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Cancer epidemiology in Hispanic populations: what have we learned and where do we need to make progress?

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Abstract

The Hispanic/Latino(x) population (H/Ls) in the United States of America is heterogenous and fast-growing. Cancer is the number one cause of death among H/Ls, accounting for 21% of deaths. Whereas for the most common cancers incidence rates are lower in H/Ls compared with non-H/L White (NHW) individuals, H/Ls have a higher incidence of liver, stomach, cervical, penile and gallbladder cancers. H/L patients tend to be diagnosed at more advanced stages for breast, colorectal, prostate and lung cancers, and melanoma compared to NHW individuals. Etiological and cancer outcomes research among H/Ls lags other populations. In this review, we provide a summary of challenges, opportunities and research priorities related to cancer etiology, cancer outcomes, and survivorship to make progress in addressing scientific gaps. Briefly, we prioritize the need for more research on determinants of obesity, non-alcoholic fatty liver disease and its progression to liver cancer, stomach and gallbladder cancer, and pediatric acute lymphoblastic leukemia. We emphasize the need to improve cancer screening, early detection of cancer, and survivorship care. We highlight critical resources needed to make progress in cancer epidemiological studies among H/L populations, including the importance of training the next generation of cancer epidemiologists conducting research in H/Ls.

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THE DEMOGRAPHIC LANDSCAPE OF HISPANIC/LATINO(X) (H/L) POPULATIONS

Numbering more than 62.1 million in 2020, the Hispanic/Latino(x) population represents 18.7% of the total United States of America (USA) population, having increased 20% since 2000 (1). Terminology applied to this population varies, largely due to USA regional variability, political and historical reasons, and generations. More recently, the term Latinx has emerged as a gender-neutral adjective, as an alternative to gendered nouns in Spanish. However, only 3% of Hispanic/Latino(x) use it, and it has been adopted largely among those who are younger, USA born, and college educated (2). For this review, we use the term Hispanic/Latino(x) to be as inclusive as possible. To avoid repetition, we simplify the use by referring to a Hispanic/Latino(x) individual in the USA as H/L and Hispanic/Latino(x) population groups as H/Ls.

Across the USA the proportion of H/Ls vary substantially, with New Mexico (49.3% of state population), Texas (39.7%), California (39.4%), Arizona (31.7%), and Florida (26.4%) having the highest proportions. However, the H/L population is fast growing, and there are several other areas in the country where the H/L population is increasing at rapid pace. An example is North Carolina where the H/L population is growing at a faster rate than the population nationwide, with ~40% of H/Ls being foreign-born.

Although H/Ls are the youngest of racial/ethnic groups nationally, their median age has increased from 27 in 2010 to 30 in 2019 (3). This is also a dynamic population in terms of demographic changes over time, reflecting concomitant declines in immigration from Central America, but increases from Puerto Rico post 2017 hurricanes, especially to Florida (3,4).

The H/L population is highly heterogeneous, descending from generations of admixing of Indigenous Latin American, European and African populations, with various degrees of admixture across Latin America, and further admixing after immigration to the USA. Among USA H/L groups, Mexican Americans are the largest, at 61.4%, followed by Central Americans (9.8%), Puerto Ricans (9.6%), South Americans (6.4%), and Cubans (3.9%)(5). There are substantial sociodemographic differences across groups (6). For example, among Mexican H/Ls, 31% are foreign-born, compared to 56% of Cubans, 50-60% of Central American H/Ls, and 60% of South American H/Ls. A higher proportion of Mexicans (20%), Puerto Ricans (23%), and Guatemalans (24%) H/Ls are living in poverty relative to Argentines (9%) and Peruvians (11%). About 10-12% of Guatemalans, Salvadorans, Hondurans, and Mexicans H/Ls have a college education, compared to 43% of Argentines and 55% of Venezuelans H/Ls. More than one-third of Guatemalans and Honduran H/Ls do not have health insurance, relative to 8% of Puerto Ricans. More than 70% of Mexicans, Argentines, Puerto Ricans, and Panamanians H/Ls are English proficient, whereas this is the case for less than half of Guatemalans and Honduran H/Ls. Mexicans and Guatemalan H/Ls are the youngest with median age of 27-28 years, while Argentines and Cuban H/Ls are the oldest with a median age of 39-40. These sociodemographic characteristics have vast implications for heterogeneity in cancer patterning across H/L populations (6).

THE CANCER BURDEN AMONG H/Ls

Cancer is the leading cause of death among H/Ls, representing 21% of all deaths (7). In 2021, there are approximately 176,600 new cancer cases projected to occur among H/Ls, and 46,500 cancer-related deaths are estimated, with age-adjusted incidence rates for 2014-2019 of 339.2/100,000 among women and 370.2/100,000 among men, and age-adjusted mortality rates for this same period of 132.2/100,000 for women and 93.9/100,000 for men (7). Overall, cancer incidence rates among H/L men have been decreasing in the past two decades, whereas rates among women have been increasing, like the non-H/L White (NHW) population. Overall, cancer mortality rates have declined at similar rates as in the NHW populations. For the most common cancers (e.g., lung, breast, colorectal, and prostate cancers), incidence rates are lower in H/Ls compared with NHW individuals, whereas they have higher rates for liver, stomach, cervical, penile and gallbladder cancers (7,8). In spite of their lower incidence rates for the most frequently occurring cancers, H/L patients tend to be diagnosed at more advanced stages for breast, colorectal, prostate, lung, and melanoma cancers (7).

Studies that considered genetic ancestry and/or country of origin of H/L populations show that the risk of cancer differs depending on ancestral origins. For example, H/L women with higher European ancestry have higher risk of breast cancer (9), and those with higher African ancestry have higher risk of developing rectal tumors (10). Additional disparities have been documented by nativity, with USA born H/L individuals having higher incidence and worse survival for breast, colorectal, prostate, lung, and liver cancers, than foreign born H/L individuals (11). Puerto Ricans who reside on the island have higher incidence of prostate cancer compared to those on mainland USA (7). Moreover, differences in incidence rates have been reported by country or region of origin for selected cancers, with Puerto Ricans and Cubans experiencing higher overall cancer incidence rates than Mexicans or Central Americans (11,12). These differences across H/Ls groups may result from variation in genetic ancestry, variation in health behaviors (e.g., cancer screening) and lifestyle-related factors (e.g., obesity, sedentary life, chronic diseases, unhealthy diets), among yet-to-be identified determinants. Among H/Ls, higher socioeconomic status is associated with higher risk of breast, lung, colorectal and prostate cancers, a pattern less pronounced among NHW for breast and prostate cancer, and opposite for NHW with colorectal and lung cancer (13).

Summary of high burden cancers among H/Ls

Liver and intrahepatic bile duct cancer is the second most common cancer in H/Ls, and third cause of cancer death (7). It is almost twice as common among H/L than NHW populations. Overall, Puerto Rican H/L men experience higher liver cancer incidence rates than Mexican H/Ls (12), however, Puerto Ricans living on the mainland have higher rates than those living on the island (14). USA born H/L men have higher liver cancer incidence rates than foreign born H/L men (15,16). Critically, H/Ls in the USA show an increasing trend of liver cancer incidence (17,18) and higher liver cancer mortality rates compared to NHW populations (7). Given the poor survival for this cancer, <20% after 5 years from diagnosis, the impact of liver cancer in the H/L community is of great public health importance (7). The most well established risk factors among H/Ls are hepatitis C virus

(HCV), diabetes (15), chronic hepatitis B infection (HBV), obesity, alcohol and smoking, and the emerging role of non-alcoholic fatty liver disease (NAFLD) and its progression to non-alcoholic steatohepatitis (NASH) (11,19). Compared to other racial/ethnic groups, H/Ls show the highest prevalence of NAFLD (20,21), and are more likely to have NASH when diagnosed with liver cancer (22).

Stomach cancer incidence among H/Ls is 70% higher than among NHWs, with H/L women having greater incidence than men (7). Currently, it is the 6th and 9th most common cause of cancer death among H/L men and women, respectively (7). H/Ls have a greater proportion of late diagnoses than NHWs, and H/L women have lower 5-year survival rate than NHW women (7). Importantly, H/Ls have a greater proportion of younger diagnoses compared to all other racial/ethnic groups, and incidence rates are increasing among young adults (23). Mortality rates for this cancer have been reported to differ by origin, with individuals from Puerto Rico and Mexico having the highest mortality rates, followed by Central and South American H/Ls, while Cuban H/Ls have the lowest rates (24). Cancers that occur in the antrum and body of the stomach are likely due to infection with *Helicobacter pylori* (*H. pylori*). Cancers that occur in the cardia have been linked to obesity and gastroesophageal reflux. Additional risk factors that may play a role in both cancer localizations include smoking, diets high in processed meats and other salt-preserved foods, alcohol, diets high in meats, meats and fish cooked at high temperatures, and low consumption of fruits (25,26). There is no universal screening for stomach cancer, and individuals with symptoms are typically tested for *H. pylori* and may receive an endoscopy. Whereas the prevalence of *H. pylori* testing was reported to be higher among H/Ls with conditions related to stomach cancer, compared to other racial/ethnic groups, the use of endoscopy was the lowest, which may explain the finding that H/Ls show the lowest proportion of localized cancer diagnoses (27).

Cervical cancer among H/L women is 40% more common than among NHW women, and they also have mortality rates that are 26% higher than NHW women (7). This cancer is caused by the Human Papilloma Virus (HPV), which is preventable and amenable to screening; furthermore, early lesions are treatable. Thus, public health efforts to increase Pap/HPV screening and HPV vaccination among H/L women (28) are a priority to reduce disparities in preventable cervical cancer deaths.

Gallbladder cancer is a relatively rare cancer but has the highest incidence rate among H/L women and Native American women. In general, the majority of gallbladder cancers are diagnosed at an advanced stage due to lack of symptoms, with a 5-year survival of 23% (7). Putative risk factors include obesity, formation of gallstones, and use of hormone replacement therapy (7).

Childhood and adolescent cancers account for about 2% of all cancers among H/Ls, compared to 0.5% among NHWs (7). The most common five cancers among H/L children ages 0-14 are leukemias, especially acute lymphocytic leukemia, followed by brain tumors, lymphomas, soft-tissue sarcomas, and neuroblastomas. Among adolescents 15-19 years old, the most common five cancers are brain tumors, followed by leukemias, germ cell tumors, lymphomas, and soft-tissue sarcomas. Both leukemias and germ cell tumors have higher

incidence among H/L than among NHW children and adolescents (7). Survival rates for all childhood and adolescent cancers combined are lower in H/Ls than NHW patients, with the greatest disparity observed for brain tumors among children and leukemias among adolescents (7)

CANCER ETIOLOGY AMONG H/Ls: PRIORITIES, CHALLENGES, AND OPPORTUNITIES

Summary of known risk factors

Obesity.—Being overweight or obese increases the risk for at least 14 different types of cancer (29). The prevalence of overweight and obesity varies by education, income, and race/ethnicity. H/Ls have one of the highest rates of excess body weight, with 44.8% of H/L adults being obese, and 60.6% having abdominal obesity, with even higher proportion among H/L women (71%) (30).

Diet Quality.—Established dietary cancer risk factors for the general population include suboptimal intake of vegetables and fruits, and higher intake of processed meats and foods, sugary beverages, and sodium, and diets containing a variety of whole grains, legumes, fish, vegetables, and fruits are associated with reduced cancer risk (29). H/Ls consistently report dietary patterns associated with higher cancer risk (31–34). Furthermore, 22% of H/L households in the USA are food insecure, and food security, defined as the access of all household members to enough food for a healthy life, is directly associated with adherence to 2005 USA Department of Agriculture (USDA) dietary guidelines (35). H/L patients are more likely to be food insecure than NHWs, especially among younger cancer survivors (36,37). Diet quality in the USA has improved over the years, except for H/Ls (38). Moreover, dietary quality was observed to vary considerably across different H/L populations; therefore, interventions should be attentive to cultural differences and preferences by origin and USA region (31,39).

Sedentary lifestyle/Physical Activity.—Physical inactivity is a prevalent lifestyle risk factor for cancer (29). H/Ls were more likely to report lower levels of physical activity (PA) compared to other racial/ethnic groups, with 34.3% of H/L men and 37.2% of H/L women reporting no leisurely PA. H/L men with lower levels of education are more likely to engage in work-related PA, whereas H/L children and women are more likely to face barriers in obtaining recommended amounts of PA due to a lack of access to recreational facilities, fewer parks and safe neighborhoods (40,41).

UV Exposure.—Skin cancer is one of the most common cancers in the USA, with UV radiation being the main risk factor. Whereas the overall melanoma incidence rate is lower in H/Ls compared to NHWs, H/Ls are more likely to be diagnosed with melanoma at advanced stages and have lower survival rates compared to NHWs (42). H/Ls have been reported to have less knowledge about sun protection, and to be less likely to use sunscreen than NHW individuals (43,44).

Infectious agents.—*Helicobacter pylori* (*H. pylori*) is associated with 31.2% of stomach cancers. About 35.6% of the USA population is infected with *H. pylori* (45,46), with prevalence being significantly higher among H/Ls, in particular Mexican Americans, (64%), compared to NHW individuals (21%). H/Ls with higher BMIs and lower incomes have significantly higher risk of infection (47). *H. pylori* infection is predominantly high among foreign born H/Ls, reflecting higher *H. pylori* prevalence in their countries of origin (7).

Persistent infection with HPV accounts for 100% of all cervical cancer cases, 88.2% of all anal cancers, 64.6% of all vaginal cancers, 56.9% of penile cancers, 38.9% of vulvar cancers, and 33.2% and 5.1% of oropharynx and oral cavity cancer cases (23). Among H/Ls, 21.9% of men and 21.7% of women are infected with oncogenic HPV strains, compared to 25.1% and 19.4% of NHW men and women (48). Cervical cancer is the most common HPV-related cancer among women and oropharyngeal is the most common in men, with H/L men developing HPV-related cancers at higher rates than other racial/ethnic groups in recent years (49,50). Incidence rates for several HPV-related cancers have been increasing (oropharyngeal, anal, and vulvar), however cervical cancer incidence rates have decreased mainly due to screening (7,50) and HPV vaccination among young women (49,51). However, H/Ls seem less likely (36.1%) than NHWs individuals (42.1%) to have ever received one or more doses of the HPV vaccine (52), and are less likely to be aware of HPV vaccination as a way to reduce cervical cancer risk.

Chronic hepatitis C virus (HCV) and hepatitis B virus (HBV) infections can cause liver cancer and are associated with a higher risk of non-Hodgkin lymphoma (53). The prevalence of HBV in the USA is about 0.3% and has remained unchanged since 1999. The primary prevention strategy for HBV infections is vaccination. Among adults 19-49, vaccination rates were lower among H/Ls (22.5%) than NHWs (34.9%) (28,53). HCV-related mortality has increased in the USA for several decades. These increases may be due to the HCV epidemic that started in the 1960s due to injection drug use (53,54). In H/Ls, 89% of those who use injectable drugs have positive cases of HCV (55). Currently, there is no vaccine available for HCV. Instead, one-time screening is recommended for people born between 1945 and 1965 given that they experience the highest rates of infections and HCV-associated mortality in the country. Testing for HCV is lowest among H/Ls, people with no insurance, and those with high school or lower education, and those born outside the U.S. (53,56).

Genetic risk factors.—Germline genetic variation plays an important role in cancer risk, with heritability for cancer overall being approximately 33% with some variation across cancer types (57). Despite the limited representation of H/Ls in cancer genome wide association studies (GWAS) (58), there is sufficient evidence demonstrating that high, intermediate, and low penetrance variants discovered in studies including mostly European or Asian ancestry participants are also associated with cancer risk in H/Ls (59–61). Studies including Latin Americans or U.S. H/L individuals have discovered population-specific mutations and unique allele frequency patterns suggesting that germline diversity should not be ignored when trying to understand cancer etiology to ensure equity in cancer prediction for individuals who identify as H/L (59,62,63).

Other relevant risk factors.—Compared to other racial/ethnic groups, H/Ls have reported higher exposure levels to outdoor air pollution (64), which is a cancer-causing agent primarily for lung cancer but possibly other cancers as well (65). H/Ls also experience a higher burden of pesticides and endocrine disrupting chemicals (EDCs) exposure, compared to NHW (66). Pesticide exposures have been associated with non-Hodgkin lymphoma and multiple myeloma, and lung, pancreatic, colorectal, prostate, brain, breast, leukemia, and bladder cancers (67,68). Stress-related psychosocial factors can also influence cancer burden via their effects on behavior or due to direct impact on cellular processes that may contribute to cancer formation and progression (69). Among these factors, of particular concern for H/L populations are chronic stress, social isolation, linked to increased morbidity and mortality among racial/ethnic minorities (70), and perceived structural racism and discrimination (71–74), which have been reported to increase breast cancer risk among Black women (75,76). Moreover, these social and structural determinants of health, and the downstream stress-related psychosocial factors, can contribute to decreased cancer screening, and late diagnosis. Finally, night shift work, a probable carcinogenic agent (77), is more prevalent among H/Ls, along with shorter sleep duration (78) whose effects are still largely unknown. All these factors are understudied among H/Ls and deserve further attention.

Challenges and opportunities in understanding cancer etiology among H/Ls

Etiological research among H/Ls lags other populations. Most available studies are observational, with few large prospective cohorts and intervention studies with multi-level data. Many studies include H/Ls as a small proportion of the overall study sample, and often, instruments used to assess exposures may not have been tailored to this population. Thus, measures may not fully or validly capture potential cancer risk factors of relevance for H/L populations. Moreover, results are rarely presented for H/Ls defined by nativity or region of origin, limiting the identification of risk factors that might be more relevant to particular H/L communities. Given that H/Ls are a population in transition, with both a large proportion of recent immigrants as well as H/Ls with several generations in the USA, cancer epidemiological studies can provide unique insights into the key determinants of higher cancer burden among one group or the other, which can guide future cancer prevention interventions. Identification of key cancer determinants, considering the complex diversity of H/Ls based on region of origin, immigration patterns, and places of residence in the US is crucial to reduce the cancer burden of this fast-growing population through appropriate and culturally tailored interventions. Finally, studies among H/Ls offer the unprecedented opportunity of disentangling genetic susceptibility factors across ancestral continental groups (European, Indigenous American and African), from environmental, cultural, and social determinants. Knowledge learned from these studies can be of benefit to other populations.

CANCER OUTCOMES AND SURVIVORSHIP AMONG H/Ls: PRIORITIES, CHALLENGES, OPPORTUNITIES

Despite decades of progress that have led to earlier cancer detection and advancements in cancer treatments and outcomes, H/Ls are more likely to be diagnosed with advanced

stages of the disease, and for many cancers, they experience poorer survival than NHWs (7). Research on outcomes and survivorship among H/Ls lags other racial/ethnic groups. Key challenges that prevent progress include lack of representation of H/Ls in existing tumor characterization efforts, such as the Tumor Cancer Genome Atlas (TCGA), where H/Ls represent only 3% of the sample (79). This disparity in inclusion translates into lack of knowledge about mutations that might be more prevalent among H/Ls, which could serve as targets for novel therapies, and/or serve as markers of prognosis. In addition, there is low representation of H/Ls in clinical trials, and cancer research in general, thus H/Ls are not often benefitting from the latest therapies available. There is also a greater proportion of H/L cancer patients who do not receive guideline-concordant treatment, adhere to treatment recommendations, or have access to usual care, compared to NHWs (80,81). Moreover, H/Ls often suffer disparities in health-related quality of life and greater financial toxicity during their survivorship years (7,82,83). We summarize below some of the salient disparities across the continuum of cancer care and survivorship.

Disparities in tumor characteristics that impact cancer outcomes

Data on the tumor landscape among H/Ls are scarce, limiting comparisons to NHWs. We summarize below three examples of cancers that have been investigated and illustrate associations between specific tumor characteristics, racial/ethnic category, and genetic ancestry.

Triple negative breast cancer.—H/L women have lower risk of developing breast cancer but are more likely to be diagnosed with aggressive subtypes associated with poorer prognosis compared to NHW women (7,84). Studies assessing the distribution of immunohistochemically determined subtypes by race/ethnicity category show higher proportion of human epidermal growth factor receptor 2 (HER2) positive and triple negative tumors (TNBC) in H/L women compared to NHWs (84). Furthermore, analyses including breast cancer patients from Peru, Mexico and Colombia suggest a positive association between tumor HER2 status and proportion of Indigenous American ancestry (85). Differences observed in subtype distribution by racial/ethnic category, nationality or ancestry proportions are likely to result from a combination of study design biases as well as risk factor differences at multiple levels and domains of influence, including: 1) the nature of the studies (population vs. hospital based) and age distributions of study participants (TNBC will be more common among younger patients compared to older patients), 2) the strength of association between race/ethnicity category or genetic ancestry proportions and sociodemographic characteristics in different countries/regions (e.g., education, socioeconomic status, access to and use and quality of screening and care), 3) behavioral and environmental exposures (e.g., reproductive behavior, nutrition, exercise) with concomitant impact on body mass index and insulin resistance, and 4) germline genetic variation that could contribute to breast cancer risk in a subtype specific manner (86,87)(85). These are possible explanations and contributing factors that need to be investigated further to understand patterns in breast cancer subtype distribution among H/Ls.

Lung cancer mutations.—Lung cancer is the leading cause of cancer death among H/L men and the second leading cause of cancer death among H/L women (49). Non-small

cell lung cancers (NSCLC) harboring mutations in the *EGFR* gene have been found to respond to tyrosine kinase inhibitors (TKIs), changing prognosis for patients (88). *EGFR* alterations have been observed in approximately 15% of European ancestry patients, 40% of East Asians, 15% to 20% of African Americans and ~30% of Latin Americans (88). Latin American studies and USA studies including H/L individuals have shown heterogeneity in the frequency of *EGFR* mutations in patients from different countries with alterations being more common in Peru and Mexico, intermediate in Colombia, Panama, and Costa Rica, and lowest in Argentina (88–90). Differences in the frequency of other common mutations have been described, with *KRAS* and *STK11* mutations being less common in H/Ls compared to NHWs (88–90). Germline genetics and environmental exposures are potential factors explaining observed differences in the mutational profile of lung cancer across populations (88). Well-designed multinational studies including harmonized collection of exposure information (e.g., wood burning, air quality, smoking, second-hand smoke) and biospecimens could provide important insights.

Acute Lymphoblastic Leukemia (ALL).—H/L children have 10-40% higher rates of ALL than NHWs (91,92). It has been demonstrated that common genetic variants associated with increased risk of B-cell ALL are associated with Indigenous American ancestry in H/L children (92). In particular, common alleles in the *CDKN2A*, *PIP4K2A*, *CEBPE* and *ARID5B* genes, explain a large proportion of the difference in ALL incidence between H/L and NHW children (92). Additionally, a germline variant in *GATA3* has been shown to increase the risk of a particular subtype of ALL, the Philadelphia chromosome-positive-like (Ph-like), which has been associated with a high probability of relapse (93). This variant was linked to somatic lesions typical of Ph-like ALL: *CRLF2* rearrangement, *JAK* mutation, and *IKZF1* deletion. The germline variant associated with increased risk of Ph-like ALL is consistent across ethnicities, but most common in highly Indigenous American individuals, which partly explains the association observed between genetic ancestry and risk of relapse among H/L children with ALL (93,94).

Access and barriers to cancer care

Cancer screening.—In general, cancer screening rates are lower among H/Ls compared to NHWs. Mammography screening within the past two years was 71% for H/Ls and 73% for NHW, with H/L women experiencing longer delays between abnormal findings from mammography or self-exams and medical follow-up (95). Pap smear screening within the past 3 years was 79% for H/Ls and 82% for NHW, with USA-born H/Ls having higher rates of screening than foreign-born (95). Colorectal cancer screening through colonoscopy was 52% for H/Ls and 63% for NHWs (95). These disparities in cancer screening rates are driven by multiple factors, including socioeconomic status and education, limited access to healthcare, co-morbid conditions, medical mistrust, and suboptimal patient-physician interactions (96–98).

Social determinants of health.—H/Ls experience health disadvantages due to the compounded effect of multiple social determinants (99,100), including structural factors, discrimination, low income, low education, and lack of health insurance and usual source of healthcare or medical home (83,101). These inequalities are associated with higher rates

of late-stage cancer diagnosis resulting in more aggressive treatments which may cause significant side effects and quality of life burden among H/Ls (83). H/L cancer survivors are also more likely to experience psychosocial barriers that may affect their healthcare quality and quality of life, including language and cultural challenges, and financial toxicity (7,82). Many patients with no insurance or partial coverage are forced to skip cancer screening and delay diagnostic or cancer treatment services, which make them more likely to experience poor cancer outcomes, low quality of life, and higher cancer-specific mortality. Patients with insurance coverage may face similar barriers due to high deductibles and/or treatment-related out of pocket expenses not covered by their health insurance plan (102,103).

Participation in clinical trials.—Despite the large number of available studies and improvements in public awareness about cancer therapeutic clinical trials, fewer than 1 in 20 adult patients enroll in trials nationwide (104), and even fewer H/Ls (2.2%) participate in cancer therapeutic trials (105). Despite this, research demonstrates that minority patients, including H/Ls, are as or more willing to participate in clinical research as NHWs, indicating that structural barriers are keeping these patients from participating (106). The lack of diversity in clinical trial study populations limits opportunities for discovering effects that may be relevant to underrepresented populations and their cancer care (107). These issues highlight the need for evidence-based interventions to improve participation of H/L patients in clinical research (105,108,109).

Structural and social factors including access to care, language, and rurality influence opportunity, intent, and actual participation in biomedical research (110). Specific to participation in clinical trials, some of the most frequently cited patient-related barriers specific to H/Ls include lack of awareness of available CTs, lack of knowledge about disease and treatment options, lack of understanding about the trial process (i.e., randomization), and treatment preference (107,110–113). Attitudinal barriers (i.e., fear of being a guinea pig, etc) also may deter H/L patients from considering a CT as a treatment option for cancer (107,110,112–114). In addition, cultural and language barriers, lower levels of health literacy and practical barriers, such as lack of transportation, lack of health insurance, financial constraints, and lack of family support, have been found to deter H/Ls from considering participation in clinical research (107,111,112,114). With an estimated 19% of H/Ls uninsured, this group has the highest uninsured rates compared to other racial/ethnic groups posing an additional challenge for this population in regards to healthcare and clinical trial participation (115,116).

Evidence-based strategies for improving recruitment of minorities into health research include culturally sensitive educational tools for community members, patients, and physicians, community education and outreach activities, building social networks with minority organizations and community providers, and community engagement in cancer research (117).

Disparities in cancer survivorship

Research on cancer survivorship among H/Ls is limited, but the existing studies, most focused on breast cancer, highlight several barriers and disparities (102,118). Compared

to NHW women, H/Ls are at higher risk of psychosocial and physical sequelae of breast cancer, experiencing more anxiety, depression, fear of recurrence, fatigue, and pain, and worse health-related quality of life and shorter disease-free survival (119–121). Spanish-speaking H/L immigrant breast cancer survivors experience worse quality of life and emotional well-being compared to their English-speaking H/L and NHW counterparts (121). Structural factors place many H/Ls with cancer at increased risk of poor cancer outcomes and quality of life including limited English proficiency, low literacy, lack of access to culturally and linguistically appropriate clinicians and information about their illness and treatment, limited employment and insurance coverage; lack of transportation; unfamiliarity with the health care system, greater existential concerns and fear; more symptoms; and later stage at diagnosis and more aggressive disease (122). H/Ls who are Spanish-speaking, in particular, have less access to survivorship information (122) and are more likely to report unmet symptom management needs (123).

RECOMMENDATIONS AND PRIORITIES TO MAKE PROGRESS IN CANCER EPIDEMIOLOGY AMONG H/Ls

Data sources needed

Cancer surveillance patterns among distinct H/L populations in the USA are hampered by incomplete information on birthplace, H/L origin, language, and time in the USA in cancer registry data. Given the diversity of the H/L population, these data are essential for providing a meaningful picture of the cancer burden among distinct H/L groups. Specifically, birthplace data are unknown for more than 40% of H/Ls cancer cases, which has been increasing over time, and is more complete for deceased patients due to additional report from death certificates. Moreover, from a validation study compared to self-reported nativity data, cancer registry birthplace data are less complete for US-born than foreign-born H/L (124). These data issues limit the ability to reliably report cancer statistics for distinct H/L groups.

We encourage linkages among existing health care and cancer surveillance databases to improve completeness of birthplace and H/L origin data. The NCI Surveillance, Epidemiology, and End Results (SEER) Program (<https://seer.cancer.gov>) has undertaken a linkage to Social Security Administration data to obtain information on birthplace and nativity; however, these data are not currently available outside of NCI. Birthplace and H/L origin information is relatively complete in death certificate data, and indeed, several publications have reported on cancer mortality trends by nativity and H/L origin using this source (24,125). Cancer registries should systematically integrate this information extracted through routine linkages to death certificate files. Finally, we encourage policies that require healthcare facilities and research studies to systematically collect sociodemographic information of relevance to the H/L population, including birthplace, H/L origin, and language preference and English proficiency.

There is also concern that deaths may be underestimated for USA H/L cancer patients due to reverse migration, which can introduce biases in survival studies done with cancer registry data. A detailed analysis of cancer registry data showed that, while reverse-migration may

be of concern, missed deaths may be more likely due to invalid social security numbers (126). We recommend further research into the extent of death under-ascertainment and development of statistical approaches to adjust for the degree of under-ascertainment in cancer statistics and models.

Population-based studies focused on H/L

There is a need for more and larger population-based prospective studies focused on H/Ls, with adequate representation of H/L populations across the USA, including newer areas with rapid growth of H/Ls, and appropriate exposure assessment tailored to this population, such as food frequency questionnaires that include foods consumed by the H/L population, inclusion of risk factors that might be of high prevalence in H/L communities across the USA (e.g. pesticides and EDC exposure), psychosocial factors, cultural values, behavioral changes after migration, and migration history. Important findings have emerged from prospective studies such as the Multiethnic Cohort (MEC) study, which includes over 47,000 H/Ls from Los Angeles (127), the H/L Community Health Study/Study of Latinos (HCHS/SOL), which includes 16,000 H/Ls from across the USA, and the Mexican American Mano a Mano Cohort, a population-based prospective cohort study including >23,000 adult participants self-identified as Mexican Americans in Houston, Texas (128,129). Despite these efforts, the representation of H/Ls across existing epidemiological studies is inadequate given the proportion of H/Ls in the population. Similarly, pan-cancer efforts to characterize H/L tumors are needed.

There is a need to establish population based long-term survivorship cohorts, with adequate numbers and clinical data, and multilevel data collection including biospecimens, culturally appropriate lifestyle questionnaires that capture life course exposures, ecological momentary assessments, and linkage to geocoded information on structural, social, and environmental stressors. A recently awarded NCI grant to study H/L cancer survivorship to follow a cohort of 3,000 H/Ls over 3 years is a move in the right direction, but historical de facto exclusion of H/Ls in cancer research suggests that we have a long way to go to address the cancer survivorship care needs of this population (130). Moreover, there is a need for developing culturally appropriate patient and community engagement approaches to increase participation of H/Ls in etiological, precision medicine studies, and clinical and behavioral trials. The new NCI Patient Engagement and Cancer Genome Sequencing network (PE-CGS) is a promising new initiative that may partially help address this gap if enough projects focused on H/Ls are funded (pe-cgs.org). Finally, community-engaged research efforts that are supported by patient navigation and financial assistance programs would greatly enhance study recruitment and retention and coordination of care.

Consortia needs and collaborations with Latin America

For multiple cancer types, foreign-born H/Ls in the USA have lower risk of developing cancer compared to USA-born individuals (12,33,125,131). It has been proposed that lifestyle changes and changes in environmental exposures associated with migration and time in the USA could explain the observed trends (49). To better understand the differences in incidence, outcomes, and tumor biology between USA-born and foreign-born H/Ls, as well as differences between H/L individuals of different national origins, collaborations

with Latin American countries are needed. Thus, it is important to establish international collaborations to harmonize the collection of relevant epidemiological, clinical, and genomic data for international comparisons (132,133). A limitation in comparing USA H/Ls with Latin American studies is the lack of population-based studies and population-based cancer registries in the latter region. Most studies in Latin America are hospital based, and often include patients from multiple health centers mixing data from private and public hospitals (134). Lower screening rates in Latin America also contribute to bias towards recruitment of patients with more advanced and aggressive tumors (33,85). Given the diversity of Latin American populations, well-designed, population-based multinational studies could provide important insights to disentangle environmental and genetic factors contributing to cancer risk and prognosis.

SUMMARY OF RECOMMENDATIONS

To make progress in addressing scientific gaps in cancer etiology and outcomes among H/L populations and better serve the needs of this fast-growing population, the following areas deserve attention in future epidemiological studies.

More research is needed on prevention strategies for obesity among H/Ls, particularly in childhood, as well as on determinants of progression of non-alcoholic fatty liver disease to liver cancer, and etiological factors for stomach and gallbladder cancer, and pediatric acute lymphoblastic leukemia.

Second, given that cost-effective, evidence-based cancer screening methods exist for certain common cancers, more implementation science is needed to identify optimal methods for improved uptake and dissemination of these screening technologies and learn whether strategies need to be tailored for certain H/L populations. For some cancers, proven prevention methods, e.g., HPV vaccination and colorectal cancer screening also merit additional implementation science efforts. Such efforts must comprehensively engage communities and safety net providers who provide most of the care for these populations.

Finally, we need increased targeted investment of critical resources to conduct large prospective studies and collection of longitudinal data on multi-level risk factors, including harmonized self-reported data, biospecimens, clinical data, and neighborhood and environmental exposure data. We need nationally representative data on the prevalence of treatment side effects, long-term sequelae, psychosocial distress, and quality of life among H/L cancer survivors. In addition, more efforts are needed to leverage existing data through consortia, and to expand collaborations with Latin America. Patient engagement strategies and patient navigation programs remain vital to ensure adequate participation of H/Ls in cancer research and clinical trials. Engagement of affected communities in a bi-directional manner is essential to ensure prevention strategies meet the needs of the communities, and can be sustained, and study results can be readily translated. Finally, it is pressing to invest in training the next generation of cancer epidemiologists conducting research among H/L populations and increase the representation of H/L scientists in the biomedical workforce.

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