelines for HBV[28,29] and the CDC's recommendations[10,30,31]. In addition, increasing serological testing for HBV aligns with the 2014 United States Preventive Services Task Force grade "B" guidelines[32]. The decision of limiting this review to Federally-funded, randomized controlled, community-based interventions to increase HBV screenings and those listed in ClinicalTrials.gov was based on the premise that randomized, controlled trials represent greater scientific rigor than one-time health fair-type screenings or uncontrolled or quasi-experimentally conducted interventions. Likewise, we limited our focus on progress for documenting increased HBV vaccinations and linkage to care for HBV positive Asian Americans to PubMed retrievable peer-reviewed papers. For the third objective, we used the Centers for Disease Control and Prevention's Recommendations for Public Health Management of Persons with Chronic HBV infection and Strategy for the Elimination of Hepatitis B Transmission[10] and the recommendations of the Advisory Committee on Immunization Practices[30,31] as the framework for compiling empirically-derived findings that have demonstrated impact on reducing the HBV burden.

RESULTS

HBV prevalence among Asian Americans

The National Health and Nutrition Examination Survey (NHANES), the only source of nationally representative hepatitis B seroprevalence data for the United States[33], has acknowledged limitations of under-representation of Asian Americans and the lack of nativity data in their survey which are critical to identify at-risk populations[11]. At press time, the report from the 2011-12 NHANES survey that intentionally over-sampled Asian Americans had not been released**.** Meanwhile, to address these data deficiencies, various investigators have taken different approaches to determine HBV prevalence among Asian Americans on a national and community basis.

On a national basis, Kowdley *et al*[6] used CHB rates from countries of origin and United States Census data of distinct population groups by national origin to determine rates. Their findings indicated that of the 1.32 million people living with CHB, 58% (about 765000 individuals) migrated from Asia. Similarly, on a national basis, Mitchell *et al*[5] estimated that during 1974-2008 there were about 1.3 million new cases of chronic HBV infection imported into the United States. The largest number of imported CHB cases came from the Philippines, China, and Vietnam, who together accounted for 37% of the total imported CHB cases during this period. The only published composite report based on accumulating data from 31 community-based efforts in various parts of the United States indicated that over 21817 people have been screened annually with an average hepatitis B surface antigen rate of 8.1%[34].

At the community level, the numbers of publications that report on HBV screenings in PubMed are now in the triple digits and is increasing monthly. By using the search term, "hepatitis B AND Asian Americans", 175 articles were identified in April 2015. These screenings were open to all and hence reflect convenience samples resulting in varying numbers of individuals screened for HBV and with HBV positivity rates reported either by ethnic group or as an aggregated Asian American group. Typically more female than male participated and there were generally higher HBV positivity rates among males. Despite limitations in generalizability by ethnicity, in later funded studies, CDC concluded that the 9 community sites could appropriately identify CHB individuals from high HBV prevalence populations and refer them to care; they highlighted the findings from three of those sites[35]. Reflecting on the composite 6.6% hepatitis B surface antigen (HBsAg) positivity rate for those three sites, our own "Thousand Asian American Study" (that was not among the three reported in the MMWR article) resulted in a similar overall HBV positivity rate of 6.5%.

However, by dis-aggregation by ethnicity and gender, Hmong and Vietnamese men had considerably higher rates, 14.3% and 13.6% respectively, signifying the importance of interpreting dis-aggregated rates[36]. Having dis-aggregated data by ethnicity and gender allows us to target our screening and HBV prevention and control efforts more precisely as these efforts require linguistically appropriate and culturally-specific approaches.

Progress being made

In addition to the localized HBV prevalence rates gathered through community-based efforts, NIH-funded investigators have elucidated theoretically-based and culturally appropriate interventions that have empirically guided measures to promote hepatitis B testing in Cambodian, Hmong, Korean, and Vietnamese[37-40]. These investigators offer principles that have guided community-centered screening interventions.

From the three NIH-funded randomized controlled community-centered interventions that have been published, we documented that bilingual/bicultural Cambodian ($P < 0.001$)[41], Hmong ($P < 0.0056$)[42], and Korean ($P < 0.001$) lay health educators[43] are effective in increasing HBV serological testing rates in community settings, however, the physician's role in influencing serological testing within the context of a healthcare system appears to be far more efficient and desired[42,44]. Undoubtedly, community-based HBV screenings reach many who might not otherwise be reached; however, validating receipt of HBV screening results and follow up of care can be challenging due to a lack of health insurance and the administrative burden of reviewing paper medical charts from a mosaic of healthcare providers[42,43,45]. This is in contrast to the efficiency and effectiveness of electronic health records as a means of identifying those needing to be tested and follow-up of test results which also achieved statistically significant screening and testing in a randomized, controlled study[46]. Leveraging electronic medical records systems to determine whether HBsAg have been completed coupled with an algorithm that selects for typical Asian surnames as surrogate markers of nativity in intermediate to high HBsAg regions represent perhaps more efficient means of targeted screening. However both approaches: "out-reach" (clinical) through community-centered efforts and "in-reach" (nonclinical) are needed[47].

Among the more sophisticated and controlled studies to evaluate screening interventions are studies registered on the National Library of Medicine operated website, ClinicalTrials.gov: *e.g.*, "Community-based Hepatitis B interventions for Hmong adults" and "Increasing Hepatitis B screening among Korean church attendees" that have reported their results[42,43]. The third study, "Patient-Centered Care and Asian Americans" is currently in progress and through a randomized, controlled trial will evaluate a mobile app plus a physician panel notification (intervention) compared to a physician panel notification only (control), in increasing hepatitis B and C testing among Asian Americans[48].

Information on HBV vaccination efforts among Asian Americans in PubMed retrieved literature is sparse. Out of the 7 articles retrieved using the search term, "Increasing HBV vaccinations for Asian Americans", none reported actual numbers of vaccinations but rather referred to vaccinations in the context of preventing HBV infections. Substantial progress due to vaccinations can be inferred through the 68% decline in HBV infection prevalence among United States children (which includes both United States born[49] and foreign-born Asian children). Among United States adolescents as a whole, the HBV vaccination rate is at 93.2% but is slightly lower among Asian teens (87.8%)[50] and so there is room for improvement. However, the greatest need is the high CHB rates among adults[36]. Screening efforts were sub-optimal (under 50%) even among Asian primary care providers who realize the significance of HBV and vaccination levels for their adult Asian patients[51].

Thus, progress in preventing and controlling HBV among must transcend screening to HBV vaccinations where appropriate and linkage to care as needed. Among the CDC-funded screening to linkage to care grantees, referral to care ranged from 56%[47] to 86%[35] to 92%[36]. These percentages exceed the estimated national baseline of about 40%[4] or approximately 33% among Racial and Ethnic Approaches to Community Health communities[52]. More work will be needed in this arena.

DISCUSSION

In the United States, deaths due to cancers of the liver and intrahepatic bile duct lead all organ sites in terms of annual percent change (3.6% for males and 2.9% for females) while deaths for cancers as a whole dropped by 1.4% and 0.2% for males and females respectively. At the same time, cancers of the liver and intrahepatic bile duct also experienced a considerably lower five-year survival rates (18%) compared to all sites (68%)[17]. Liver cancer mortality rates lead all other organ sites in the cumulative increases in cancer deaths (50.28% among men and 28.83% among women)[13]. Liver cancer mortality rates have continued to increase with age in all racial/ethnic groups between 2006 to 2010[14]. While multiple conditions contribute to these increases in mortality including Hepatitis C viral infections[53], high body mass index[54], diabetes[55], liver cancer, and in particular, CHB for Asian Americans[56], HCC is a cancer with an extremely dismal survival rate, especially for Asian Americans[29,57]. Thus, the importance of focusing on mitigating the HBV-HCC burden among Asian

Table 2 Recommendations to mitigate the hepatitis B virus burden among Asian Americans

CDC's recommendations	Evidence-based strategies
1.Screen persons born in areas with ≥ 2% hepatitis B surface antigen (HBsAg) rates[10]	a.Ask persons which country they were born b.Encourage providers to recommend HBsAg testing for their at-risk Asian American patients c.Educate and encourage patients to ask their providers whether they should be tested for HBsAg[44] d.Use typical Asian names from EHRs to determine if they have been tested for HBsAg and then to screen them at the next opportunity[46] e.Collaborate with Asian American-serving organizations to hold screening events[36]
2.Vaccinate Asian American infants and children[30]	a.Verify that hospitals and birthing facilities are providing birth dose vaccinations b.If not vaccinated at birth, vaccinate. Note that in many states, verification of hepatitis B virus (HBV) vaccinations may be a requisite for school enrollment
3.Vaccinate Asian American adults. Note: serologically test for HBsAg first and after test results are known, determine if vaccination is appropriate[31]	a.Consider follow up vaccination programs for adults after serological testing for HBV for those who need vaccination[36]

Americans cannot be discounted while the under-resourced efforts cannot be denied[58].

Mitigating the progression to HCC through earlier detection and preventing CHB infections and appropriate medical management of CHB for infected individuals is the recommended pathway to eliminating these disparities and carries with it the possibility of being a health disparity that could be eliminated[59,60]. The 2014 designation by the United States Preventive Services Task Force of a grade of "B"[32], plus the evidence for the cost-effectiveness of screening, particularly in outpatient settings[29,57] are factors that support HBV screening and referral to treatment[61,62]. Unfortunately, because CHB is typically asymptomatic, testing is infrequent and 65% of infected Americans are unaware of their HBV status[30,31]. Even in the Chronic Hepatitis Cohort Study of 1.2 million people with access to care, only 18.8% were tested for HBV[32]; our results were similar, 17.3%-18.5%[46]. In addition, of those diagnosed with CHB, only about 40% are referred and linked to care[4], an inadequate number of providers are trained in appropriate care, and few patients are referred to appropriate care[12,63,64].

CONCLUSION

After tobacco use, chronic hepatitis B viral infections are the most important cause of cancer in the world. While Asian Americans only comprise 6% of the United States population, they bear almost 60% of that burden and the disparity rate is 110:1 for the HBV seroprevalence rate among foreign-born Asian American women of childbearing ages compared to non-Hispanic White mothers. Based on calculations of CHB rates from countries of origin and United States census data, the numbers of Americans of Asian ancestry with chronic hepatitis B is approaching a million. Unfortunately, less than 50% of at-risk Asian Americans know their HBV status and/or have been serologically tested and while the vaccination rates for Asian American children and adolescents are higher, vaccinations for Asian American adults are sub-optimal.

Based on this review, the authors suggest the following strategies that align with the three principal CDC recommendations as they relate to mitigating the HBV burden among Asian Americans (Table 2).

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