Amelie G. Ramirez
Edward J. Trapido *Editors*

Advancing the Science of Cancer in Latinos

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

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Institute for Health Promotion Research

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Editors

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Preface

The *Advancing the Science of Cancer in Latinos* national conference was a call to action for addressing cancer health disparities observed among Hispanic/Latino communities. It emerged from the need for Latino disparities researchers to seek solutions through multidisciplinary collaborations and to keep pace with the substantial advancement in cancer prevention, screening, diagnosis, treatment, and survivorship. Held in San Antonio from February 21 to February 23, 2018, the conference was co-hosted by the Mays Cancer Center and the Institute for Health Promotion Research at the UT Health San Antonio and sponsored by the National Institute on Minority Health and Health Disparities. The conference uniquely reviewed the state of the science and set an agenda for future initiatives to specifically address cancer health disparities and improve outcomes in Latino communities. While most conferences on cancer health disparities focus on policy and public health issues, this conference incorporated perspectives from basic scientists, clinicians, and population health experts in conjunction with policy and public health to emphasize the need for timely translation of research. To this end, the conference assembled an international, multidisciplinary group of speakers and attendees who explored wide-ranging issues including Latino-focused basic research, clinical best practices, effective community interventions, and policy implications. Much of the research presented was on the cutting edge of science.

Much of the Latino cancer research happening today occurs in silos by researchers who often only attend specialty meetings narrowly focused on their specific discipline, creating a missed opportunity for discussing broader, systemic issues across sectors. The value of *Advancing the Science of Cancer in Latinos* conference is that it united researchers, scientists, physicians, healthcare professionals, patient advocates, and students from across the nation and beyond in an open dialogue, under one roof, to discuss the broader field of study in Latino cancer and foster collaborations that would not have occurred otherwise.

These conference proceedings give readers an overview of what is known about cancer disparities in Latinos, what is not known, and suggestions for a way forward. With the ongoing rise in the US Latino population and cancer burden, we believe these pages hold many key insights into actionable targets for basic science research,

suggestions for clinical best practices and community interventions, as well as other novel strategies and advocacy opportunities to reduce these disparities.

We hope that you, the reader, will explore all of the vital research delivered, discussed, and disseminated at *Advancing the Science of Cancer in Latinos* in order to gain a fresh, comprehensive perspective on Latino cancer health disparities. We anticipate this will inspire critical thinking and strategizing about how you can apply some of this research and practice into your own work at your program, institution, business, and nonprofit. We are optimistic that our scientific conference and the information in these proceedings will provide a much-needed spark that will lead to many more conferences, more collaboration, more research, and more success in reducing and eliminating cancer health disparities and improving the health and lives of the US Latino population.

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We would also like to extend our utmost gratitude to the team at the Texas Department of State Health Services (DSHS) for collating and analyzing the current South Texas, Texas, and national data on cancer: John Arend, MPH; Ashley Dixon, MPH; Erin Gardner, MPH; Paige Miller-Gianturco, PhD, MPH; Rebecca Sardell, PhD; Melanie Williams, PhD; and Michael Wu, MPH. Our sincere appreciation to Nina Caris, PhD, for her editorial contributions to this publication. Finally, we are grateful to our lead program coordinator, Sneha Prabhu, MPH, for her significant efforts in organizing the *Advancing the Science of Cancer in Latinos* conference from concept to completion.

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Part I
Introduction

Chapter 1
Advancing the Science of Cancer in Latinos

Amelie G. Ramirez and Edward J. Trapido

Introduction

While the overall rate of cancer deaths in the USA has declined by 27% during the past 25 years, socioeconomic gaps are widening and cancer remains the leading cause of morbidity and premature death among vulnerable populations such as Latinos [1–4]. Latino cancer rates are expected to rise 142% in the next 20 years [5]. This health crisis is especially alarming given that Latinos, already the nation's largest minority group, are expected to compose at least 30% of the nation's population by 2050 [6].

Latinos as a group have a unique demographic profile that departs from the US public health pattern. For example, even though life expectancy is going down in the United States, the US Latino population has the longest life expectancy for both women (84.3 years) and men (79.3) compared to non-Latino white women (81) and men (76.3) and black women (78.1) and men (71.9). This Latino survival advantage increases with age, and the probability that a person will survive from birth to age 85 is 52.1% in Latinos and 41.9% in non-Hispanic whites [7].

Cancer is the leading cause of death among Latinos; however, the lifetime probability of developing cancer is lower for Latino men (36%) and women (35%) than for non-Latino white men (40%) and women (39%) [2]. Even though Latinos are less likely to receive a cancer diagnosis, cancer incidence varies by cancer site. As a group, Latinos have a lower incidence than non-Latino whites for some common cancers such as breast, colorectal, lung, and prostate. However, there are some less common cancers that disproportionately affect Latinos, including gall bladder and

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infection-related cancers of the liver, intrahepatic bile duct, stomach, and uterine cervix [8]. Latino men and women are twice as likely to develop and die from liver cancer than non-Latino whites; Latino women are over twice as likely to develop stomach cancer as non-Latino white women; and Latino women are 1.6 times as likely to develop cervical cancer and 1.3 times as likely to die from it [9, 10].

In addition to increased incidence for some cancers, US Latinos experience other cancer disparities. For one, cancer is often diagnosed at a later stage in Latinos when the disease is more difficult to treat, perhaps the result of economic and cultural barriers to cancer care and lower use of prevention screening. Second, accurately characterizing Latino cancer risk is challenging because Latinos are underrepresented in cancer registries, research, and clinical trials. Thus, these data do not reflect the proportion of Latinos in the US population. Compounding the problem is the fact that these data commonly consider Latinos as a single group when, in fact, Latinos are heterogeneous and may differ by genetic admixture, country of origin, nativity, degree of acculturation, and socioeconomic status—all factors that have been implicated in cancer risk.

Advancing the Science of Cancer in Latinos was a timely and critical call to action for addressing these cancer health disparities in Latinos. The conference brought together researchers, scientists, physicians, healthcare professionals, patient advocates, and students from across the nation, engaging them in open dialog that moved beyond known cancer disparities to summarize research advancements, identify gaps, and develop actionable goals to translate basic research into clinical best practices, effective community interventions, and professional training programs to eliminate cancer disparities in Latinos. Held in San Antonio on February 21–23, 2018, the conference was co-hosted by the Institute for Health Promotion Research (IHPR) at UT Health San Antonio and the Mays Cancer Center, and was sponsored by the National Institute on Minority Health and Health Disparities.

The idea for the conference emerged years ago from collaborations among members of *Redes en Acción*: The National Latino Cancer Research Network (*Redes*), which formed almost two decades ago, to address persistent cancer disparities among the Latino population in the United States. Created by the IHPR and funded by the National Cancer Institute's (NCI) Center to Reduce Cancer Health Disparities (formerly the Special Populations Networks Initiative), *Redes* is still ongoing and connects professionals whose shared purpose is fighting cancer among Latinos through community-based education, research, and training. At the time the conference was discussed, there were a number of new developments in seemingly unconnected areas of science that, if brought together, could be woven into a better understanding of cancer in Latinos and where the science ought to go next. Making this synthesis happen would require a venue for collaboration among professionals from diverse disciplines and perspectives. *Advancing the Science of Cancer in Latinos* provided such a setting for disparities researchers to discuss the latest research findings, identify knowledge gaps, and stimulate ideas for new research in cancer health disparities among Latinos.

Session topics that support the overall conference theme were set by the Scientific Planning Committee members, who had expertise in cancer health disparities

research. The intent was to focus on topics related to the entire cancer continuum, specifically, advancements and improvements in risk assessment, primary prevention, screening, detection, diagnosis, treatment, and survivorship. The papers that follow are organized into parts that reflect topics of the conference symposia, paper sessions, and poster sessions.

Part II: Genetics, Environment, Lifestyle, and Cancer

In a keynote address, Dr. Eliseo Pérez-Stable, Director of the National Institute on Minority Health and Health Disparities, presented an overview of the science of cancer in Latinos. He pointed out that most US cancer databases report on Hispanics/Latinos as a single group; however, it is now widely accepted that this ethnic group is, in fact, a heterogeneous mix of subgroups that may differ in country of origin, acculturation, nativity (US- or foreign-born), and other factors. Latino ancestry is the result of 500 years of admixture in Latin America among indigenous populations; European colonizers who came from Spain and other parts of Europe; and Africans who arrived during the slave trade, most of whom went to the Caribbean and Brazil. The proportion of admixture in modern US Latinos is influenced by the country of origin and is one important source of variability that exists within this group. In addition to genetic ancestry, country of origin, and nativity, Latinos may vary also by degree of acculturation, socioeconomic status, and US region in which they reside; all of these factors have been implicated in cancer risk and outcome.

In Part II of this volume, Pinheiro, Callahan, and Kobetz make a compelling argument for disaggregating Latino data into subgroups by country of origin and nativity in order to accurately characterize the cancer experience in Latinos. Aggregation of Latinos into one group masks nuances in the data and obscures differences among subgroups. They describe some of the methodological challenges in determining accurate incidence, survival, and mortality for Hispanic subgroups and offer ways to overcome these obstacles.

Gonzalez-Pons and Cruz-Correa report on their studies of colorectal cancer disparities among Puerto Rican and US mainland Hispanics. They propose that disparities between these subgroups may result from a combination of environmental and genetic factors including level of European ancestry, genetic predisposition, diet, and gut microbiome composition.

Part III: Cancer Risk, Prevention, and Screening

Incidence rates for cancer vary by cancer site and subgroup. Cancer incidence among Latinos as a group is lower than non-Hispanic whites, but cancer is still the leading cause of death among Hispanics. Breast cancer is the most common cancer diagnosed in Hispanic women and prostate cancer the most common cancer

diagnosed among Hispanic men; in both cases the disease is more likely to be diagnosed at a later stage than in non-Hispanic whites. Hispanics/Latinos as a group have lower incidence rates than non-Hispanic whites for some common cancers such as breast, colorectal, lung, and prostate; however, they have higher rates of some rarer cancers such as gall bladder and infection-related cancers of the liver, intrahepatic bile duct, stomach, and uterine cervix [3]. Strategies for cancer prevention focus on improved screening and altering modifiable risk factors such as smoking, obesity, alcohol use, unhealthy diet, and physical inactivity; infection-related cancers may be prevented through vaccination, behavioral change, and treatment for infection. Promoting cancer screening and modifying health-related behaviors among US Hispanics requires the development of culturally sensitive interventions to overcome health disparities and barriers.

In Part III, Fejerman, Serrano-Gomez, and Tamayol summarize what is known about breast cancer risk, characteristics, and survival in women of Latin American origin. In their review, they point out that the risk of developing breast cancer varies among and within Latino subgroups based upon country of origin, nativity, and genetic ancestry. The authors also describe some challenges of acquiring the right data to predict, prevent, and treat breast cancer in women of Latin American origin, such as underrepresentation in large-scale genomic studies and underfunding of population-level registries in Latin America.

Stern reviews current knowledge on prostate cancer (PCa) in Latinos and points out that while PCa incidence among Latino men is lower than non-Latino whites or blacks, there are also reported incidence disparities among Latino subpopulations. Other reported disparities include the fact that Latinos have lower rates of PSA cancer screening and a higher proportion of cases diagnosed with advanced stages than non-Latino white men. Additionally, there are differences in clinical characteristics and survival pattern among foreign- and US-born Latinos, Latinos with different socioeconomic status, and Latino subpopulations defined by the country of origin. Why these disparities exist are unknown, but could result from the interplay between differences in genetic ancestry, environmental exposures, and attitudes toward screening and care. Stern highlights important gaps in knowledge that deserve further study such as research on PCa determinants and outcomes among Latinos that takes into account Latino heterogeneity.

Tucker and Flanagan describe what is known about diet as a modifiable risk factor for cancer, specifically obesity; excess alcohol; low intakes of fruits, vegetables, fiber and calcium; and high intakes of processed meat and red meat. In addition to studying associations between single dietary factors and cancer risk, newer research focuses on dietary quality and dietary pattern, that comprises all components of the diet. The authors point out that dietary quality differs across Latino subgroups and that most Latino groups, particularly Puerto Ricans, fall short of the ideal preventative diet. Latinos are underrepresented in studies of nutritional risk factors and cancer, and the authors recommend that ethnic and cultural background be considered when researching dietary habits, in order to reduce bias and establish reasonable portion sizes.

Part IV: The Biology of Cancer Health Disparities

Using new molecular technologies such as next-generation sequencing, large genomics databases (e.g., The Cancer Genome Atlas), and microarray analysis, researchers are taking new approaches to study how cancer biology, among other factors, contributes to disparities in cancer incidence and outcome. In Part IV of this volume, the first two papers discuss the biology of disparities in gastric cancer and the second two the biology of disparities in breast cancer among Hispanics/Latinos.

Gastric Cancer

Gastric cancer (GC) in the United States disproportionately affects Latinos, and the incidence varies among Latino subgroups based upon country of origin. Because early stage tumors produce no symptoms, gastric cancer is often diagnosed as stage IV disease, and the 5-year survival rate is only 29% among Hispanic men and 24% among Hispanic women in the United States [3]. Infection with the bacterium, *Heliobacter pylori*, is a risk factor for non-cardia intestinal type gastric cancer, and geographic variation in *H. pylori* prevalence is partly responsible for higher gastric cancer incidences and mortality in Latin America than in the United States. Infection with *H. pylori* induces a cascade of predictable (and treatable) pre-malignant, pro-inflammatory stages that occur before the onset of dysplasia and gastric cancer. Garai, Li, and Zabaleta describe their efforts to find biomarkers of these inflammatory stages and their progression/regression through time. Using samples from African American and Caucasian individuals with gastritis, they identified single-nucleotide polymorphisms (SNPs) and haplotypes in cytokine genes associated with ethnicity. In a cohort of Hispanic/Latino individuals, they identified *CD44* as a marker of disease progression and *DMBT1* as a marker of disease aggressiveness.

Carvajal-Carmona provides an overview of GC epidemiology and describes Latino GC disparities including research gaps in etiology and translational research. In a discussion of genomic and genetic research disparities, he points out that Latinos are underrepresented in all gastric tumor whole exome or whole genome sequencing studies; for example, only 1% of GC patients included in The Cancer Genome Atlas (TCGA) are Latinos, a population with the highest GC burden. The TCGA study divides GC into molecular subtypes that have been associated with prognosis or response to therapy. To establish the prevalence of GC molecular subtypes in Latinos, the author's research group conducted a pilot study of targeted sequencing in tumors from Latino patients, and their results differed from the TCGA study. They also found that the mutation frequency of known gastric cancer driver genes in Latinos differed from the frequency reported in the TCGA. These results suggest that the molecular profiles of GCs in Latinos are unique, pointing to the need for more comprehensive tumor genomic studies.

Breast Cancer

Even though Hispanic woman have lower incidence and mortality from breast cancer than non-Hispanic white women, breast cancer outcome disparities do exist and are greatest among young Hispanic women (<40 years) who are more likely to have aggressive disease and present in advanced stage. Colon-Otero speculates that this early onset disparity is likely a result of genetic factors, environmental factors, and altered estrogen metabolism resulting from childhood obesity. Recent data support his working hypothesis that increased stress and poor dietary habits associated with low socioeconomic status lead to childhood obesity in Hispanics. Obesity results in increased production of serum IL-6 and other adipokines, promoting aromatase transcription and increased serum estrogen and genotoxic estrogen metabolites. He recommends that new studies are needed to clarify the biological factors that promote outcome disparities among Latinas with breast cancer.

The advent of gene-expression profiling with microarray technology has allowed the classification of breast cancer into intrinsic molecular subtypes such as luminal A and luminal B, which are estrogen receptor positive (ER+), and HER2-enriched and basal-like, which are estrogen receptor negative (ER−). These subtypes are prognostic, and their relative prevalence varies among and within subgroups. Serrano-Gomez and Zabaleta review what is known about molecular profiles of breast cancer in different subgroups and point to the growing evidence that differences in gene expression profiles may be a consequence of ancestry. In their own studies, the authors determined the frequency of intrinsic subtypes of breast cancer in Colombia, and they found that the Luminal B subtype was the most prevalent and that African ancestry was associated with more aggressive cancer. Using next-generation sequencing, they identified 67 genes that were differentially expressed between luminal A and luminal B subtypes, six of which were common between patients with high European/low Indigenous American ancestries. Their results suggest that ethnicity influences modulation of these genes in breast cancer and may be used to study breast cancer susceptibility in minority groups.

Part V: Advances in Cancer Therapy and Clinical Trials

Biomarker testing, which is now often the standard of care for patients diagnosed with cancer, can be used by physicians to assess cancer risk, diagnose a particular cancer, select treatment, and/or assess treatment response. In a keynote address, Edith Perez, Professor of Medicine at the Mayo Clinic, discussed basic concepts and issues of biomarker-based precision medicine in clinical trials and oncology practice. In a summary paper presented in Part V of this volume, she describes general features of well-designed biomarker-driven clinical trials and offers specific suggestions for designing clinical trials to support FDA approval. Perez predicts that in the near future, tumor sequencing will become standard clinical practice;

liquid biopsies will become available to sample circulating tumor DNA (ctDNA); tumor classification will become molecular-based and tumor-agnostic biomarker strategies may be used to manage patients; and clinical trials in oncology will use sequencing at both enrollment and follow-up. Additionally, she describes some basic concepts and challenges in the use of cancer immunotherapy (CIT) biomarkers, which are revolutionizing oncology. A new Program for Accelerated Cancer Therapies (PACT) was cited as an example of a multidisciplinary collaboration with NIH, NCI, and biopharma that aims to support development of standardized biomarkers for immunoprofiling and exploratory biomarkers of high relevance to patient care. Finally, Perez explains why bringing biomarker-based trials to patients is challenging and predicts that large collaboratives such as PACT will move precision medicine and oncology forward by linking clinical retrospective and prospective cancer genomic and proteomic data with longitudinal clinical outcomes.

A recurring theme throughout the conference was that Hispanics are greatly underrepresented in the large cancer and genomic databases and that by placing all Latinos into one category, these datasets do not capture the variation in cancer determinants and outcomes that exist among Latino subgroups. Part of the solution is to improve Latino recruitment into cancer clinical trials, which is historically low. Ruben Mesa, Director for the Mays Cancer Center in San Antonio, points out that cancer clinical trials must reflect the population being studied in order to capture differences among ethnic groups and to make inferences that are generalizable. How to improve Latino accrual into clinical trials is so important and problematic that it has become an active area of research. In his presentation, Mesa discusses the challenges of enrolling patients into clinical trials and the additional barriers that must be overcome to recruit a representative number of Latinos. He describes research and model programs from the Massey Cancer Center at Virginia Commonwealth University and the Mays Cancer Center at UT Health San Antonio that are designed to enhance Hispanic accrual and address underrepresentation in clinical trials. Recommended next steps to improve accrual into clinical trials are to educate physicians to better promote enrollment, build awareness among Hispanics about the role of clinical trials in improving cancer care, enhance care navigation for treatment planning including matching the right patient with the right study, develop language- and culture-appropriate educational materials, and share lessons learned among centers and investigators.

Part VI: Cancer in the Era of Precision Medicine

Biomarker testing and genetic profiling of tumors are revolutionizing cancer care, leading to more refined risk assessment, diagnosis, and targeted treatment. In Part VI, two papers address cancer care disparities and the application of precision medicine in Hispanic populations. Zabaleta et al. make the case for including more Hispanics in precision medicine research. Because most genomic and transcriptomic studies are based on tumors from Americans of northern European ancestry,

precision medicine based on these data may actually worsen health disparities. In the case of breast cancer, another problem is that most epidemiological studies not only consider Hispanics/Latinas as a single group, but they also treat breast cancer as a single disease. Even though Hispanics have a lower incidence of breast cancer than non-Latino whites, they have a higher mortality risk, which may result from differences in the prevalence of breast cancer subtypes or molecular differences within subtypes. Results from their own research on breast cancer in Colombian women and the work of others have led the authors to suspect that luminal subtype tumors in Hispanics may be biologically different from other ethnic groups and that these differences may result from non-genetic or ancestry-linked factors. Thus, the interpretation of gene expression tests and treatment choices may have to take this into consideration.

Lorna Rodriguez-Rodriguez, from the Rutgers Cancer Institute of New Jersey, describes her team's study of precision medicine and cancer care disparities within the Latino population in New Jersey. They performed a small, longitudinal study of patients with rare or refractory tumors who underwent genomic profiling and compared outcomes between Latino and non-Latino white patients. Even though Latino patients had more advanced disease at the time of diagnosis, those who received targeted therapy survived an average of 10 months longer than their white counterparts; Latino patients who did not receive targeted therapy survived an average of 4 months longer. Further, they found no disparity between Latino ancestry patients and non-Latino white patients in the implementation of precision medicine in their clinical care. Their final conclusions will be based on a larger sample from their ongoing analysis.

Part VII: Cancer Outcomes and Survivorship in Latinos

Ethnicity, socioeconomic status, and culture can profoundly impact cancer outcome and survivorship in Latinos. Culturally and linguistically appropriate interventions are needed for Latino cancer survivors to reduce disparities and address the long-term physical and psychological effects of cancer treatment on quality of life. In Part VII, there are two examples of such interventions—*Nuevo Amanacer* and *Nueva Vida*.

Cancer centers are often not equipped to meet the needs of Spanish-speaking Latinos with cancer, who have limited access to survivorship care that is linguistically and culturally appropriate. Nápoles provides a vision for improving the quality of life among Latina survivors of breast cancer by engaging Latino communities in design and implementation of behavioral interventions that can be delivered in community settings and are linked to cancer care systems. She reviews the randomized controlled trial to test *Nuevo Amanacer*—a peer-delivered stress management intervention to improve the psychosocial health of Spanish-speaking Latina survivors of breast cancer. Using community-based participatory research methods, her research group created the program by integrating an evidence-based intervention, a

community best-practices program, and their formative research. Participants in the trial were urban Latinas with breast cancer, and their results showed that this intervention improved several quality of life domains, decreased breast cancer concerns, depression, and bodily symptoms. They are now translating and testing the program in rural, low income areas where there are greater disparities in cancer support. Nápoles describes their conceptual framework to guide research on behavioral interventions for Latino cancer survivors and opportunities for future research.

Patient-centered outcomes research (PCOR) involves patients and other stakeholders in study design, implementation, and evaluation. Graves presents an example of PCOR using "research democracy"—a process in which individuals involved in research (e.g., team members, participants, and advisors) have a vote and a voice in research decisions and procedures. She describes their *Nueva Vida* intervention study designed to improve quality of life outcomes among Latina breast cancer survivors and their caregivers. To evaluate the intervention, her research group conducted a randomized controlled trial using research democracy, and their initial results suggest that this can be an advantageous approach that improves PCOR and benefits both patients and their caregivers.

Part VIII: Engaging Latinos in Cancer Research

One of the challenges in eliminating cancer disparities and achieving health equity among Latinos is that successful interventions must elicit behavioral change, which requires messaging in a culturally nuanced manner that resonates with the targeted Latino subgroup. Model interventions with the shared goal of changing health-related behaviors are presented in Part VIII, and they range from community-based participatory research (CBPR), peer modeling, social reinforcement, and integrating the effects of culture operating at various levels of influence.

Community-level interventions that engage Latinas from the beginning of research through data dissemination can potentially help reduce cancer disparities and save lives. In her paper, Baezconde-Garbanati examines key elements for engaging Latinas in cervical cancer research and discusses the importance of CBPR principles in facilitating knowledge transfer from researchers to the community. Also discussed is how citizen scientists/patient advocates and *promotores de salud* can enhance community participation and engagement in patient-centered research. She provides specific examples of how their research group has engaged Latinas in cervical cancer research through two campaigns—*Tamale Lesson* and *Es Tiempo*. The widely disseminated *Tamale Lesson* is a culturally tailored narrative in film format that provides information on the human papillomavirus as a cause of cervical cancer, prevention with vaccination, and detection with Pap test screening. *Es Tiempo* uses the annual blooming of the Jacaranda tree as a visual reminder to take steps to prevent cervical cancer. It includes an outdoor media campaign, clinical intervention, and community educational workshops delivered by *promotoras de salud*. These two initiatives demonstrate ways to create a research environment

conducive to engagement, and the cultural strategies used in these cervical cancer interventions are generalizable to other diseases.

Text messaging can promote smoking cessation by providing peer modeling and eliciting social reinforcement for behavioral change. Chalela et al. present results from Quitxt, a tobacco cessation program using bilingual text-messaging promoted by social media. The target population was young adult Latinos aged 18–29 in South Texas, a marginalized population with low access to smoking cessation services. Text messages included links to web pages with additional content and YouTube videos that peer modeled reasons and skills to quit smoking. They found that 21% of participants reported abstinence at the 7-month follow-up.

Lechuga and Melo present gaps in cervical cancer prevention research and intervention development. These gaps point to a need for interventions that simultaneously target cultural factors operating at multiple levels of influence and that broaden focus on outcomes beyond cancer screening to include improvement in sexual and reproductive health. Additionally, few interventions uniquely target Latinas, and few are informed by theories explaining how culture may affect screening and treatment. The authors present results of two research studies to bolster the case for a more nuanced conceptualization of the potential effect of culture, which may operate at various levels of influence. They found from these studies that a larger proportion of mothers who had vaccinated their daughters engaged in discussion about sexuality than mothers who had not vaccinated and that embarrassment and shame ascribed to sexuality were significantly associated with negative attitudes toward cancer screening.

Cancer research studies often collect biospecimens as part of the research participation process, and it is important that Hispanics are not underrepresented. Rodriguez and Erwin describe the *Hoy y Mañana* (HyM) study as a model of a novel application of a community-based approach to biobanking and biospecimen research. These studies developed and tested community-based interventions in a Northeast Hispanic population to identify factors that influence participation in biospecimen donation to a biorepository for future cancer research. The authors use the development of the HyM study as an example to highlight critical steps for engaging Hispanic communities in cancer research.

Conclusion

Basic scientists and clinicians as well as policy makers and public health professionals gathered in San Antonio to tackle Latino cancer disparities on numerous fronts—from basic research on biological differences behind disparities to community-level interventions that aim to overcome barriers to cancer care and address the unique needs of Latino populations. Unlike past conferences on cancer health disparities that focused primarily on policy and public health issues, *Advancing the Science of Cancer in Latinos* incorporated perspectives from a variety of disciplines with the view that collaboration among diverse professionals is

what is necessary now to move the field forward. The papers and posters presented here represent just a beginning, and the hope is that the dialog and collaboration that started here will continue into the future, providing new solutions for the elimination of cancer health disparities among Latino populations.

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Part II
Genetics, Environment, Lifestyle, and Cancer

Chapter 2
Disaggregated Hispanic Groups and Cancer: Importance, Methodology, and Current Knowledge

Paulo S. Pinheiro, Karen E. Callahan, and Erin N. Kobetz

Introduction

Hispanics living in the United States are heterogeneous: US-born and foreign-born; Mexican, Puerto Rican, Cuban, Dominican, Central American, South American, and a small number from Spain; wealthy and impoverished; English and/or Spanish speaking; residing in the North, South, East, or West; situated in cities or rural areas. These varying socioeconomic circumstances, nativity and/or immigration experiences, and cultural values and practices are strongly associated with cancer risk factors and thus impact cancer outcomes.

Epidemiology of Cancer in Hispanics: Aggregated

Cancer is the leading cause of death of all Hispanics combined [1], with the annual number of new cases diagnosed in 2014 exceeding 128,000 [2]. To address the increasing cancer burden of the burgeoning Hispanic population, including the

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development of cancer prevention and control strategies, all stakeholders, from clinicians to researchers to policymakers, must have timely and accurate population-based cancer indicators, namely incidence, survival, and mortality. Incidence patterns are routinely reported by the North American Association of Central Cancer Registries (NAACCR) in their Cancer in North American (CiNA) Annual Reports [3] and the Annual Reports on Cancer, which group data from the Surveillance, Epidemiology, and End Results Program (SEER) and the National Program for Cancer Registries (NPCR) [4]. In addition, SEER provides data available for survival estimates of Hispanics [5], and mortality data are provided by the National Center for Health Statistics within the Centers for Disease Control and Prevention (CDC) [6].

However, accurate indicators for Hispanics are affected by specific problems. Hispanics are known to be undercounted at the cancer registry level [7, 8], largely due to incompleteness of the ethnicity variable. NAACCR protocols for the calculation of incidence rates reduce this undercount by using the NAACCR Hispanic Identification Algorithm (NHIA) which relies partly on Hispanic surname [9]. Mortality data also suffer from some degree of undercount, potentially up to 5% [10]; however, routine use of similar algorithms does not take place. Nonetheless, Hispanic incidence and mortality estimates are generally consistent with each other and show that US Hispanics in aggregate have lower cancer incidence and mortality rates (overall and for the most common cancers) than the non-Hispanic white (NHW) referent group [1]. Important and well-known exceptions to this pattern are infection-related cancers, in particular cervix, liver, and stomach, for which Hispanics, examined in aggregate, have shown consistently higher rates than NHWs [1]. For survival, follow-up for foreign-born in general and Hispanics in particular can be difficult to perform, especially in comparison to NHWs and non-Hispanic Blacks [11]. However, SEER registries show that for all stages combined, cancer survival of Hispanics is similar or only slightly lower than NHWs, depending on cancer site [5].

Given the lower incidence, lower mortality, and relatively comparable survival among Hispanics in relation to NHWs, cancer has been frequently cited as another example of the "Hispanic Paradox," whereby Hispanics have positive health outcomes despite documented challenges with lower socioeconomic status and access to quality health care [12]. Another often cited positive characteristic in the study of health outcomes for Hispanics is the Healthy Immigrant Effect [13] (whereby immigrants are healthier on average than both their counterparts at home and the populations in the host countries) as a sizable portion of Hispanics are immigrants to the United States. The reality, however, may well be more complicated. Evidence from Fenelon et al. [14] has shown that the "Paradox" in terms of cancer mortality (and thus incidence) may largely be tobacco-related, and analyses of the potential survival parity or advantage for Hispanics on a population basis may be in part artifactual, a problem addressed later in this manuscript [11, 15–17]. Additionally, cancer patterns among US-born Hispanics in relation to NHWs are not nearly as favorable as their foreign-born counterparts in the United States [18], offering a persuasive counterargument to the contention that any advantage stems from being

Hispanic per se; rather, the advantage is at least partly being foreign-born, an advantage not exclusive to Hispanics, but also present among foreign-born Asians and Blacks [19, 20].

Such complexities are challenging, justifying the need for a distinct focus on cancer among Hispanics. Hispanics are demographically young, considerably heterogeneous, and, by and large, recent arrivals, as shown by the sevenfold increase in the Mexican Hispanic population between 1970 and 2010 [21]. Thus, they differ from the more established NHW and non-Hispanic Black populations and need a more critical and refined evaluation of their cancer indicators for a full understanding of their epidemiological patterns. Simply stated, aggregate estimates for all Hispanics that do not consider birthplace and the distinct Hispanic groups are masking considerable variation, with poor cancer outcomes seen among some segments of the Hispanic population that deserve additional targeted efforts to reduce disparities. Equally compelling is that careful examination of the determinants of these vast differences, whether risk or protective factors, can provide crucial information needed for effective public health and clinical intervention. In addition, any existing survival advantages among Hispanics could be hypothesis-generating and/or provide insights into improving cancer outcomes for other populations. Lastly, we demonstrate that specific Hispanic group analyses can provide new insights into the etiology of some cancers, insights only revealed by examining patterns among distinct Hispanic groups.

Epidemiology of Cancer in Disaggregated Hispanic Groups

Challenges in the Data

Cancer Registry Data (Incidence and Survival) Given their heterogeneity, much can be learned from examining the unique cancer profiles of all sizable Hispanic groups in the United States. These can be divided into 35 million Mexicans, 5.5 million Central Americans, 5.3 million Puerto Ricans, 4.1 million South Americans, 2.1 million Cubans, and 1.8 million Dominicans as of 2015 [22]. Additionally, examining differences between US-born and foreign-born (FB) groups adds clarity to the profiles, albeit only feasible with Mexican and Puerto Rican populations (for whom birth on the island is often analyzed as equivalent to FB), because of the sparsity of US-born cancer cases among the other Hispanic groups. NAACCR standards currently include the following specific categories of Hispanic ethnicity (group) for cancer cases: Mexican, Puerto Rican, Cuban, Dominican, and a single category for Central/South American, a convenient aggregation of very diffuse populations, despite having sociodemographic characteristics that are substantially different between the two. In addition, there are categories for other specified Hispanics including those from Spain, Hispanics by surname only, and Hispanics not otherwise specified (NOS) [3].

Overall, population-based analyses of cancer outcomes by Hispanic group and birthplace are obviously dependent on the completeness of these two data pieces. Unfortunately, both variables are substantially incomplete in cancer surveillance data required for incidence and survival statistics. In the most recent CiNA report released by NAACCR in 2017 [3], known specific group for 2010–2014 among Hispanic cancer cases was as low as 32% in Texas and only 58% in New York and New Jersey, all states with high Hispanic populations. Birthplace was only 50% complete for registry data in California (CA) [23] and 43% in Florida (FL) [24], ideal states for studying differences between US-born and FB Mexican Hispanics (CA) and specific Hispanic groups (FL).

Mostly because the underlying data is complex and because of this considerable incompleteness, incidence rates of Hispanic groups have been estimated only a few times. Some researchers assigned groups ecologically at the county level, for example, Puerto Rican for all Hispanic cases residing in counties in New York City, Mexican for all Hispanics in Los Angeles County, and Cuban for all Hispanics in Miami-Dade and Broward counties in Florida [25, 26]. However, these methods are subject to substantial misclassification of Hispanic group at the individual level, leading to inflated estimates for some groups and underestimates for others. Other researchers assessed heterogeneity in risk among Hispanic groups using proportional incidence ratios (PIRs) [27, 28]; however, because PIRs do not depict the actual incidence of disease and are highly dependent on the relative frequency weight of each cancer, they have the potential to be misleading. To date, the only incidence rates for Hispanic groups calculated with individual level data was determined based on three years of Florida data (1999–2001) and included imputation of 32% of Hispanic cases to specific groups based on county of residence, cancer site, age and sex [29]. The study found that Mexicans in Florida had low cancer risk for most cancers except liver, cervical, and stomach, while Cubans and Puerto Ricans shared higher cancer risk compared to other Hispanic groups and had rates of endometrial, prostate, and colorectal cancer similar to NHWs [29]. Cubans more closely resembled NHWs with lower cervical and stomach cancers than other Hispanics, yet they surpassed NHWs for colorectal cancer, while Puerto Rican males showed particularly high liver cancer rates [29]. Some of these relative patterns observed for incidence are similar to current mortality analyses [30], suggesting that the underlying risk factors for each of these populations have not substantially changed in the last decade and attesting to their persistence in the respective Hispanic populations. Since then, no other study has attempted to estimate population-based incidence rates for Hispanic groups.

Like incidence research, and owing to many of the same shortcomings, few studies have analyzed differential cancer survival by Hispanic group. These projects were mostly conducted in Florida [15, 31], the state with sufficient heterogeneity and numerically sizeable Hispanic groups to conduct such studies, but were subject to some important biases, as discussed in more detail below. SEER provides survival statistics for Hispanics, which are predominantly reflective of the experience of Mexican Hispanics given the overwhelming proportion of this group in the SEER

coverage area [5]. However, because of incompleteness of place of birth, SEER survival statistics reports do not make a distinction between US- and foreign-born Hispanics [5]. Overall, the consequence of this obstacle in the data and its consequences (see below) is a virtual dearth of knowledge regarding differences in survival among specific Hispanic groups and compared to other non-Hispanic populations.

Vital Statistics Data (Mortality) In contrast to surveillance data (used for incidence and survival), mortality data, particularly when obtained directly from states, can be assembled to achieve near completeness for Hispanic specific groups. Another advantage of mortality data is that with additional work using specific place of birth and text fields, it is possible to study Central Americans and South Americans separately, which is not possible in cancer registry data. Thus, mortality data are optimal to analyze Hispanic heterogeneity in detail.

While the National Vital Statistics System data from the CDC [6] have the advantage of covering the entire nation, the available data lack sufficient detail on some key variables, such as specific country of birth and ethnicity text fields. These federal datasets are compiled from each state's data and rely on broader variables (e.g., US versus foreign birthplace, South/Central American ethnicity) which inevitably leads to some degree of misclassification [6]. As an example, for cancer deaths that occurred between 2010 and 2016 in the diverse state of Florida, 29%, 24%, 17%, 10%, and 9% of individuals born in Paraguay, Spain, Argentina, Venezuela, and Honduras, respectively, were coded as non-Hispanic [32]. Furthermore, of all Argentinians categorized as Hispanic, coded Argentina by birthplace and/or text fields, 38% were not correctly categorized in the South/Central American category, most likely falling into the Ethnicity Other category. The pattern continued with at least 20% of those who were known to be from Central/South America (Nicaraguans, Colombians, etc.) and not found in the South/Central American grouping category [32]. On the other hand, individuals born in countries such as Brazil, Italy, and Portugal have substantial proportions recorded as Hispanic ethnicity, when this does not correlate with the US Office of Management and Budget (OMB) definition of Hispanic [33]. While this misclassification results in some underestimation of Hispanics as a whole, its final effect on estimated rates is more pronounced when studying specific Hispanic groups, with misclassification across groups as well as a variable proportion of Not Otherwise Specified Hispanic cases (NOS).

However, at the state level, mortality data for some states contains the necessary detailed information that allows for accurate specific group classification based on codes for ethnic groups and specific birthplace, augmented with revealing text descriptive for otherwise incompatible or incomplete cases. In our studies [18, 30, 34], we found data in three states (California, New York, and Florida) to be more than 97% complete with a traceable specific Hispanic group leaving only 3% of cases as Hispanic NOS. Notably, the availability of ethnicity group, birthplace, and text fields was partial for other states (Texas) and unavailable for Maryland and New Jersey, limiting their use for this purpose.

Challenges in the Analyses

Primary to the accurate disaggregation of Hispanics into unique groups is the identification of all those in the population who are indeed Hispanic. While acknowledging that race and ethnicity are social constructs that vary by geography across the globe, within the United States, disparities research has followed the OMB-defined division [33] of races into four mutually exclusive categories (and mixed race) while ethnicity is coded as Hispanic or Latino, via a binary Yes/No. Once a case is coded Hispanic, then depending upon the data source and how it is collected, specific group allocation follows. One of the greatest challenges in population-based studies is how to best handle those persons who cannot be allocated definitively to a group, commonly referred to as Not Otherwise Specified, or Hispanic NOS. Importantly, these persons do not constitute an actual distinct group, as each case logically belongs to a specific group (or combination of groups) at some point whether in the present or by heritage from past generations. Despite that, a minority of cases (mostly US-born) self-identify as Hispanic only. However, a comparison of incidence data (low completeness of Hispanic specified group) to mortality data (very high completeness of Hispanic specified group) shows that more often, specific group information is known to the individual case, but is not asked, not known, or not available to those who record the data. Thus, assignment to the Hispanic NOS category is commonly a result of incomplete information. How researchers attend to these cases determines the accuracy of resulting calculated indicators.

Incidence and Mortality Rate Problems for Disaggregated Hispanic Groups Management of Hispanic NOS cases varies between the sources of data used for calculating cancer outcomes. Cancer registry data for cancer incidence and death data for mortality rates are used in the numerators, and census-based population data are used in the denominators. Census reports have traditionally grouped Hispanics into five categories, with only three corresponding to specific groups: Mexicans, Puerto Ricans, and Cubans. Other Specified Hispanics (which includes any specified group such as Dominican, Central American, South American, Spaniard, etc.) make up a fourth group, and a very sizeable Hispanic NOS group is the last. Thus, Hispanic NOS cases in the numerator, whether derived from incomplete incidence data or more complete mortality data, do not correspond to the NOS cases in the denominator, which raises a critical compatibility issue. When estimating rates for these specific groups, the lack of proper handling of NOS cases with the correction of this imbalance can truly confound our understanding of patterns among Hispanics.

Mortality rates are a good example. Without attending to the fact that the total number of NOS cases in census data logically includes Hispanics from potentially all groups (including Mexican, Puerto Rican, and Cuban) [35], people will be missing from the denominator for the three groups that are specified: Mexican, Puerto Rican, and Cuban. Another common problem arises in studies which combine the fourth (Other Specified, i.e., South and Central Americans, Dominicans) and fifth

census groups (Hispanic NOS) into one denominator group and combine all non-Mexican, non-Puerto Rican, and non-Cuban cancer cases into one numerator group. These NOS mismatches between numerators and denominators result in an overestimation of death rates for the Mexican, Puerto Rican, and Cuban groups, with a meaningless underestimation of the Hispanic NOS mortality rates (often labeled as Other Hispanics or South and Central American, more for convenience than accuracy). For incidence rates, the problem is even worse because the specific group information in the numerator is substantially less complete than mortality data; and without accounting for the Hispanic NOS, these group-specific rates are inevitably underestimated. Sadly, some research published in reputable journals fail to meet the basic logical tenet that the sum of the parts should equals the whole; rather these studies present disaggregated results where the sum of the weighted rates for each group does not correspond to the total All Hispanics rate. Errors of this nature arise from the complexity of managing the Hispanic NOS cases; treating NOS cases as an included unique group and excluding them are both problematic. Thus, as in our research, exhaustive ascertainment of specific group in both the cancer data and the denominator data from available detailed sources [22], followed by treatment of the remaining (hopefully minimal) NOS cases via appropriate partition and/or imputation strategies, is essential for the presentation of the true cancer incidence and mortality rates in Hispanic groups. In addition, the partition and/or imputation should always take into account birthplace distributions [36] in both the cancer data and the population data.

Survival Estimation Problems for Disaggregated Hispanic Groups

Hispanic NOS Survival estimates on a population level are derived from one data source, cancer registries, and thus theoretically should avoid the problem of numerator/denominator mismatch. Survival denominators are all the cancer cases, while numerators are those who have survived up until a certain designated period of time. However, a crucially important methodological barrier to calculate accurate survival for groups also includes the "nebulous" Hispanic NOS category and who it represents. In cancer surveillance data (registries), a proper specific group is more likely specified when the death has occurred because extra information on ethnicity and/or birthplace is available from direct access to and/or linkages with death certificate data. Consequently, having a specified Hispanic group in registry data is positively correlated with death, the exact outcome of interest in survival analysis [16, 17]. Conversely, if a Hispanic case is not deceased, the information available for precise group and birthplace is much less available, making it more likely to be ascribed as Hispanic NOS, rather than Mexican, Cuban, etc. The resulting survival estimates for the specified Hispanic groups will thus be underestimated, or lower than reality, precisely because those who are alive from any given specific group are more likely

to be coded NOS while those who are dead are more likely to have a specified group [16, 17]. In practical terms, this results in a specific group likely appearing to have worse (lower) survival than reality, while the Hispanic NOS survival will have better (higher) survival than that seen for all Hispanics combined, as these NOS cases are more likely to appear alive [16, 17]. Thus, exclusion of Hispanic NOS cases in survival analysis, under the false assumption that membership in the NOS group is random, results in highly biased results, with a specified group having biased low survival compared to other non-Hispanic groups (e.g., NHWs), since some alive cases are being excluded. Additionally, even if Hispanic NOS cases are excluded and analysis is restricted to Hispanic known groups only, survival comparisons will still be biased. This is because Puerto Ricans and Cubans are two groups for which death matches are more complete than Mexicans and Central and South Americans, given the higher proportion among Puerto Ricans and Cubans of a workable social security number, the essential variable for death linkages [11, 15]. As it stands, on a population basis, exclusion of NOS cases misses the population-based characteristics of the data for each of the Hispanic groups and results in making their outcomes look worse than reality.

Disproportionate Loss to Follow-up Survival studies have identified artifactual factors impacting death linkages to cancer registry data, particularly for minority groups with substantial proportions that are foreign-born such as Hispanics [11, 15]. Linkage problems arise from an inability to match social security numbers (SSN) because of diverse reasons including lack of SSNs, incorrect SSNs resulting in non-matches, or different structure of surnames or misspellings, common among Hispanics as well as among Asians from countries with non-Roman alphabets [11]. Missed deaths also arise from cases that are diagnosed in the United States but die in another country. These may be non-residents who are falsely coded as resident when coming to the United States solely for diagnosis and treatment, often referred to as "medical tourism." Others may be residents who are diagnosed here but return to their home countries to die, a phenomenon referred to as the "Salmon Bias" [37].

In all the described scenarios, persons from minority populations, especially those with late stage disease, are disproportionately lost to follow-up [11]. This may bias their survival upward (better than reality), especially in non-SEER states with registries associated with the CDC's National Program of Cancer Registries (NPCR). The difference between the registry types arises because SEER registries benefit from the requirement of a minimum of 95% of cases having a precise date of alive contact over time [38]. Unfortunately, this requirement is not specific to ethnicity or birthplace; thus, the remaining 5% are alive/living cases, disproportionately foreign-born and minority cases. By accruing more accurate survival time, SEER substantially reduces the potential for bias from non-random censoring among the foreign-born. However, in NPCR registries, no date of last alive contact is recorded, and if a specific patient does not match any record in a mortality list at a given date, then that patient is presumed alive at that date, which is called the "presumed alive" assumption of survival [11]. The following example illustrates the

current difference between SEER and NPCR survival data: Mrs. X is a US resident of Venezuelan origin who had lung cancer diagnosed in the United States. After 4 months of treatment in the United States, she returns to her birth country and subsequently passes away in Venezuela. The death data for Mrs. X never reaches mortality records in the United States. In SEER registries, her vital status would be counted as alive, but only for 4 months of survival time, based on her last medical encounter recorded in the United States. In NPCR registries, she would be presumed alive until the date of cut-off for the survival estimation, often 5 years. Thus, the NPCR registry would have substantially more months of survival for Venezuelans than the SEER registry. Similarly, having an unworkable SSN or a misspelled last name (both problems more prevalent among the foreign-born) would work the same way even if there was no return to Venezuela, because they could more likely result in a missed death after routine death linkages. Compared to other groups, deaths of Puerto Ricans and Cubans are more likely to be fully captured and linked in cancer data [15]. This is because Puerto Ricans are US citizens, and Cubans have lower likelihood of returning to Cuba and historically greater facility in acquiring legal status in the United States. While on a population basis the proportion of missed deaths is small, these missed deaths, particularly for poor prognosis cancers, in Hispanic groups that are largely foreign-born (especially Central and South Americans [15] and Mexicans born in Mexico), result in inflation of survival estimates, making comparisons inaccurate [11]. To make things even more confusing, the combined effect of these biases—Hispanic NOS and higher loss to follow-up—can send survival estimates in any direction away from reality depending on which one is stronger or just balance each other out.

Current Knowledge: Cancer in Hispanic Groups, Based on Mortality Data

Using mortality data, we conducted research that either addressed or bypassed the common deficiencies in the literature for disaggregated Hispanic groups. We used death certificate data and carefully assembled multiple race/ethnicity fields, text fields, and available birthplace variables to accurately classify Hispanic group. Here we summarize our findings from population-based studies using disaggregated Hispanic groups, highlighting four examples to show the importance of disaggregation.

Mexicans and Puerto Ricans in the United States Compared to Those in Mexico and Puerto Rico Mexicans and Puerto Ricans are the largest US Hispanic groups traceable to a single country of origin. (The island of Puerto Rico, although an American territory, is considered here as a country of origin for convenience.) Using methodology from other studies, we compared cancer rates for these specific groups in the states where they are most populous, California for Mexicans and New York for Puerto Ricans, to cancer rates among their counterparts in Mexico and Puerto Rico, respectively (Table 2.1) [34, 39].

For the vast majority of cancers, mortality during the studied time period (2008–2012 in California and 2008–2014 in New York) was higher in the Hispanic groups residing in the United States than in their countries of origin [40, 41] (Table 2.1). Given that cancer survival is higher in the continental United States than in Mexico and Puerto Rico [42], higher mortality suggests that cancer incidence must be substantially higher in the United States for the majority of cancers. Differences in risk among genetically and culturally similar populations such as these are commonly attributed to a higher prevalence of lifestyle risk factors in the United States, including smoking, obesity, alcohol, and other substance abuse [43]. Thus, results showing higher mortality in the United States are not surprising for many cancers including lung and other tobacco-related cancers; breast cancer, linked to obesity but also likely to differences in fertility patterns; liver cancer, linked to obesity and chronic infection with the hepatitis C virus (HCV); and other obesity-related cancers such as kidney and endometrial. The significantly higher pancreas and non-Hodgkin lymphoma mortality patterns are more intriguing, given how little etiological knowledge is known for these cancers that could be explained logically on a population basis. For a few cancers, mortality rates are lower in the United States among the Mexican and Puerto Rican groups compared to their country-of-origin counterparts. These include prostate cancer, an interesting pattern seen in other migration studies [20, 39, 44] and likely reflective of better survival in the United States including more aggressive treatment in older ages and more access to varied and complex treatment regimens, notwithstanding the potential effect of the comparatively higher PSA screening patterns in the United States.

Interesting patterns that emerge between these two distinct Hispanic groups include Mexican American women seeming to escape the adverse HCV impact, with lower liver cancer rates than women in Mexico. Also, excesses in colorectal cancer for Mexican American men compared to Mexico are not mirrored in Puerto Rican patterns. Conversely, the gains seen among Mexican Americans for cervical and stomach cancers are not realized among Puerto Ricans in New York, who share similar high mortality with their island counterparts (Table 2.1). Some findings from similar analyses using available data from US minorities and their countries of origin extend to childhood cancer: for instance, Mexican American children have higher rates (incidence and mortality) of brain cancer and neuroblastoma compared to Mexican children in Mexico [39], which raises provocative questions about an increased risk for these cancers in the US environment. Yet, very few of these questions have received attention from the research community.

Differential Cancer Patterns over the Lifespan (Based on Birthplace) among Hispanics in the United States Of the 35 million Hispanics in the US Mexican group, 22 million are US-born and 13 million are foreign-born [45]. Leveraging this distribution in analyses disaggregated by birthplace provides additional insights into the role of environmental factors in the development of cancers. While birthplace is by no means a perfect indicator of residential history or indeed any risk factors for cancer, on a population basis, it is the most complete proxy of early life environmental influences, as most immigrants arrive as adults [45]. Using mortality data from California and Texas, we showed that cancer patterns of Hispanics vastly

Table 2.1 Annual age-adjusted[a] mortality rates of Mexicans in California and Puerto Ricans in New York State compared to their counterparts in Mexico and Puerto Rico and the referent non-Hispanic white population

	California 2008–2012				Mexico 2008–2012[b]		New York State 2008–2014				Island of Puerto Rico 2008–2014[c]	
	Non-Hispanic white		Mexican				Non-Hispanic white		Puerto Rican			
	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI
Male												
Oral cavity and pharynx	4.2	(4.0–4.4)	2.5	(2.2–2.8)	2.2	(2.2–2.3)	3.2	(3.0–3.3)	4.9	(4.1–5.8)	5.0	(4.6–5.5)
Esophagus	7.6	(7.4–7.9)	4.4	(4.0–4.8)	2.4	(2.2–2.5)	7.8	(7.6–8.1)	7.2	(6.2–8.3)	5.0	(4.6–5.4)
Stomach	3.9	(3.8–4.1)	8.1	(7.6–8.6)	10.0	(9.8–10.2)	4.2	(4.0–4.4)	7.8	(6.7–9.0)	7.1	(6.6–7.6)
Colorectum	17.0	(16.6–17.4)	15.6	(14.9–16.4)	7.1	(7.0–7.3)	16.9	(16.5–17.3)	21.7	(19.9–23.6)	20.6	(19.9–21.5)
Liver[d]	8.0	(7.7–8.2)	14.6	(13.9–15.3)	9.0	(8.8–9.1)	7.2	(6.9–7.4)	21.3	(19.7–23.1)	10.4	(9.9–11.0)
Pancreas	12.6	(12.3–12.9)	10.6	(10.0–11.2)	5.8	(5.7–5.9)	13.7	(13.4–14.0)	10.4	(9.2–11.7)	7.4	(6.9–7.9)
Lung[e]	49.5	(48.8–50.1)	26.5	(25.4–27.5)	15.4	(15.2–15.7)	53.1	(52.5–53.8)	40.0	(37.5–42.5)	21.1	(20.3–21.9)
Prostate	22.3	(21.9–22.7)	18.9	(18.1–19.9)	23.0	(22.7–23.2)	17.6	(17.2–18.0)	21.6	(19.6–23.7)	29.4	(28.5–30.4)
Kidney	5.4	(5.2–5.7)	5.7	(5.3–6.2)	3.5	(3.4–3.6)	5.3	(5.1–5.5)	3.7	(3.0–4.5)	2.5	(2.2–2.8)
Bladder	8.5	(8.3–8.8)	3.6	(3.2–4.0)	2.4	(2.3–2.5)	9.1	(8.9–9.4)	5.3	(4.4–6.4)	4.5	(4.2–4.9)
Brain	6.8	(6.6–7.1)	3.6	(3.3–3.9)	2.9	(2.8–3.0)	5.4	(5.2–5.6)	3.1	(2.5–3.8)	3.0	(2.7–3.3)
NHL	8.2	(8.0–8.5)	7.2	(6.7–7.7)	3.7	(3.6–3.8)	7.8	(7.5–8.0)	6.8	(5.8–7.8)	4.7	(4.3–5.1)
Leukemia	9.8	(9.5–10.1)	6.0	(5.5–6.4)	5.0	(4.9–5.1)	9.5	(9.2–9.8)	5.5	(4.7–6.5)	5.5	(5.1–5.9)
All sites combined[f]	200.7	(199.4–202.0)	151.6	(149.2–153.9)	116.3	(115.7–116.9)	193.3	(192.0–194.6)	190.7	(185.2–196.2)	159.9	(157.7–162.1)
Female												
Oral cavity and pharynx	1.6	(1.5–1.7)	0.9	(0.7–1.1)	1.0	(1.0–1.1)	1.1	(1.0–1.2)	1.1	(0.8–1.5)	1.0	(0.8–1.1)
Esophagus	1.7	(1.6–1.8)	0.7	(0.6–0.8)	0.7	(0.7–0.8)	1.7	(1.6–1.8)	1.6	(1.2–2.0)	1.0	(0.8–1.1)

(continued)

Table 2.1 (continued)

	California 2008–2012				Mexico 2008–2012[b]		New York State 2008–2014				Island of Puerto Rico 2008–2014[c]	
	Non-Hispanic white		Mexican				Non-Hispanic white		Puerto Rican			
	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI
Stomach	1.9	(1.8–2.0)	4.9	(4.5–5.2)	7.5	(7.4–7.6)	2.1	(2.0–2.2)	3.8	(3.2–4.4)	3.5	(3.3–3.8)
Colorectum	12.9	(12.6–13.2)	8.9	(8.4–9.4)	5.7	(5.6–5.8)	12.3	(12.0–12.6)	13.3	(12.1–14.5)	12.8	(12.3–13.4)
Liver[d]	3.2	(3.0–3.3)	6.7	(6.3–7.2)	8.5	(8.3–8.6)	2.9	(2.8–3.1)	6.2	(5.5–7.1)	4.4	(4.1–4.8)
Pancreas	9.9	(9.6–10.2)	8.7	(8.2–9.2)	5.9	(5.7–6.0)	10.2	(9.9–10.4)	8.4	(7.5–9.3)	5.6	(5.3–6.0)
Lung[e]	38.7	(38.2–39.3)	13.8	(13.2–14.4)	7.0	(6.8–7.1)	39.4	(38.9–39.9)	20.6	(19.2–22.1)	9.1	(8.6–9.5)
Breast	24.6	(24.1–25.0)	15.1	(14.5–15.7)	13.2	(13.0–13.4)	21.0	(20.7–21.4)	18.1	(16.8–19.5)	18.3	(17.7–19.0)
Cervix	1.9	(1.8–2.1)	2.9	(2.7–3.2)	10.4	(10.2–10.5)	1.8	(1.7–1.9)	3.9	(3.3–4.5)	2.6	(2.3–2.8)
Uterus	4.5	(4.3–4.7)	3.8	(3.5–4.1)	2.0	(1.9–2.1)	4.9	(4.7–5.1)	4.8	(4.1–5.5)	4.2	(3.9–4.6)
Ovary	8.9	(8.6–9.1)	6.3	(5.9–6.7)	4.8	(4.7–4.9)	8.4	(8.2–8.6)	5.6	(4.8–6.4)	4.1	(3.8–4.5)
Kidney	2.3	(2.2–2.4)	2.9	(2.6–3.2)	2.0	(1.9–2.0)	2.2	(2.1–2.3)	1.4	(1.0–1.8)	1.1	(1.0–1.3)
Bladder	2.3	(2.2–2.5)	1.3	(1.1–1.5)	1.1	(1.1–1.2)	2.6	(2.5–2.7)	2.1	(1.7–2.6)	1.7	(1.5–1.9)
Brain	4.4	(4.2–4.6)	2.6	(2.4–2.9)	2.2	(2.1–2.2)	3.7	(3.5–3.8)	2.4	(1.9–2.9)	2.1	(1.9–2.3)
NHL	4.8	(4.6–5.0)	4.8	(4.4–5.1)	2.8	(2.7–2.9)	4.8	(4.6–5.0)	4.1	(3.5–4.8)	3.0	(2.7–3.3)
Leukemia	5.5	(5.4–5.8)	4.0	(3.7–4.3)	3.9	(3.8–4.0)	5.1	(5.0–5.3)	4.3	(3.7–5.0)	3.4	(3.1–3.7)
All sites combined[f]	151.8	(150.8–152.8)	106.0	(104.4–107.7)	98.3	(97.9–98.8)	145.4	(144.4–146.3)	119.7	(116.2–123.2)	97.2	(95.7–98.8)

CI confidence interval, *NHL* non-Hodgkin's lymphoma

[a]2000 US Standard Population.

[b]Ref. [41]

[c]Ref. [40]

[d]Includes intrahepatic bile duct

[e]Includes bronchus

[f]All sites combined includes those listed as well as those not listed here

differ by birthplace [18]. Contrary to the purported Hispanic advantage portrayed when rates are calculated in aggregate, overall cancer mortality rates for US-born Hispanic males are for the most part no better than non-Hispanic whites, albeit with site-specific variation including lower rates of tobacco-related cancers such as lung and bladder cancers and higher rates of liver, stomach, colorectal, and kidney cancers [18]. Conversely, foreign-born Hispanics are a relatively low-risk group, burdened only with higher rates of stomach, cervix, and prostate cancers than their US-born counterparts [18], a finding further confirmed when analyzing Mexican Hispanic populations alone [39]. Most striking are the excesses seen for male colorectal, kidney, and liver cancers, likely reflecting higher prevalence of obesity and HCV infection among US-born Mexicans than their foreign-born counterparts. Barring ascertainment of detailed risk factor information, virtually impossible at the individual-level on a population basis, these patterns may be the best evidence we have so far of the impact of spending formative years in a US environment characterized by overconsumption of fats and sugars, sedentary lifestyle, and low age of experimentation with drugs and alcohol as well as unique stressors associated with discrimination [43]. Moreover, disaggregated rates by birthplace provide opportunities to identify protective factors seen in foreign-born populations, identify strategies to maintain these protective factors, and potentially use this information in risk reduction strategies among US-born populations.

Puerto Ricans and Divergence from Favorable Aggregated Hispanic Patterns Using mortality data from New York State (NYS) [34], we revealed considerable cancer mortality disparities for Puerto Ricans compared both to the majority NHW population and to other Hispanic groups [34]. These disparities, which should be addressed by targeted cancer prevention and control programs, were largely masked by the presentation of Hispanic cancer mortality rates in aggregate.

Puerto Ricans are the largest Hispanic group in NYS [22]; moreover, most cancer deaths (81%) in this group occurred among Puerto Ricans born in the continental United States [34]. Thus, examination of this group in this state provides a unique lens with which to examine the influence of extended acculturation as a minority in the United States. Three prominent findings emerged from our study. First, similar to US-born Hispanic males in California and Texas, overall cancer mortality rates of Puerto Rican males in NYS are not lower than, but rather similar to rates of the majority NHW reference group. Again, different cancer sites afflict the two populations: tobacco-related bladder and lung cancer mortality are higher among NHWs; infection-related cancers (stomach, liver and cervix) are higher among Puerto Ricans [34]. Secondly, the disparity between Puerto Ricans and NHWs for these infection-related cancers, more commonly associated with developing countries, is consistent with patterns seen for another socio-economically deprived US minority: the US-born black population [34]. Prior assumptions that the high burden among Hispanics in aggregate for infection-related cancers was being driven by the foreign-born (carrying their risk from developing countries) should be urgently re-examined. This evidence from disaggregation of rates suggests US poverty, proportionately

higher in NYS among Puerto Rican and US-born blacks, is driving the burden, and thus appropriate resources should be shifted to eliminate this disparity. Lastly, Puerto Rican males in NYS have significantly higher mortality than any other Hispanic group for oral, esophageal, colorectal, lung, bladder, and especially liver cancer, while Puerto Rican females have higher mortality from colorectal, lung, postmenopausal breast, liver, and cervix cancers [34]. With the exception of colorectal and breast cancers, these are the cancers associated with low SES [46]. Thus, these patterns, revealed only because of disaggregation, not only are consonant with the negative effects often associated with acculturation, but also correlate with prevailing economic disparities that adversely impact health possibly more acutely in second-generation immigrants [34].

Liver Cancer: Etiological Insights from Disaggregation of Hispanic Groups Our fourth and final example illustrating the importance of disaggregation focuses specifically on liver cancer, drawing again from our study conducted in NYS [34]. As a multi-causal disease [47], liver cancer incidence and mortality are difficult to interpret given disparate etiological factors, including HCV, obesity, heavy alcohol consumption, diabetes, and chronic infection with the hepatitis B virus, the latter especially among Asians and the foreign-born [48]. We examined Hispanics as a whole and disaggregated: Puerto Rican male liver cancer rates were higher than other analyzed groups in NYS, including Asians and blacks [34]. Within the 1945–1965 birth cohort, known for its high prevalence of HCV infection [49], excesses in liver cancer mortality were exceedingly high among not only male but also female Puerto Ricans. Patterns were similar to US-born blacks, but diverged completely from other Hispanic groups in New York, which include overwhelmingly foreign-born Hispanics (Dominicans, Central Americans, South Americans, etc.) as well as non-Hispanic blacks born in the Caribbean; all showing relatively low mortality for liver cancer [34]. Differences are more pronounced in males and within the birth cohort of 1945–1965, suggesting just from a descriptive analysis that socially and economically deprived minority populations physically present in NYS during the 1960s–1980s (when transmission of HCV was likely caused by IV drug use and needle sharing) who also share disproportionately high rates of incarceration [50], linked to HCV transmission [51], are particularly prone to higher mortality from liver cancer. While undeniably other etiological factors contribute to the excess of liver cancer among Hispanics in general, especially in older populations, the existing patterns suggest a compelling association between the known high prevalence of HCV [52] and liver cancer [34] in the Puerto Rican population, even in relation to NHWs within the same birth cohort, who are also considered high-risk. Notably, neither Hispanics overall nor Puerto Ricans specifically are currently considered a priority population for viral hepatitis control programs [53]; yet, our finding, which would have been totally missed had it not been for the disaggregation of Hispanics, suggests that HCV testing and viral hepatitis control could help alleviate this disparity particularly for Puerto Ricans. Further study of the etiology of liver cancer by disaggregated groups will provide additional clarification into the specific etiological forces driving high cancer rates among other Hispanic groups, particularly in older populations.

Conclusions

US Hispanics number 55 million, which is 17% of the total US population [22]; they are highly heterogeneous, with unique genetic admixtures and widely variant socioeconomic profiles [45, 46]. While the population structure of Hispanics is relatively young, these currently younger Hispanics will soon reach the ages at which cancer is more common. Prevention strategies are needed now to meet this need. Special attention should be directed to the distinct disparities among US-born Hispanics, whose cancer numbers are rapidly trending upwards and who may not profit from the same protective health benefits of their first-generation immigrant counterparts. Accurate incidence, survival, and mortality rates of Hispanics by specific group are critical because aggregation provides at best a fuzzy picture and at worst a lie. Not all Hispanics are doing well, as would be suggested by aggregated rates. There are many challenges to studying population-based cancer indicators by disaggregated Hispanic groups, especially for incidence and survival, which we described above. Yet, overcoming these challenges can provide critical insights, as we demonstrated here through a synthesis of our results from several recent studies.

While cancer surveillance and vital statistics data have the advantage of being available on an individual level for entire populations, they are limited to basic demographic information. Certainly, while our findings are hypothesis-generating, further research that incorporates individual-level risk factor information will be required to substantiate and further explain these findings for Hispanic groups, including prevalence of obesity, smoking, diabetes, age at immigration, and length of time residing in the United States (for immigrants). Studies should also examine other social, economic, and cultural factors that impact access to health care and attitudes toward health, which may differ substantially by specific Hispanic group. Moreover, finding answers to the innumerous questions arising from these comparisons will require the inclusion of biological characteristics of tumors, including genetic and molecular subtypes.

Continued epidemiological research on the intra-ethnic cancer experience among Hispanics in the United States is imperative, not only to identify and address disparities, but also because this highly heterogeneous population provides opportunities through specific group analyses to further explore the etiology of cancers and discover potential avenues for cancer prevention and control efforts.

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Chapter 3
Colorectal Cancer Disparities in Latinos: Genes vs. Environment

Maria Gonzalez-Pons and Marcia Cruz-Correa

Overview of Colorectal Cancer Disparities in Hispanics

For many years, science has been moving toward a better understanding of factors that contribute to colorectal cancer (CRC) health disparities. In 2012, CRC was the third most diagnosed cancer (1.4 million cases) and the fourth most common cause of cancer-related death causing 694,000 deaths worldwide [1]. An analysis of Globocan 2012 data shows that among countries in the Americas with the highest age-standardized rates (ASR) for CRC incidence, Canada ranks first with the highest ASR, closely followed by the United States (US) and Puerto Rico which rank fourth and fifth, respectively [1]. In the US, CRC is the third most commonly diagnosed malignancy and the third leading cause of cancer-related death [2]; however, marked differences in incidence and mortality have been noted among racial/ethnic groups [3].

It is important to note that US mainland Hispanics comprise a heterogeneous group of Hispanic subgroups from various countries in Central and South America. Hispanics are the result of more than 500 years of admixture of European, Indigenous American, and African individuals [4], and the extent of admixture varies according to the country of origin. CRC incidence rates among US mainland Hispanics also vary according to their country of origin, which supports the hypothesis that

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differences in ancestry may contribute to the variability of CRC incidence. Moreover, after Hispanic subgroups move to the US, the CRC incidence among them is higher than in their native country, supporting the idea that interactions between ancestry and environmental exposures resulting from acculturation are a major risk factor for the development of CRC [5]. Disparities in the age of onset of CRC have been reported between Hispanic subgroups. From 1993 to 2007, the overall incidence of CRC declined in Hispanics, but a dramatic 45% increase was reported among Hispanics younger than 50 years of age (early-onset CRC) [6]. The increase in incidence of early-onset CRC was markedly greater in Hispanics than in non-Hispanic Whites (NHW) and African Americans (AA), which increased 27% and 15%, respectively [6]. In a study investigating the demographic and clinical characteristics of 36,133 US mainland Hispanics with CRC living in California during 1995–2011, differences were observed in age at diagnosis according to the country of origin [7]. A statistically significant higher number of early-onset CRC was diagnosed in Hispanics (16%) compared to NHW (7%). Mexican and Puerto Rican Hispanics (PRH) were among the subgroups with the highest proportion of CRC cases among individuals <50 years old (20% and 9%, respectively). When comparing all Hispanic subgroups with NHW, a higher number of Hispanics were diagnosed at advanced stages.

Factors Contributing to Colorectal Cancer Disparities in Puerto Rican Hispanics

In order to better understand CRC health disparities in Puerto Rico, our research team has worked on various transdisciplinary projects examining the epidemiological, environmental, and genetic factors that contribute to the CRC health inequities observed in this population.

Epidemiology

In a comparison of age-adjusted CRC incidence in the US and Puerto Rico from 2009 to 2013, AA and PRH men had the highest rates with 59.2 and 51.6 per 100,000, respectively. US mainland Hispanic men had the second lowest age-adjusted CRC incidence rates during the same time period. However, in a comparison of age-adjusted CRC incidence rates among women during the same time period, AA women had markedly higher rates (44.8 per 100,000) than the other racial/ethnic groups (<36.8 per 100,000). A comparison of age-adjusted CRC mortality rates during the same time period shows a similar trend among AA and PRH men, who had the two highest mortality rates; however, age-adjusted mortality rates are comparable among women in all racial/ethnic groups. We recently reported the

baseline CRC survival for PRH living in Puerto Rico [8]. Our study compared relative survival rates to those from racial/ethnic groups in the US, and found that PRH had the lowest survival rates in regional cancers and were the only racial/ethnic group in which there was a marked 5-year survival advantage among females (66.0%) compared to males (60.3%). Similar to the findings reported in California, 9.0% of the total CRC cases and 6.7% of total CRC deaths correspond to patients with early-onset CRC in Puerto Rico. These are nearly twice the percentages reported in the overall US population, thereby demonstrating a high burden of early-onset CRC in Puerto Rico [9]. Moreover, a comparison of 5-year survivorship according to age at CRC diagnosis during 2005–2010 showed that early-onset CRC patients in Puerto Rico had worse survival (57%) than CRC patients diagnosed at 50–64 years (66%) and ≥65 years of age (62%) [10]. In this same study, 5-year survival was also analyzed according to the type of health insurance coverage (government vs. non-government health plan). When combining all age groups, CRC diagnosis at advanced stages was more common in patients with the government health plan than those with non-government plans (44.3% vs. 40.2% diagnosed at regional stages, and 13.6% vs. 10.4% diagnosed at distant stages, respectively). Patients with the government health plan aged 50–64 (RR = 6.59; CI: 2.85–15.24) and ≥65 (RR = 2.4; CI: 1.72–4.04) years were at greater excess risk of death than patients with non-government health plans.

Environmental Factors

CRC still remains a major public health problem. However, very few CRC prevention strategies are available other than routine screening. In addition to genomic alterations, dietary and environmental factors are believed to contribute to colorectal carcinogenesis [11]. Factors that may increase the risk of CRC include physical inactivity, obesity, alcohol consumption, smoking, gut microbiome composition, and diet [12]. Dietary patterns are widely believed to act as pro- and anti-tumor risk modifiers across the entire multistep process of colorectal carcinogenesis, and they have also been shown to have a pivotal role in modulating the gut microbiota [13, 14]. Moreover, in 2015 the International Agency for Research on Cancer (IARC) concluded that high red meat consumption is a risk factor for CRC [15].

Accumulating evidence supports the hypothesis that changes in gut microbiota composition may contribute to the development of CRC [16], but the specific mechanisms by which the gut microbiota contribute to colorectal carcinogenesis are not fully understood. Differences in gut microbiota composition among ethnic/racial groups, as well as between African American and rural Africans, have been reported [17, 18]. Differences in bacterial community profiles and metabolites have been studied, but in our laboratory we are spearheading a study evaluating the association between dietary patterns, presence of bacterial toxins in stool and colonic mucosa, and colorectal neoplasia. Using a case–control study design, we examined the association between the presence of bacterial toxin genes (*pks*, *tcpC*, *gelE*, *cnf-1*, *murB*,

and *usp*) in stool and colorectal neoplasia using samples from individuals from the US and Puerto Rico [19]. These bacterial toxins promote inflammation, cell proliferation, and/or DNA damage, all of which are hallmarks of cancer. Differences were observed in the prevalence of these bacterial toxin genes between stool samples from individuals in the US and Puerto Rico. Moreover, stronger associations were observed between the presence of >2 bacterial toxin genes in stool and the likelihood of having colorectal neoplasia in PRH. In stool samples from the mainland US, individuals with ≥2 of the genes in the panel were 9.33 times more likely to have colorectal neoplasia than individuals without these bacterial toxin genes. PRH individuals with ≥2 of the genes were 11.3 times more likely to have colorectal neoplasia and 24 times more likely to have colorectal adenomas than individuals without these bacterial genes.

Genetics

Significant advances have been made toward a better understanding of the molecular landscape of colorectal tumors. The TCGA's effort is significant because it provides a comprehensive molecular characterization of tumors from the colon and rectum, and this study demonstrated the molecular similarities between colorectal tumors regardless of their location (colon vs. rectum) [20]. In this genome-scale analysis of 276 samples, 16% of colorectal carcinomas were found to be hypermutated. Although a wealth of molecular information is available on the tumors included in the TCGA, it is important to note that there are very few tumors from ethnic/racial minorities (12% Black, 3% Asian, and 3% Hispanic) [21]. To better understand the molecular pathways that may contribute to the CRC health disparities observed among Hispanics, our group analyzed somatic molecular markers in PRH tumors (n = 488). We found that most tumors were microsatellite stable (98.4%), CIMP-low (92.1%), and had wild-type KRAS (68.8%) and BRAF (90.8%) genes. When compared to other US ethnic/racial groups, Hispanic CRC tumors had a lower percentage of microsatellite instability (MSI), lower incidence of CIMP-high tumors, and lower mutation rates for both the KRAS and BRAF genes. A recent genome-wide association study (GWAS) reported 17 variants across four independent regions that merit further investigation because of suggestive CRC associations [22]. There is limited information regarding ethnic-specific risk variation in Hispanics. Our group recently collaborated with colleagues at the National Cancer Institute in order to elucidate risk variants for CRC among PRH. In another effort to understand germline genetic predisposition for CRC among Puerto Ricans, we spearheaded a study evaluating the association between ancestry and increased cancer risk in 425 controls, 99 adenomas, and 414 CRC cases. Previous studies reported that Hispanics with adenomas and CRC have higher African mean ancestry; positive associations between African ancestry and adenomas were observed [23]. However, in our PRH cohort, we observed a trend of increased risk of CRC with increasing levels of European ancestry. Puerto Rican individuals with higher

than mean levels of West African ancestry were at increased risk of presenting with CRC tumors that are located in the distal colon, had moderate or low differentiation, and had BRAF mutations. Individuals who consumed high amounts of processed meat had 2 times higher CRC risk regardless of genetic ancestry.

Summary

- CRC health disparities have been reported among Hispanic subgroups, including PRH.
- CRC is the leading cause of cancer death in Puerto Rico. PRH had the lowest survival rates in regional cancers and were the only racial/ethnic group where a marked 5-year survival advantage was observed among females (66.0%) compared to males (60.3%).
- Marked disparities were observed according to age at CRC diagnosis and type of medical insurance within the Puerto Rican population.
- Dietary patterns are widely believed to act as pro- and anti-tumor risk modifiers across the entire multistep process of colorectal carcinogenesis and also play a pivotal role in modulating the gut microbiota.
- Differences were observed in the prevalence of bacterial toxin genes between stool samples from individuals in the US and Puerto Rico. Associations between having ≥2 bacterial toxin genes in stool and the likelihood of having colorectal neoplasia were stronger among PRH.
- PRH colorectal tumors were mostly microsatellite stable (98.4%), CIMP-low (92.1%), and had wild-type KRAS (68.8%) and BRAF (90.8%) genes. When compared to other US ethnic/racial groups, PRH CRC tumors had a lower percentage of MSI, lower incidence of CIMP-high tumors, and lower mutation rates for both the KRAS and BRAF genes.
- In our PRH cohort, we observed a trend of increased risk of CRC with increasing levels of European ancestry.

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Part III
Cancer Risk, Prevention, and Screening

Chapter 4
Breast Cancer Risk and Mortality in Women of Latin American Origin

Laura Fejerman, Silvia J. Serrano-Gómez, and Lizeth I. Tamayo

Introduction

The categories of Hispanic or Latino refer to individuals of diverse national origin (Mexico and all countries in the Caribbean, Central and South America), place of birth (individuals born in the United States whose ancestors were born in Latin America or individuals born in Latin America), and continental ancestral backgrounds (mostly European, Indigenous American (IA), and African, but also including Asian and other minor components). This diversity had not been systematically addressed in cancer epidemiology until recent years, and the lack of extensive datasets with detailed information about subgroups of Latinos has resulted in the placing of a very diverse set of individuals into one category. This is surprising given that Hispanics/Latinos represent the second largest US census racial/ethnic category including ~17% of the US population (50 million individuals) [1].

Breast cancer is the most common cancer in US Latinas [2], but compared to other population groups, incidence is relatively low. Age-adjusted breast cancer incidence rates based on 2010–2014 cases were 127.7 in non-Latina Whites (NLWs), 125.1 in non-Latina Blacks (NLBs), 98.5 in Asians/Pacific Islanders, 93.1 in Latinas,

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and 82.2 in Native Americans/Alaskan Natives [3]. Some studies have shown that despite the lower incidence of breast cancer in Latinas, their mortality risk is higher than NLW women, even after adjustment for tumor characteristics and socioeconomic status [4–8]. However, this observation is not consistent across studies, with several reporting lower risk of breast cancer-specific mortality for Latinas compared to other population groups [9–12]. In addition, Latinas have been reported to have a higher risk of developing aggressive subtypes [13] and of being diagnosed at more advanced stages of the disease [12, 14].

This chapter summarizes works conducted by our group and others on breast cancer risk, characteristics, and survival, in women of Latin American origin, with particular emphasis on observed differences among Latino subgroups.

Breast Cancer Risk in Women of Latin American Origin

The group usually designated by the category of Hispanics/Latinos is not homogeneous, and the risk of developing breast cancer among these women varies by national origin [15], place of birth (US-born vs. foreign-born) [16, 17], and genetic ancestry [18, 19].

A study that was based on cancer registry data from Florida, including diagnosis between the years 1999 and 2001 and ~30,000 Latinas, reported overall age-adjusted incidence rates of 106.4 (100.8–112.3) in this group, 140.4 (137.6–143.2) in NLWs, and 104.9 (98.5–111.7) in NLBs. Incidence rates varied greatly among Latinas by national origin, with Puerto Ricans having the highest rates (116.9; 103.7–131.4), followed by Cubans (108.0; 96.7–120.3) and Mexicans (71.9; 53.1–95.2). The incidence of breast cancer in Caribbean women was markedly higher than that in AAs [15]. The 2000 and 2005 National Health Interview Survey (NHIS) Cancer Control Modules observed a higher 5-year absolute risk in Cubans/Cuban-Americans compared to Mexican/Mexican-Americans and a higher lifetime risk in Dominicans compared to Mexican/Mexican-Americans [20].

Studies have reported that foreign-born Latinas have lower breast cancer incidence than their US-born counterpart [16, 17]. In California, foreign-born Latinas have lower risk of developing breast cancer than US-born [17], with increasing risk with longer US residency [16]. The study based on the Florida Cancer Registry also reported marked differences in incidence between Latinas residing in the United States and those in their countries of origin. Breast cancer incidence rates were reported to be twice or even three times higher in US women of Latin American origin, as in the case of Cubans (31 per 100,000 in Cuba vs. 78 in Florida) [15]. Concordant with these results, a study that compared cancer incidence between Puerto Ricans in the United States and in those residing in the Island found a significantly lower breast cancer incidence among Puerto Rican women who reside in Puerto Rico [21]. Differences in risk of breast cancer by place of birth could be explained by lifestyle changes related to the adoption of a more westernized reproductive behavior (i.e., lower parity, shorter duration of breast-feeding, and later age

at first full-term pregnancy) and dietary or other lifestyle choices (i.e., more fast food, higher alcohol intake, less exercise) [16, 22].

Genetic ancestry also varies among Latinas, and it has been reported that women with high IA ancestry have lower risk of developing breast cancer than those with high European ancestry. This difference was statistically significant after controlling for most established risk factors that are known to differ between Latina and NLW women [18, 19]. The inverse association between IA ancestry and breast cancer risk was partly explained by a genetic variant located near the estrogen receptor 1 gene (ESR1), shown to be of relatively high frequency in women with IA ancestry [23]. In Colombia, patients diagnosed with estrogen receptor-negative breast cancer (HER2-enriched, basal-like, and non-basal triple negative) had the highest African ancestry [24]; however, the role of African ancestry in defining breast cancer risk by Latina national origin has not been fully examined.

Breast Cancer Mortality in Women of Latin American Origin

The described heterogeneity among Latinas not only translates into differences in breast cancer risk but also mortality. Cubans and Puerto Ricans have the highest mortality rates [25], while Mexicans, Central Americans, South Americans, and Dominicans have lower breast cancer mortality rates [25].

Few studies have analyzed differences in cancer mortality by genetic ancestry in women of Latin American origin. In 2013, Fejerman et al. analyzed the association between genetic ancestry and survival in Latina women from the San Francisco Bay area and reported higher mortality hazard in women with more than 50% of IA ancestry compared to women with 50% or less of IA ancestry [26]. Nevertheless, when the association was re-tested in women with uniform access to healthcare, the previously observed disparity in breast cancer-specific mortality was no longer apparent [27].

Ellis et al. showed that stage at diagnosis explained 11% of the survival disparities in Latina women compared to NLW women [28]. Socioeconomic status is an important contributor to health disparities in breast cancer outcomes as reduced screening, diagnostic delays and barriers to comprehensive treatment can lead to later stage at diagnosis [29]. Latina women are less likely to use mammography screening compared to NLW women [29–31]. In addition, delays in the diagnostic biopsy after an abnormal screening study might contribute to the more advanced stages at presentation [29] and delays in treatment initiation [12]. Results of a study based in Chicago showed an inverse association between European genetic ancestry and the risk of late stage at diagnosis (OR 0.70, 95% CI: 0.54–0.92) among Latina patients even after adjusting for multiple social and behavioral risk factors [32].

While breast cancer incidence is relatively low in foreign-born Latinas, they are more likely to be diagnosed with breast cancer at more advanced stages, initiate treatment later, and are less likely to receive guidelines-concordant treatment when compared to US-born Latinas [17]. Some studies have reported that even though

foreign-born Latinas are more likely to be diagnosed with more advanced stages, they have better survival than US-born Latinas [17, 33, 34]. This is a well-known phenomenon called the immigrant paradox that refers to the better health outcomes observed for certain immigrant populations in the United States compared to non-immigrant individuals of similar socioeconomic background [35]. The fact that Latina women experience survival advantages can be related in part to the lifestyles adopted in Latino enclaves, in which they may promote better health attitudes and behaviors such as healthier diets and social support [17, 34, 36]. These enclaves are neighborhoods with dense US-born Latino or Latino immigrant populations that hold certain cultural norms and practices [33, 35]. It is important to mention that the better survival of foreign-born Latinas could be partly an artifact related to the return of these women to their native countries leading to an under-ascertainment of deaths [33, 36].

Breast Tumor Subtypes in Women of Latin American Origin

Breast cancer is a complex and heterogeneous disease that has been classified into four main intrinsic subtypes based on gene expression profiles: luminal A, luminal B, HER2-enriched, and basal-like [37, 38]. Luminal subtypes belong to the estrogen receptor-positive (ER+) group and are characterized by the expression of genes such as the estrogen receptor gene (ESR1) and genes regulated by estrogen such as GATA3 [39]. Although globally, luminal subtypes show the best outcomes, luminal B have a more aggressive phenotype as they express higher levels of proliferation-related genes and growth factor receptors such as HER2 [40, 41]. HER2-enriched and basal-like subtypes are ER-negative (ER−) subtypes. HER2-enriched tumors express ERBB2 and genes in the 17q22.24 locus [39, 42, 43] while basal-like subtype express basement membrane cytokeratins and lack the expression of ESR1 and its co-expressed genes [39]. ER− subtypes have the poorest prognosis when compared to luminal subtypes [44].

The distribution of breast cancer intrinsic subtypes varies among women from different populations, and Latina women have a higher proportion of more aggressive intrinsic subtypes such as ER− tumors than NLW women [13]. This is very important as these subtypes of disease have fewer treatment options and a poorer prognosis than other subtypes [3, 6, 45–48].

This differential distribution of subtypes in Latina compared to NLW women has been shown not only in population-based studies but also in hospital/clinical-based studies in Latin America. In population-based studies from the United States [49–60], the proportion of the triple-negative subtype in Latinas ranged between 10 and 18%, while in NLW women, it ranged between 8 and 15%. On the other hand, HER-enriched tumors ranged between 4 and 24% in Latinas and between 3 and 17% in NLW women. Not only US Latinas, but also Latin American women more generally, have a 20–40% higher risk of developing ER−/PR− and triple-negative breast cancers (TNBC) than NLW women [19, 54, 61–67].

Most studies performed in Latin America are hospital-based [24, 65, 68–73]. The reported proportion of triple-negative subtype in Latin America ranged between 12 and 24% and between 7 and 24% for the HER2-enriched subtype [47] (Fig. 4.1). Countries such as Mexico [47], Peru, and Colombia have higher relative frequency of triple-negative tumors (23%, 21%, and 21%, respectively) compared to other countries in Latin America such as Costa Rica (17%) [69], Brazil (17%) [65], and Puerto Rico (17%) [70]. When comparing hospital-based studies with those performed at national referral centers such as the National Cancer Institutes from each country, differences are also observed. For example, a hospital-based study in Peru reported that the proportion of triple-negative breast cancer was 17% [73] while in the study from The National Cancer Institute from Peru, it was 23% [71]. A similar scenario was observed in Colombia where a hospital-based study reported a proportion of 12% [72], while the Colombian National Cancer Institute reported a proportion of 21% [24] (Fig. 4.1). More studies are needed to decipher the distribution of intrinsic subtypes in a population-based scenario in Latin America and also to analyze the relationship between genetic ancestry tumor subtype.

The heterogeneity in the distribution of breast cancer subtypes in women of Latin American origin can be partly attributed to the differences in the source of

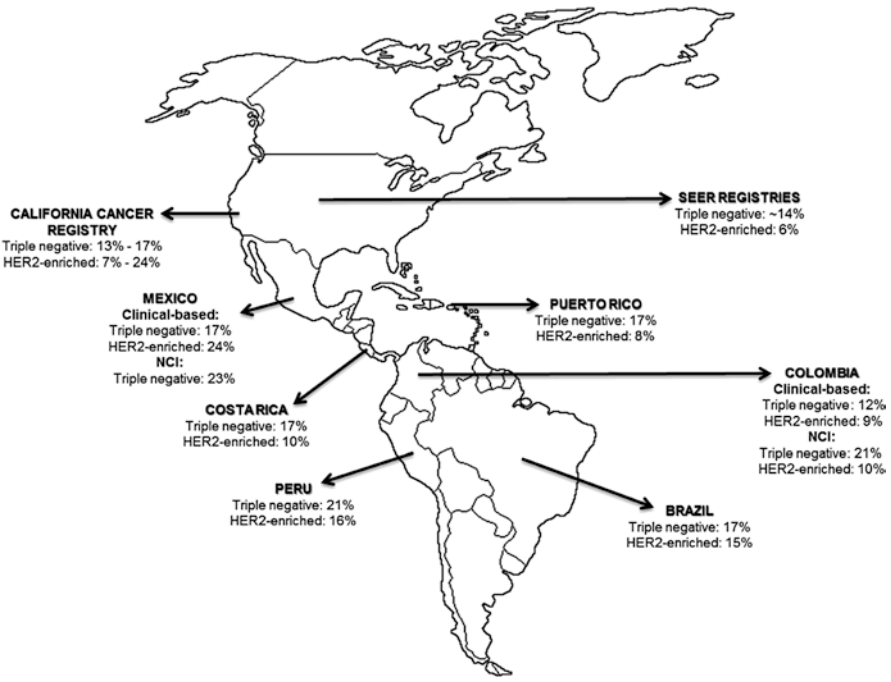

Fig. 4.1 Prevalence of triple-negative and HER2-enriched breast cancers in women of Latin American origin. Differences in the prevalence of these subtypes are noted between the different Latin American countries and also within the same country according to the source used, hospital-based, or reference center

information. National Cancer Institutes in Latin America are usually reference centers that receive patients that could not be adequately served by local hospitals/clinics, likely because of their advanced stage at diagnosis and tumor aggressiveness. Additionally, differences could result from the surrogates used to classify breast cancer into intrinsic subtypes (PAM50 or St. Gallen surrogates), although most studies used the basic classification that includes the evaluation of ER, PR, and HER2 [13].

Recent studies suggested that genetic ancestry could be acting as a modulator of gene expression and a risk modifier for the development of specific subtypes of breast cancer in Latina women [74]. Serrano-Gómez et al. reported that Colombian breast cancer patients with higher IA ancestry showed higher expression of the ERBB2/GRB7/MIEN1 genes in breast tumors of luminal B subtype [74]. These three genes, located in the same region of chromosome 17, have been reported as co-amplified in breast cancer and this event has been associated with poor prognosis [42, 75–77].

Gaps: Do We Have the Right Data to Learn to Predict, Prevent, and Treat Breast Cancer in Women of Latin American Origin?

Genomic technologies have offered new perspectives to expand and improve human health [78]. However, it has been shown that the proportion of samples from minority populations included in large-scale genomic studies remains low [79, 80]. Individuals of Latin American origin only represent 0.54% of the samples included in genome-wide association analyses compared to 81% for those of European ancestry [80]. A similar scenario was observed in The Cancer Genome Atlas (TCGA) where only 3% of the samples are from Latino patients [79]. Increasing the representation of diverse populations in future "omics" research efforts will improve our understanding of the drivers of aggressive tumor biology across different population groups and subgroups [79].

The need for cancer control in Latin America has received significant attention, with specific recommendations to increase investment in cancer registration, given that cancer registration covers approximately 7% of the populations in Latin America, while the equivalent coverage is 83% in North America and 32% in Europe [78, 81].

To assure comprehensive registries, the implementation of population-based cancer registries (PBCR) in Latin America require government support in order to incorporate all sources of information such as data from social security and the private sector [82, 83]. Biorepositories in Latin America hold diverse tissue samples that could enrich our knowledge of the molecular diversity of cancer in Latinos from different regions, but they tend to lack the resources to conduct the research. Therefore, it is through international collaborations, including support from US

institutions and investigators, that we can begin to generate the complex data that we need to better understand cancer risk and outcomes with the consideration of biological, environmental, cultural, and access-related factors in individuals of Latin American origin.

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Chapter 5
Prostate Cancer in US Latinos: What Have We Learned and Where Should We Focus Our Attention

Mariana C. Stern

Prostate Cancer Among Latinos

After skin cancer, prostate cancer (PCa) is the most commonly diagnosed cancer among Latino men, with approximately 13,000 cases diagnosed every year in the United States; 1800 Latino men die of PCa every year, making it the fourth leading cause of cancer death among Latinos [1]. PCa is also the most common cancer among non-Latino men, although the incidence rates are higher among non-Latino White (NLW) men and highest among non-Latino Black (NLB) men. In spite of the high burden of PCa in the United States and many other Western countries, there are few established risk factors, and even fewer are modifiable and can be targeted for cancer prevention. Most PCa will be diagnosed in men with localized disease (~80% of men), most of whom will have indolent disease, although a small minority will not. Distinguishing clinically significant from clinically insignificant cancer is one of the key challenges that men with prostate cancer face [2–4]. Across the continuum from PCa etiology to PCa survival, there are several other challenges and knowledge gaps, which overall are larger for Latino men, who are greatly understudied. We summarize below some of the salient findings about the characteristics of PCa in US Latinos along this continuum and highlight the unique challenges faced by this population and that deserve further study.

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Prostate Cancer Incidence and Etiology

The incidence of PCa in US Latino men is ~9% lower than NLW men; however, the incidence observed among US Latino men is higher than the incidence among men in most Latin American countries, which show wide differences in incidence and mortality across countries [5]. Studies done among various migrant populations have shown increases of PCa among US immigrants in comparison with their countries of origin [6]. It is not clear whether these increases are exclusively due to increased detection of PCa in the United States or changes in environmental factors or a combination of both.

Few established risk factors for PCa are age, African ancestry, family history of PCa, and genetic susceptibility markers identified among NLW and NLB populations [7, 8]. However, all these factors together explain a very small proportion of the variability of PCa incidence. Several modifiable risk factors have been reported for which the evidence is still inconclusive; however, they deserve consideration as probable PCa risk factors. Among them are body fatness [9], red meat [10], calcium, vitamin D, and lycopene [11]. Less than 2000 Latinos have been included in epidemiological studies in the United States; thus, the knowledge gap for PCa etiology in Latinos is larger than for other racial/ethnic groups. Among the few studies that included Latino men, positive associations were reported for some of the same risk factors reported among non-Latino individuals such as obesity [12], alcohol [13], genetic variants [14], and diets high in red meat cooked at high temperatures and meat mutagens [15]. In addition, positive associations were reported uniquely among Latinos, such as exposure to agrichemicals and PCa risk [12, 16], and inverse associations between high intake of legumes and soy products were stronger among Latinos [13, 17].

Most PCa diagnoses are triggered by elevated PSA detected through routine screening, although the landscape of PCa detection is currently changing given the original 2012 recommendation against PSA-based screening from the U.S. Preventive Services Task Force (USPSTF), which in 2018 has evolved into mutual decision between patients and their doctors [18]. These newer recommendations are directly aligned with what the American Urologic Association (AUA) has recommended since 2012 which is sharing decision-making for men aged 55–69 years considering PSA screening, taking into account individual risk factors (e.g., African American, positive family history) [19, 20]. Thus, even though PSA testing nationwide has decreased, debate on the value of PSA screening continues, and the effects of its reduction in use are still too early to detect with current cancer registries data. Importantly, Latino men show lower rates of use of PSA screening [21–23] than NLW men, associated with these lower rates of screening are low PCa literacy and overall low educational status [24, 25], as well as specific Latino values (e.g., fatalism) [25] and lack of health insurance [26]. It is not clear if lower screening alone can explain the reduced incidence of PCa compared to NLW men. To consider, disparities in incidence are also observed when considering aggressive disease only, which is less likely to be detected by PSA, suggesting that other factors may explain

the reduced incidence among Latinos and remain to be uncovered [27]. Socioeconomic status (SES) is an important modifier of PCa risk, with men in the lowest SES categories having the lowest PCa incidence and differences being more pronounced for Latinos [27].

A key challenge in understanding cancer determinants among US Latinos is the fact that they constitute a highly heterogeneous population. Latinos are a highly admixed population given the history of colonization of the Americas; all Latinos are descendants from generations of admixture among European, Amerindian, and/or African ancestral populations, with varying degrees of admixture across different Latin American countries. Further, there are differences due to local traditions, culture, lifestyle, and prevalence of various environmental agents [28, 29]. In the United States, this heterogeneity is greater, because US Latinos might be foreign-born with various degrees of acculturation to the US lifestyle, or they might be US-born first or subsequent generation with Latino parents or grandparents of same or different Latino origin or with only one Latino parent/grandparent. Therefore, Latinos are likely to be among the most heterogeneous ethnic groups in the United States. In spite of this, they are typically considered as one single group in cancer studies. Therefore, estimates of incidence and cancer characteristics might not be representative of all US Latinos [29].

There is accumulating evidence that cancer incidence differs by Latino subpopulations defined by country/region of origin [30–33] or genetic ancestry [29]. Specifically for PCa, Latinos of Mexican origin have been reported to have the lowest incidence among Latinos, and definitively lower than NLW. Caribbean Latinos, such as Cuban and Puerto Rican Latinos, have higher incidence; in fact, Puerto Ricans in Florida were reported to have higher incidence than NLWs [31–33]. Moreover, Latinos living in Florida were reported to have higher incidence of PCa than their counterparts living in their countries or regions of ancestral origin [32]. Similarly, Puerto Ricans living in the island were reported to have lower PCa incidence rates than those living in the mainland United States [34] and lower than US Latinos overall [35]. Recently, we conducted analyses of PCa among Latinos living in California using California Cancer Registry, and in agreement with previous findings, we observed that PCa incidence rates were lowest among Mexican and Central American Latinos and highest among South American Latinos (unpublished results). In agreement with previous findings considering SES, Mexican and Central American Latinos in California have greater proportion of low SES, whereas South Americans have greater proportion of higher SES. However, estimates by country or region of origin must be interpreted with caution. Whereas algorithms that capture Latino status in cancer registry data are efficient and have good specificity [36, 37], and algorithms are available to obtain nativity status (US- vs. foreign-born status) [38], data for country of origin is missing for a large subset of Latinos identified in cancer registries. Some of this might be due to lack of inquiry from health professionals at the time of diagnosis and treatment, and some might be due to the fact that US-born Latinos, who might be fully acculturated to US lifestyle and might be several generations of US Latinos, might no longer identify with one particular Latin American country of origin, and thus this information might not come up

during their cancer diagnosis and care. In addition, some foreign-born Latinos may not volunteer this information due to fears triggered by their immigration status. In the California Cancer Registry, more than 70% of Latinos with missing country of origin were US-born Latinos [30]. If missingness is independent of country/region of origin, and systematic across all Latinos, then the disparities observed across Latino subpopulations would still be true. However, if missingness differed by country/region of origin, this could lead to biases in incidence rates and artifactual disparities by country/region of origin. The lack of systematic efforts to enrich data collection of Latino origin in cancer registries is an important gap that needs to be addressed to facilitate studies of cancer patterns in Latinos. For Asian populations, some cancer registries currently track subpopulation information by country of origin. Similar approaches could be developed for Latino subpopulations.

Few studies have interrogated the role of genetic ancestry and PCa risk among US Latinos. One study done in Puerto Rico reported a lack of association between global African ancestry and PCa risk; however, they replicated an association between a single-nucleotide polymorphism (SNP) of African ancestral origin and PCa risk, suggesting possible associations with African local ancestry and PCa risk that deserve further investigation [39]. To our knowledge, no studies have investigated the role of Indigenous American ancestry and PCa risk, and whether the presence of specific alleles of Indigenous American origin might explain the lower risk of PCa among some Latinos, as it has been reported for breast cancer [40].

Clinical Presentation of PCa Among Latinos

Most PCa tumors are diagnosed by 12-core systematic random prostate needle diagnostic biopsy, which can miss areas of more advanced disease already present in the prostate in as high as 30% of patients, thus introducing under-staging and under-grading error at the time of diagnosis [41–43]. PCa biopsies are used not only for cancer staging but also for treatment decision-making [44]. Patients diagnosed with clinically insignificant disease, typically Gleason 6 and no biopsy core with more than 5 mm of cancer, will likely be offered to avoid treatment and enroll in active surveillance, whereas those with clinically significant cancer, those with Gleason 7 or higher or any Gleason with biopsy cores with more than 5 mm of cancer, will be offered definitive treatment. If the diagnostic biopsy missed the most aggressive part of the tumor, patients diagnosed with clinically insignificant cancer might be at risk by not choosing adequate treatment. The rate of misclassification of PCa biopsy has been reported to be higher among African-American men compared to NLW men [45, 46], and it has been proposed that this could be due to higher proportion of anterior tumors, which are more likely to be missed by random systematic biopsies [46, 47]. The proportion of anterior tumors and rate of biopsy misclassification among Latinos are understudied. One study, of modest sample size, compared the Gleason grade at biopsy to the one obtained at surgery and reported that the rate of misclassification in PCa biopsy among Latinos was ~36%, which was in between

the rate in NLWs (27%) and NLBs (~52%) [48]. Interestingly, the majority of tumors with misclassification had anterior localization [48]. Recently, in analyses done with data from the California Cancer Registry from 1995 to 2012, we observed that foreign-born Latinos had higher rate of upgrade from biopsy to resection than NLWs and even NLBs, with Mexicans showing the highest proportion of misclassification (~30%) and Caribbean Latinos showing a proportion that was even lower than NLWs (~18%) (unpublished results). These results are intriguing and deserve further investigation. If a higher proportion of anterior tumors localization was confirmed among Latinos, along with higher rate of misclassification on biopsy, this would strongly advocate for a greater proportion of Latinos receiving more accurate biopsies coupled with imaging, such as magnetic resonance imaging (MRI)-guided targeted biopsies, which can more accurately identify clinically significant cancer and sampling error [49–51]. However, these procedures are currently costly and are only available at specialized centers. Given that a great proportion of US Latinos have low SES, they may lack insurance, or their insurance may not cover these procedures, which are not yet standard of care. More research in this area is needed to advocate for changes in healthcare coverage.

Analyses done with California Cancer Registry data showed that foreign-born Latinos had greater proportion of advanced stage at diagnosis than US-born Latinos [52]. Moreover, our recent analyses in the same California registry (1995–2012) showed comparable proportion of high grade at diagnosis, positive lymph nodes, and metastasis as NLBs, with disparities observed by country of origin among foreign born (unpublished results). A separate report using SEER data showed that Latinos had higher proportion of metastatic disease at diagnosis than NLBs and NLWs [53].

PCa Treatment Patterns Among Latinos

The Prostate Cancer Outcomes Study reported that Latinos received radical prostatectomy in greater proportions than NLWs and NLBs and received radiation therapy in lower proportion [54]. Among Latinos in California, foreign-born Latinos were reported to be more likely to undergo surgery than US-born Latinos and less likely to receive radiation [52]. Our own analyses within the California Cancer Registry showed that foreign-born Latinos, Mexicans, Central Americans, and South Americans had the highest proportion of surgery utilization (unpublished findings). In contrast, a study done in Texas reported that Latinos were less likely to receive radical prostatectomy, or radiation therapy, than NLWs [55]. Further, a study done using data from the National Cancer Database reported that a lower proportion of Latinos than NLWs received radical prostatectomy and that a greater proportion than NLWs received radiation or androgen deprivation therapy [56]. The different conclusions between these studies might be partially driven by different definitions of Latino status and consideration of nativity.

Our analyses also showed that Latinos, especially foreign-born, had a greater proportion of men without any treatment reported (unpublished results). This might be indicative of higher proportion of men choosing active surveillance, although we cannot confirm this. Analyses using SEER data show that along with NLBs, Latinos are more likely to enroll in active surveillance instead of choosing treatment [57–59], and an association has been reported between low-income patients and selection of watchful waiting [60, 61]. Alarmingly, Latinos under active surveillance seem to be less likely to receive medical monitoring [57, 62], and we recently reported that Latinos under active surveillance were more likely to be lost to follow-up than NLWs [63]. These findings are concerning and require additional studies to identify determinants of lack of adherence to active surveillance in order to reduce loss to follow-up and possible disparities in overall survival.

Survival and Mortality

Historically, US Latinos have been reported to have lower mortality rates from PCa than NLWs [1]. However, this finding might be heavily influenced by the heterogeneity within Latinos and may not accurately reflect the experience of all Latinos in the United States. In Florida, Latinos from the Dominican Republic were reported to have the highest PCa mortality rates, followed by South Americans, Central Americans, Cubans, Puerto Ricans, NLWs, and then Mexicans [64]. A recent study from California and Texas focused exclusively on US-born Latinos and reported mortality rates for PCa that were comparable to those among NLWs in both states [65]. These studies highlight the importance of considering Latino national origin and the biases that are introduced when this consideration is not given. Disparities have been reported between US and foreign-born Latinos; foreign-born Latinos living in high enclave neighborhoods had better survival than US-born Latinos in similar neighborhoods, whereas both had comparable survival if they lived in low enclave/higher SES neighborhoods [52]. It is possible that among foreign-born Latinos, specially low SES Latinos, there might be missing data on mortality if many of them return to their home countries ("salmon hypothesis") to seek care or to die back home, or if missing social security numbers impair proper tracking of death via vital statistics. These and other related circumstances may bias estimates of mortality among Latinos yielding the false notion that survival patterns are more favorable, as discussed by Pinheiro et al. in previous studies [64, 65] and in Chap. 2 in this same issue.

In terms of survival patterns, a study done with SEER data, taking into account possible clinical determinants, concluded that when considering all Latino men combined, there were no differences in survival with NLWs; however, when considering country of origin, several disparities emerged, with Puerto Ricans having less favorable survival than NLWs [66]. In recent analyses using the California Cancer Registry, we did not find differences in survival between Caribbean Latinos and NLWs, or between US-born Latinos and NLWs, and we only observed marginally

improved survival for South American Latinos (unpublished results). Lack of consideration of nativity may explain these disparate results between studies. Overall, results from foreign-born Latinos need to be interpreted with caution given the large number of missing data, potential issues with missing social security numbers, and uncertainty over final place of death.

Final Conclusions and Key Knowledge Gaps to Address

Research on PCa in Latinos lags behind our current knowledge for other racial/ethnic groups. This is a disparity of great public health relevance given that PCa is the number one cancer that affects Latino men and that Latinos are the largest and fastest growing minority population in the United States, and majority population in some US regions, such as California. Among the key knowledge gaps we need to address are the following:

- Great need for more epidemiological studies with adequate risk factor data including Latinos; currently, there are less than 2000 individuals ascertained across studies in the United States.
- Data collection on Latino national origin needs to be improved at all levels so that cancer registries can allow for more accurate analyses taking into account Latino heterogeneity.
- Analyses of the role of genetic ancestry and PCa risk among Latinos are needed, as these studies may help inform some of the cancer incidence findings.
- The tumor landscape of Latino men is largely unknown, as scarcely any Latinos have been included in ongoing efforts such as The Cancer Genome Atlas. Moreover, patterns of tumor localization need to be understood in order to improve PCa detection strategies among Latinos accordingly.
- More studies are needed on patterns of care and adherence to active surveillance among Latinos, with emphasis on their determinants, to design culturally-sensitive interventions to address any disparities.
- Similar to other cancers, clinical trials focused on novel treatments for advanced PCa need to include more Latinos.

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Chapter 6
Differential Cancer Risk in Latinos: The Role of Diet

Katherine L. Tucker and Kaylea Flanagan

Introduction

As summarized in the third expert report of the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), there is accumulating evidence regarding the importance of diet to cancer risk [1]. Because new research is making contributions at a rapid pace, WCRF/AICR instituted the "Continuous Update Project" to report advances in real time. Tremendous gains in new understanding of how nutrients affect gene expression through epigenetic regulation, cell signaling, and DNA damage and repair promise to clarify the important roles of foods and nutrients on risk and course of different cancers. Important conditions affected by diet that contribute to risk include inflammation and oxidative stress. What is not well covered at this time, however, is an understanding of the dietary and biological differences across populations with diverse cultural backgrounds, which may help to explain differences in patterns of cancer incidence and mortality. In the United States, Mexican Americans and Puerto Ricans are the two largest subgroups among Latinos, yet little research has been done to address the potential differences in risk for these or other Hispanic groups. This is important, particularly as the Latino population is expected to make up 25% of the total US population by 2050 [2].

Cancer Incidence Varies by Ethnicity and Gender

Cancer is the second leading cause of death in the United States [3], and thus it is imperative that preventative dietary measures be taken to lessen its occurrence. In the United States, cancer incidence is known to vary by ethnicity and gender. Between 1999 and

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2014 total cancer incidence rates were estimated to be about 475/100,000/year in Hispanic males, and 350/100,000/year in Hispanic females. Both of these statistics fall into the middle of incidence rates among different ethnicities in the United States, higher than that of American Indians/Alaskan Natives or Asians/Pacific Islanders, but lower than that of non-Hispanic whites or African Americans [4]. However, the incidence of specific cancers varies across groups. Latinos have higher incidence rates of liver, stomach, and gallbladder cancers, compared to non-Hispanic whites, and Latino women have among the highest incidence rates of cervical cancer [4, 5].

Although overall cancer rates tend to be lower among Latinos than non-Hispanic whites, cancer remains a major cause of death in this group, often discovered at later stages with higher mortality. For example, the Surveillance, Epidemiology, and End Results Program (SEER) [6] noted that, for most cancers, the incidence of localized cancers are lower for Hispanics than non-Hispanic whites, yet later stage and/or more aggressive regional or distant cancers are more common among Hispanics than non-Hispanic whites for lung, colorectal, melanoma, prostate, and female breast cancers [7].

Further, risk differences exist across Latino subgroups. For example, colorectal cancer mortality is higher among Puerto Ricans than Mexican Americans, while stomach cancer mortality is higher among Mexican Americans than Puerto Ricans [7]. The likelihood that these differences may be due to modifiable exposures rather than genetic factors is suggested by differences in incidence with migration. In a comparison of age-standardized rate ratios for Puerto Ricans living on the island of Puerto Rico with Puerto Ricans living on the mainland United States, mainland Puerto Ricans had significantly higher cancer risk than island Puerto Ricans. For all sites among island Puerto Ricans, standardized rate ratios (SRR) were 0.66 (95% CI = 0.61–0.70) for men and 0.64 (95% CI = 0.60–0.68) for women, with most significantly lower risk on the island for liver, prostate, and colorectal cancer among men and for breast and colorectal cancer among women [8]. Similarly, Mexican Americans have higher mortality from cancer than do Mexicans living in Mexico, including for colorectal, pancreatic, kidney, liver, and esophageal cancers. There is evidence that immigrants adopt unhealthy behaviors the longer that they are in the United States [9]. Among these unhealthy behaviors are declines in dietary quality.

Dietary Factors and Cancer Risk

Dietary factors have been noted to be one of the main contributing risk factors for cancer, particularly for colon, breast, and prostate cancers [10]. Up to one third of cancers in Western countries have been estimated to be associated with dietary factors [11]. A recent review [12] estimated that 42% of all cancers and 45% of cancer deaths in the United States may be attributed to preventable risk factors. The proportion of cancer cases attributable to specific nutrition-related risk factors were estimated to be obesity (8%), excess alcohol (6%), low fruit and vegetable intake (2%), low fiber intake (1%), and processed meat intake (1%), with lower contributions from red meat and low calcium intake.

Alcohol intake is one of many modifiable dietary factors that has been associated with cancer risk. The definition of an alcoholic beverage is 12 oz of beer, 5 oz of wine, or 1.5 oz of distilled spirits. There is evidence that heavy drinkers (more than one drink/day for women or two drinks/day for men) have significantly increased risk for mouth, larynx, esophagus, liver, and breast cancers. In one study, heavy drinkers had a 15% increase of lung cancer risk in comparison to occasional drinkers or those who did not consume any alcohol [13]. Two thirds of adults in the United States report exceeding the moderate amount at least once per month [4].

Fruits and vegetables pose many health benefits in relation to preventing disease and maintaining overall health. High fruit and vegetable intake has been associated with lower risk of lung, colorectal, breast, esophageal, stomach, pancreatic, uterine, cervical, and ovarian cancers. Cruciferous vegetables, for example, contain phytochemicals that are thought to reduce colorectal cancer risk [14, 15]. In one study assessing the relationship between fruit and vegetable intake and the onset of colorectal cancer, however, there was a statistically significant association between the decreased risk of prevalent colorectal adenomas only in participants who had higher intake of fruits, but not vegetables. Those authors suggested that the fiber present in fruits may be protective against colorectal adenoma and ultimately protect against colorectal cancer [16]. Antioxidant nutrients in fruits and vegetables including vitamin C, vitamin E, selenium, carotenoids, and other phytochemicals also protect against tissue damage from oxidative stress. However, several trials of antioxidant supplements did not show protection [17], demonstrating that it is important to obtain these nutrients in their natural combinations within the food matrix.

The impact of certain B vitamins is also of interest for cancer prevention, with considerable evidence for folate. Folate is required for DNA methylation and cellular repair, and low folate has been related particularly to colorectal cancer [13, 18]. Other research has suggested a relationship between folate deficiency and lung, cervical, breast, and brain cancers [19]. Food sources of folate include leafy greens, citrus fruits, legumes, nuts, seeds, and whole grains. Vitamin B_6 has also been associated with cancer prevention; this nutrient is involved in more than 100 metabolic reactions, including those involving DNA synthesis and methylation, reducing inflammation, and reducing oxidative stress. Vitamin B_6 is present in a variety of whole quality foods, such as beans, grains, meat, poultry, fish, and certain fruits and vegetables, including potatoes, bananas, and avocados. Higher vitamin B_6 status, measured by pyridoxal 5′-phosphate (PLP), a vitamin B_6 biomarker, has been associated with the reduced risk of colorectal cancer [20, 21]. A systematic review and meta-analysis found that observational data supported a strong inverse association between both vitamin B_6 dietary intake and PLP blood concentration and the risk of all cancers: diet (RR = 0.78, 95% CI = 0.73–0.84), PLP (RR = 0.66, 95% CI = 0.58–0.76). The most prominent finding among 45 studies was the relationship between gastrointestinal cancers and vitamin B_6, particularly colorectal carcinoma [22].

Red and processed meats have been identified as particular foods that contribute to carcinogenic processes. Nitrites in processed meats may be converted in the stomach to carcinogenic nitrosamines [23]. Importantly, diets high in fruits and vegetables, with vitamin C and phytochemicals, may slow this conversion. The

way in which one cooks meat and how much preservatives it contains could be the potential identifiable characteristics of interest. In particular, frying, broiling, or grilling meats at high temperature creates chemicals that increase cancer risk, making braising or stewing a better choice [24]. High consumption of red and processed meats may also affect serum obesity-related inflammatory markers, and elevated iron composition in meat may be carcinogenic because it is cooked at high temperatures [25].

Another controversial nutrient for cancer risk is calcium. On the one hand, foods high in calcium may reduce the risk for colorectal cancer [26]. On the other hand, high calcium intake has also been associated with prostate cancer risk. Several meta-analyses, for example, have related high calcium intake to risk of prostate cancer [27]. Roderick and Cook [28] explain how Ca^{2+}, the physiologically active derivative of calcium, contributes to cell growth in the body. They note that, because Ca^{2+} is regulated by proteins which exist in cancerous cells to protect the cell, it could be detrimental to cancer progression.

Dietary Patterns and Cancer Risk

Although specific nutrients have received the most attention in the past, newer studies focus on the totality of dietary patterns and dietary quality in relation to cancer risk. One dietary pattern, in particular, has been found to be protective of many aspects of health—the Mediterranean diet. A study by Benetou et al. [29] specifically assessed adherence to a Mediterranean diet in relation to cancer risk among 25,623 participants from Greece. A 10-point scale, based on data from a food frequency questionnaire, was used to assess compliance with a Mediterranean diet. Results showed that those who most thoroughly followed a Mediterranean diet had significantly lower incidence of cancer. Important aspects of the Mediterranean diet include abundant use of fruits, vegetables, beans, nuts, and seeds, and olive oil as the major source of fat, with moderate use of dairy and limited use of red meat. This study noted that, within this population, specifically reducing intake of meat, increasing intake of legumes and vegetables, and replacing butter with olive oil yielded a 12% decrease in the incidence of cancer [29].

While evidence for the importance of these nutritional risk factors continues to grow, most studies have been conducted with non-Hispanic whites. Understanding the specifics of Mexican and Puerto Rican American dietary habits and sources of these nutrients may help improve the overall diet of Latinos as well as prevent chronic illnesses like cancer. One factor that has hindered research on Latino diets and cancer has been the use of general food frequency questionnaires (FFQ) in the United States in large cancer studies. These questionnaires, including the Block and Willett, do not contain many Latino foods of importance. In addition, they do not consider portion sizes or recipes that are important to nutrient intakes of these groups. For this reason, when studying the Puerto Rican population in Massachusetts, we developed an FFQ to specifically include their foods, portions, and recipes [30].

Some lessons learned from this include the need to include foods that are widely consumed by a specific group, as well as the recipes. For example, Puerto Ricans season their rice dishes with tomato sauce and a mixture of onions and green peppers, which contribute vegetables and phytonutrients that may otherwise be overlooked. They also have significantly larger servings of white rice and lower servings of most vegetables than is assumed in the most widely used FFQ. For that reason, we added the main rice dishes to our questionnaire. Another major food for Caribbean Latinos that is completely missing in most FFQ is plantains, a starchy vegetable that contributes considerably to energy and fat intake. When compared to 24 h recalls, we found that our FFQ, relative to the Block FFQ improved intraclass correlations considerably; for example, the correlation for vitamin A improved from 0.04 to 0.36 and for folate from 0.31 to 0.79. Importantly, when foods consumed heavily by a subgroup in a population are missing from the FFQ or portion sizes are grossly underestimated, there is not only poorer correlation, but actual bias in estimation compared with other groups [31].

Given the scientific evidence of the potential role that these dietary factors play in cancer incidence, it is important that an accurate assessment is taken into consideration for intervention purposes. Moreover, it is important to consider different ethnic and cultural backgrounds with relation to dietary habits. By understanding the typical diet of Mexican and Puerto Rican Americans, health professionals may be able to offer advice and other mediations in order to decrease cancer incidence in these populations.

There are also considerable differences in dietary quality across Latino subgroups. A large study was conducted in 2014 to assess the overall dietary patterns of the Hispanic and Latino communities, known as the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). In 2011, these ethnic minority groups made up 16% of the total US population. Puerto Ricans, Mexicans, Dominicans, and Central Americans in general lived in the United States for longer periods of time in relation to Cubans [31]. Two 24-h dietary recalls were administered to assess dietary patterns among Puerto Ricans, Dominicans, Mexicans, and Central Americans. Puerto Ricans were reported to have the highest prevalence of obesity and higher intake of saturated fatty acids and sugar-sweetened beverages; lower intake of potassium, total fruits and vegetables, and fiber; and lowest intake of vitamins A and C, folate, calcium, and iron than other groups. Puerto Ricans and Mexican-Americans were second in relation to Cubans for total fat intake. Mexican-Americans also had higher intakes of vitamins A and C, potassium, and fiber than other Latino groups [31].

Data from the Boston Puerto Rican Health Study support the idea that Puerto Ricans have a relatively lower nutritional status. In our earlier studies [32, 33], we noted low intakes of fruits and vegetables, whole grains, dietary fiber, folate, vitamin B6, vitamin C, and calcium, relative to recommendations, with high intakes of refined carbohydrates. The low vitamin B status was confirmed with plasma concentrations; 8% were below 5 ng/mL in folate intake, and 28% were below 30 nmol/L in PLP (vitamin B_6). Further, in relation to neighborhood-based non-Hispanic whites, Puerto Ricans had lower intake and plasma concentration of most

carotenoids, particularly lutein-zeaxanthin (which comes mainly from green leafy vegetables), but slightly higher intake of lycopene (from tomato sauce added frequently to recipes) [34].

Food acculturation is the concept of one's dietary habits in relation to how acculturated they are with the Western diet. Batis et al. [35] used the Mexican Nutrition Survey of 1999 and the NHANES in the United States to assess Mexican dietary patterns. Mexican Americans born in Mexico had higher intakes of fruits, vegetables, and fruit juices related to all other subpopulations, with evidence of declining quality with years in the United States and even more so with the subsequent generation [35]. In contrast, evidence from Puerto Ricans shows a different pattern, at least among Puerto Ricans living in the US mainland, with higher acculturation (based on orientation to US society and English usage) associated with better, rather than worse, dietary quality [36].

The American Cancer Society recommends a healthful diet for decreasing the risk of cancer. The ideal preventative dietary intakes include at least two and a half cups of fruits and vegetables per day, reduced intakes of red and processed meat, use of whole grains instead of refined grains, and limiting intake of sugars [37] (Table 6.1). The evidence clearly suggests that most Latino groups, and particularly Puerto Ricans, are falling far short of these recommendations. Improving dietary intake in these groups will require greater attention to cultural dietary patterns, emphasizing traditional healthy foods to reduce risk of cancer along with other metabolic outcomes. Further research with appropriate dietary assessment in longitudinal studies with cancer outcomes are needed in these understudied populations to reduce the current risk and to prevent the potential for widening risk with increasing use of Western diet patterns in these groups.

Table 6.1 American Cancer Society (ACS) guidelines on nutrition and physical activity for cancer prevention [38]

ACS recommendations for individual choices
Achieve and maintain a healthy weight throughout life
• Be as lean as possible throughout life without being underweight
• Avoid excess weight gain at all ages. For those who are currently overweight or obese, losing even a small amount of weight has health benefits and is a good place to start
• Engage in regular physical activity and limit consumption of high-calorie foods and beverages as key strategies for maintaining a healthy weight
Adopt a physically active lifestyle
• Adults should engage in at least 150 min of moderate intensity or 75 min of vigorous intensity activities each week, or an equivalent combination, preferably spread throughout the week
• Children and adolescents should engage in at least 1 h of moderate or vigorous intensity activity each day, with vigorous intensity activity occurring at least 3 days each week
• Limit sedentary behavior such as sitting, lying down, watching television, or other forms of screen-based entertainment
• Doing some physical activities above usual activities, no matter what one's level of activity, can have many health benefits

(continued)

Table 6.1 (continued)

Consume a healthy diet, with an emphasis on plant foods
• Choose foods and beverages in amounts that help achieve and maintain a healthy weight
• Limit consumption of processed meat and red meat
• Eat at least 2.5 cups of vegetables and fruits each day
• Choose whole grains instead of refined grain products
If you drink alcoholic beverages, limit consumption
• Drink no more than one drink per day for women or two per day for men
ACS recommendations for community action
Public, private, and community organizations should work collaboratively at national, state, and local levels to implement policy and environmental changes that:
• Increase access to affordable, healthy foods in communities, worksites, and schools and decrease access to and marketing of foods and beverages of low nutritional value, particularly to youth
• Provide safe, enjoyable, and accessible environments for physical activities in schools and worksites and for transportation and recreation in communities

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Part IV
The Biology of Cancer Health Disparities

Chapter 7
Biomarkers of Gastric Premalignant Lesions

Jone Garai, Li Li, and Jovanny Zabaleta

Epidemiology

Despite decreasing incidence in the last 50 years, gastric cancer remains the fifth most common cancer in the world, representing 6.8% of the total global cancer cases [1], and ranks third as the most common cause of cancer-related death in men. Almost one million new cases of stomach cancer were estimated to have occurred in 2012 [1, 2]. There is a wide geographic variation in gastric cancer incidence and mortality rates, with more than 70% of gastric cancer cases occurring in less developed countries [1]. In Eastern Asia and South and Central America, gastric cancer is a significant health burden [1, 2]. In addition, both gastric cancer incidence and mortality vary widely among different race/ethnic groups in the United States. Asian, Hispanic, non-Hispanic black, and Native American populations have up to 50% higher risk for gastric cancer than non-Hispanic white populations [3–5]. Similarly, gastric cancer survival is better in Asians than in Caucasian Americans, African Americans, and Hispanics [4, 6, 7]. Hispanics are younger and more often with stage IV disease when gastric cancer is diagnosed, and they present a shorter survival time than non-Hispanic whites [8]. Lower survival rates for non-Hispanic blacks compared to non-Hispanic whites have also been reported [9].

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Etiology

H. pylori

Helicobacter pylori (*H. pylori*) is among several factors associated with non-cardia intestinal-type gastric cancer development. It is the primary cause the in initiation of the disease and has been classified as a class I carcinogen [10]. Infection with *H. pylori* occurs mainly during childhood [11], and in a proportion of those chronically infected, it results in the transformation of the normal gastric mucosa into non-atrophic gastritis (NAG), followed by multifocal atrophic gastritis without intestinal metaplasia (MAG), intestinal metaplasia (IM), dysplasia, and finally cancer [12, 13].

Current estimates of *H. pylori* prevalence in the world range from 24 to 79% [14]. The highest prevalence is in Africa (79%) and Latin America and the Caribbean region (63.4%), and the lowest in Oceania (24.4%) and Northern America (37.1%). In regions of South and Central America, which include those with high gastric cancer risk, *H. pylori* prevalence can reach up to 80–85%, some of the highest prevalence in the world [15]. In the United States, the estimated *H. pylori* prevalence is 30% [15]. However, while *H. pylori* prevalence ranges from 18.4 to 26.9% in non-Hispanic whites, it can be as high as 51.1%, 57.9%, and 75% in non-Hispanic blacks, Hispanics, and Alaskan Native Americans, respectively [14, 16, 17]. This high prevalence likely contributes to the high incidence and mortality from gastric cancer in non-Hispanic blacks and Hispanics. Despite this high prevalence of infection, it is estimated that approximately 1% of those chronically infected with *H. pylori* will develop gastric cancer [18, 19]. In fact, the majority of the population will remain asymptomatic.

In the last decades, *H. pylori* prevalence has decreased around the world, especially in the more developed regions, mostly due to improved hygienic conditions, improved diet and food preservation, and broader access to antibiotics [2]. Recently, Hooi et al. [14] compared *H. pylori* prevalence from two time periods (1970–1999 and 2000–2016) and found that from one time period to the next, *H. pylori* prevalence significantly decreased in Europe (from 48.8 to 39.8%), Northern America (from 42.7 to 26.6%), and Oceania (from 26.6 to 18.7%) [14]. In contrast, *H. pylori* prevalence remained similar during the same periods in Asia (53.6% vs. 54.3%) and Latin America (62.8% vs. 60.2%) [14]. This geographical variability in *H. pylori* prevalence explains in part the higher gastric cancer incidence and mortality observed in Latin American countries compared to more developed countries as the United States. Furthermore, Porras et al. in a recent study of the epidemiology of *H. pylori* infection in six countries of Latin America did not observe any significant changes in *H. pylori* prevalence between the oldest and youngest participants in their study, suggesting that gastric cancer incidence is not going to decrease in those countries in the near future [15].

Environmental Factors

Even though infection with *H. pylori* is considered necessary for the development of gastric cancer, it is not determinant; just 1–3% of those infected with *H. pylori* will develop gastric cancer in their lifetime [18, 19]. Additional environmental factors are associated with gastric cancer risk, including smoking, alcohol use, and a diet low in fresh produce and high in meats and salt [20]. In a recent meta-analysis, Bonequi et al. found that in Latin America, smoking and alcohol use were associated with a 47% and 61% increase of gastric cancer risk, respectively [21]. Regarding diet, the same study found that consumption of red and processed meats were associated with a 73% and 64% increase of gastric cancer risk, respectively. High salt intake was associated with 2.24-fold increase. In contrast, consumption of fruits and vegetables were associated with a 32% and 42% reduction of gastric cancer risk, respectively [21]. There is a high prevalence of smoking and alcohol use in Latin American populations [22, 23], and in regions with high gastric cancer rates as in the Andean mountains, the diet is poor in fruits and vegetables and excessively high in consumption of salt [24]. Data from the US National Health Interview Survey indicate that Hispanics have the lowest prevalence of smoking in all racial/ethnic populations and the highest consumption of fresh fruits and vegetables [25]. These habits are not in concordance with their gastric cancer incidence and mortality rates.

Genetic Bases of the Gastric Inflammatory Cascade (Correa's Cascade)

Single-Nucleotide Polymorphisms (SNPs)

In 1975, Correa et al. analyzed 1500 stomachs obtained at autopsy to estimate the prevalence of intestinal metaplasia [26]. As a result of that analysis and later updates, Correa et al. proposed that gastric adenocarcinoma is the final stage of an inflammatory cascade that leads the normal gastric epithelia to non-atrophic gastritis (NAG), multifocal atrophic gastritis (MAG), complete intestinal metaplasia (IM), incomplete intestinal metaplasia, dysplasia, and cancer [13, 27–30]. It was shown that single-nucleotide polymorphisms (SNPs) in the cytokine gene encoding interleukin-1β (IL1B) are associated with the risk of gastric cancer [31]. Since then, others have shown the association of cytokine SNPs with gastric cancer risk in several populations [32–36]; however, very few works have centered on defining the association of cytokine SNPs and the presence of advanced gastric lesions as precursors of gastric cancer. Our work has led to the identification of SNPs and haplotypes in the *IL1B* gene associated with advanced gastric premalignant stages in African American and Caucasian individuals [37, 38]. Our studies have shown that African American individuals have a higher prevalence of MAG as well as a higher rate of *H. pylori* infection [37, 38]. Using DNA samples from healthy African

American and Caucasian newborns, we performed additional analyses of cytokine SNPs and haplotypes in cytokine genes which showed that there is a differential distribution of proinflammatory SNPs and haplotypes between these two ethnic groups [39]. In the case of *IL1B* gene, there is a strong linkage disequilibrium among the SNPs analyzed [39].

Stage-Specific and Evolution-Associated Gene Profiles

The pioneer studies by Correa et al. led to the identification of a premalignant cascade suggested to precede gastric carcinogenesis [27]. However, the molecular basis for the intricate relationship between the different stages and their evolution over time is not fully known. Using baseline and 6-year follow-up samples from a cohort study established by Correa et al. in Colombia [40], we extracted RNA and performed a microarray analysis to find genes associated with stage and progression of premalignant lesions. Analyzing the genomics of lesion evolution over time, we found that the genes *CD44*, *NUMA*, and *LCN2* were associated with progression [41]. Interestingly, these three genes have been associated with several types of cancer and with advanced premalignant lesions [42–46]. Using mouse models of *H. pylori* infection in wild-type and *Cd44*$^{-/-}$ *H. pylori* mice, we found a significant activation of immune-related pathways in response to the infection, among them was the IFNγ pathway [41]. Interestingly, the gastric mucosa of *Cd44*$^{-/-}$ mice had significantly lower expression of *Ifng* and *Ifng*-related genes including *Irf7*, *Ifit3*, *Ifit2*, *Nos2*, and *Stat1* [41]. Reduction in *Stat1* expression was paralleled with reduction in phosphorylation of the Stat1 protein [41]. In order to correlate the differences found in global and immune gene expression with pathological changes in the gastric mucosa, we determined and compared the presence of gastric lesions between wild-type and *Cd44*$^{-/-}$ *H. pylori*-infected mice. We found that compared to the wild-type mice, the *H. pylori* infection did not induce tissue damage in the gastric mucosa of *Cd44*$^{-/-}$ *H. pylori*-infected mice. These data suggest that this gene, and the protein encoded by it, is essential to mount the Th1 responses associated with tissue damage induced by the infection [41, 47–49].

Using baseline samples from the same cohort of individuals described for our work with *CD44* [40], we identified 37 samples with MAG, 25 with IM, and 12 with dysplasia. Using the less advanced gastric precancerous lesion as reference (MAG), we identified 16 genes with at least a 30% change in their expression levels when compared with dysplasia [50]. However, the only one showing significantly higher expression was the gene *Deleted in Malignant Brain Tumor 1* (*DMBT1*), which was able to separate most dysplasia from MAG cases [50]. Interestingly, gastric tissue from African American and Caucasian individuals with advanced gastric lesions also had increased levels of expression of the gene [50], suggesting that this response is conserved across ethnicities. We also found that the expression of the *DMBT1* gene was significantly higher in individuals with advanced gastric lesions who also had infection with *H. pylori*, which highlights the role of the DMBT1 protein as an agglutinin [51–53]. Mouse models of *H. pylori* infection show that this gene acts as

a tumor suppressor by limiting tissue damage in response to the infection and through the activation of interleukin 33 (IL33) and pERK [50].

In summary, gastric cancer is a disease of disparities, with minority groups having increased prevalence and mortality of the disease. We have shown that precancerous lesions and their evolution over time are associated with specific patterns of genes that may be used as the basis to devise strategies for the prediction of disease aggressiveness and outcome.

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Chapter 8
Molecular Subtypes and Driver Mutations in Latinos with Gastric Cancer: Implications for Etiological and Translational Research

Luis G. Carvajal-Carmona

Gastric Cancer Is a Common Malignancy with Poor Outcomes

Worldwide, gastric cancer (GC) is the third leading cause of cancer mortality [1]. Each year ~1 million new gastric cancer (GC) cases are diagnosed and >720,000 patients die of GC [2, 3]. GC prognosis is dismal because early-stage tumors, where survival is high, are clinically silent and difficult to detect. Most GCs are detected in late stages and have 5-year survival rates <10% [2, 4, 5]. To improve GC outcomes, major limitations need to be addressed. First, new prevention and early detection tools must be developed, including the identification of susceptibility genes that allow the identification of high-risk individuals. Until recently, E-cadherin (also known as *CDH1*) was the only known GC gene; it accounts for ~40% of cases with hereditary diffuse GC (HDGC) syndrome and a very small fraction of non-HDGC cases [2, 6, 7]. We recently identified a second familial GC form, involving germline mutations in recombination DNA repair genes, which account for ~2–6% of all cases [1, 8, 9]. Even though this recent gene discovery represents an important advance, few individuals currently benefit from genetic-guided prevention. Another major limitation is the need to develop effective therapies to improve GC outcomes. The Cancer Genome Atlas (TCGA) study found that >70% of all GCs have mutations that can be targeted with existing drugs [10]. Despite this large fraction of "druggable" mutations, only two GC-targeted therapies have been approved by the

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Table 8.1 Disparities in gastric cancer incidence and mortality in Latinos and in non-Latino whites (NLW) (data from the American Cancer Society report [15])

	Incidence per 100,000 individuals			Mortality per 100,000 individuals		
	Latinos	NLW	Disparity ratio	Latinos	NLW	Disparity ratio
Men	13.5	7.8	1.7	7.2	3.6	2.0
Women	7.8	3.5	2.2	4.2	1.8	2.3

Food and Drug Administration (FDA) [11, 12]. Hence, major advances in etiological and translational research are needed to improve GC outcomes through prevention, early detection, and better treatments.

Gastric Cancer in Latinos

GC exemplifies a malignancy with strong disparities in incidence, mortality, and survival that disproportionately affects Latinos, the largest and youngest US minority population [13–16]. Table 8.1 shows incidence and mortality rates (per 100,000 people) in NLW, Latinos, and their associated disparities [15]. Latinos are between 1.7- and 2.2-fold more likely than NHWs to be diagnosed with GC and between 2.0- and 2.3-fold more likely to die when diagnosed. These disparities are among the highest in the country and are not fully accounted for by differences in the prevalence of known risk factors or access to healthcare. Addressing these disparities should be a priority in etiological and outcome research in the country.

Genomic and Genetic Research Disparities

Relative to NLW, very limited GC genetic or genomic research has been carried out in Latino populations. All published GC genome-wide association studies (GWAS) have been carried out in Asians [17–20] or NLW [21], and no data are available on the risk that GWAS variants confer in Latino populations. Furthermore, all gastric tumor whole exome or whole genome sequencing studies carried out to date have only involved either Asian [22–28] or, as in the TCGA, predominantly NLW [10]. Table 8.2 shows the ethnic/racial composition of the TCGA patients, where Latinos represent only 1% of the participants. It is unfortunate that the minority population with the highest GC burden in the country was not fully represented in such an important study. To my knowledge, there is no published Latino data on the prevalence of the four TCGA molecular subtypes (Epstein–Barr virus associated, EBV; microsatellite instable, MSI; genomically stable, GS; and chromosomally instable, CIN) or of the mutation prevalence of the TCGA driver genes. Investigating Latino GC genomics is needed, because many somatic alterations are druggable and the TCGA new molecular subtypes show important differences in prognosis and response to therapy [29]. Having such information on population-specific molecular

Table 8.2 The racial/ethnic composition of the GC patients included in TCGA [10]

Race/ethnicity	Fraction of patients (n = 295) (%)
Non- Latino whites	63
Asians	20
Latinos	1
Other	14

Table 8.3 Epidemiological profiles of gastric cancers in Latinos and NLWs from California (2010–2014) (data from [31])

	Latinos (n = 3879)	NLW (n = 4612)
Sex		
Men	2166 (56%)	3048 (66%)
Women	1713 (44%)	1564 (34%)
Age		
Early onset (≤50 years)	880 (23%)	363 (8%)
Late onset (>50 years)	2999 (77%)	4249 (92%)
Socioeconomic status		
Lowest	1285 (37%)	435 (14%)
Medium/high	2145 (63%)	2736 (86%)
Histology		
Intestinal	1929 (62%)	2739 (77%)
Diffuse	1187 (38%)	828 (23%)
Stage		
Localized	887 (23%)	1282 (38%)
Regional/remote	2580 (77%)	2895 (62%)

profiles will empower studies aimed at improving GC outcomes in this minority population. Furthermore, Latino-focused genomic research efforts will help avoid widening the pervasive gap in cancer disparities [30].

The Unique Epidemiology of Gastric Cancer in Latinos

Table 8.3 presents GC incidence and mortality data for Latinos and NLWs from California. These data are interesting because GC profiles show important population differences. Latinos have a higher fraction of women with GC (44% vs. 34% in NLWs) and more GC patients with lower socioeconomic status (37% vs. 14% in NLWs). Furthermore, Latinos are more often diagnosed with GC by age 50 years (23% vs. 8% in NLWs), diffuse tumors (38% vs. 23% in NLWs), and regional and distant metastasis (77% vs. 62% in NLWs). These data therefore suggest that the epidemiology of GC in Latinos is unique and highlights the need for research that uncovers etiological differences between Latinos and other populations.

Table 8.4 Mutation frequency data of known gastric cancer driver genes in Latinos and TCGA (Luis Carvajal-Carmona laboratory, unpublished)

Gene	Mutation frequency	
	TCGA (n = 295)	Latinos (n = 30)
ARID1A	0.14	0.00
PIK3CA	0.12	0.04
CDH1	0.11	0.04

Molecular GC Profiles in Latinos Are Unique

The new TCGA GC molecular classification is important, because some of these subtypes have been associated with the prognosis or with response to therapy. Specifically, GC patients with EBV subtype tumors have excellent prognoses, while those with the GS subtype have poorer outcomes [29]. A recent study by Sohn et al. [29] also showed that patients with GS tumors do not benefit from chemotherapy, highlighting the need for research aiming at developing effective therapies for this subtype. To establish the prevalence of GC molecular subtypes in Latinos, our group recently carried out a pilot study of targeted sequencing in 30 tumors from Latino patients. Relative to TCGA, our unpublished study found that Latinos have a lower prevalence of CIN (33% vs. 49%) tumors and a higher prevalence of the GS (39% vs. 19%) subtype. We also found that the prevalence of mutations in driver genes is very different in Latinos (see Table 8.4 for some examples). These unpublished data suggest that the molecular profiles of GCs in Latinos are unique and highlight the need for larger and more comprehensive tumor genomic studies in the population.

Conclusions

Latinos have the highest GC burden in the United States. Published data and ongoing research suggest that the epidemiology of GC in Latinos is unique. It is now critically important to carry out studies that help us understand the etiology of GC in this minority population and that further characterize genetic and genomic patterns in GC patients of Latino ancestry. Furthermore, the unique molecular patterns in Latino GCs warrants future preclinical and translation studies in driver genes and molecular subtypes that are more prevalent in this minority population.

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Chapter 9
The Biology of Breast Cancer Disparities in Hispanics: Current Knowledge, Gaps, and Research Opportunities

Gerardo Colon-Otero

Introduction

The Hispanic population in the United States has been steadily increasing over the last decades, and it currently represents over 54 million people or approximately 19% of the US population (U.S. Census Bureau data, 2014). Breast cancer is the most common cancer in Hispanics and also has the highest mortality; therefore, addressing disparities in breast cancer outcomes is a critical healthcare issue. Data from national databases clearly show that non-Hispanic whites (NHW) have a higher population-based incidence and mortality from breast cancer than Hispanic women (incidence NHW 128.1/100,000 vs. 91.9 in Hispanics; mortality NHW 21.9 vs. 14.5 in Hispanics, ACS 2015 data) [1]. On the other hand, Hispanic women with breast cancer are more likely to be younger, to present with advanced stage disease, and are more likely to have aggressive subtypes (triple negative and HER2 positive) than NHW. As a result of this, Hispanic women with breast cancer have higher mortality rates than NHW [2].

Factors Contributing to Higher Breast Cancer Mortality Among Hispanics

It has been shown that socioeconomic factors including low socioeconomic status (SES) and lack of insurance or under-insurance are the main contributors to the observed outcome disparities among Hispanic women with breast cancer [2]. A higher prevalence of obesity among Hispanics is another factor contributing to these

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disparities [3, 4]. Also, the prevalence of inherited BRCA mutations among different subsets of Hispanic women has been correlated with the presence of European ancestry [5]. These data suggest that the higher prevalence of aggressive subtypes of breast cancers among Hispanic women may result from interactions between environmental and genetic factors.

Recent Data Elucidating the Causes of Breast Cancer Disparities Among Hispanics

Martinez and colleagues evaluated California Cancer Registry data that consists of 29,626 Hispanics and 99,862 NHW women with invasive breast cancer who were diagnosed between 2004 and 2014 [2]. They analyzed the prevalence of different breast cancer subtypes and found that triple-negative breast cancer and HER2-positive breast cancers were more common in Hispanics (HR 1.29 and 1.19, respectively). Hispanic women also had a higher mortality rate ratio (MMR) of 1.24. Multivariable analysis showed that neighborhood SES and health insurance status accounted for most of the differences in mortality. The percentage of Hispanic breast cancer women aged less than 50 years was twice that of NHW. Hispanics had a higher percentage of patients living in low SES neighborhoods (52.7 vs. 21.1%) and a higher percentage of patients with Medicaid insurance (30.8 vs. 17%). Hispanics also had more advanced (stages 3–4) disease and less stage 1 disease (39.2 vs. 28.4% and 39.8% vs. 51.1%) and were more likely to present with positive nodes (41.1% vs. 31.5%). Hispanics had higher TN and HER2-positive subtypes (TN: OR 1.29; ER neg HER2 pos: OR 1.31; ER pos HER2 pos: OR 1.19). In a model that included all variables, mortality among Hispanics was significantly lower than among NHW (MRR 0.90, CI 0.87–0.94). Younger women had a higher risk of dying than older women ($p < 0.001$), and mortality differences between Hispanics and NHW were greatest in the younger group (MRR 1.42 vs. 1.13).

Fejerman et al. showed that European ancestry is associated with increased risk of breast cancer among Hispanics in the San Francisco area (OR 1.79, CI 1.28–2.79) [5]. Among Mexican women, the risk of breast cancer increases with every 25% increase in European ancestry (OR 1.20, CI 1.03–1.41) [6]. They also showed that 50% or more Native American ancestry in Hispanic women with breast cancer is associated with a doubling of mortality [7]. Engmann and colleagues in Fejerman's group recently analyzed data from the Pathways Study, a prospective study of 506 Latina women with breast cancer cared for in the Kaiser Permanente Health System. They found that equal access to care as part of the Kaiser System eliminates the association between Indigenous American ancestry and breast cancer recurrence and mortality [8].

Breast Cancer in Young Hispanic Women: The Subset with the Greatest Disparities in Outcomes

Even though breast cancers are most common in women in their fifth and sixth decades of life, breast cancer in women younger than 50 years is a significant health issue. For example, among US women aged 35–40 years, breast cancer is the number one cause of death and the number one cancer. Among women aged 25–34 years, breast cancer is the number two cause of death behind accidents. If we consider women aged 25–40 years, breast cancer accounts for 23% of all cancer deaths. Keegan et al. reviewed data from 5605 women aged 15–39 years that were diagnosed with breast cancer in the United States between 2005 and 2009. They found that Hispanic women had a 3.25 RR and African American (AA) women had a 1.65 RR relative to NHW women [9]. It was also found that in this age group, women with breast cancer are more likely to have triple-negative and HER2-positive disease as well as more likely to present with stages 3–4 and be Hispanic, AA, or Native American (NA) [9].

Conclusions from Recent Data

We can conclude from the recent data that breast cancer outcome disparities are greatest in the young age group (age less than 40 years) and that there is a need for more studies on the interplay between genetic and environmental factors. There is also a need for breast cancer preventive interventions in the young age group (age less than 40 years). Since low SES neighborhoods and uninsured/under-insured patients account for most of the disparities, efforts need to emphasize interventions in these populations.

Hypothesis for the Causes of Early Onset Breast Cancer Disparities and the Potential Role of Childhood Obesity

Figure 9.1 summarizes a working hypothesis for possible factors contributing to early onset breast cancer disparities. We hypothesize that low SES factors lead to increased stress and poor dietary habits, which in turn leads to childhood obesity. Childhood obesity leads to increased production of adipokines and IL-6 with increased transcription of aromatase in the adipose tissue leading to increased estrogen and increased genotoxic estrogen metabolites. This results in increased DNA damage, particularly in patients with DNA repair defects, leading to early onset breast cancer with its worse prognosis.

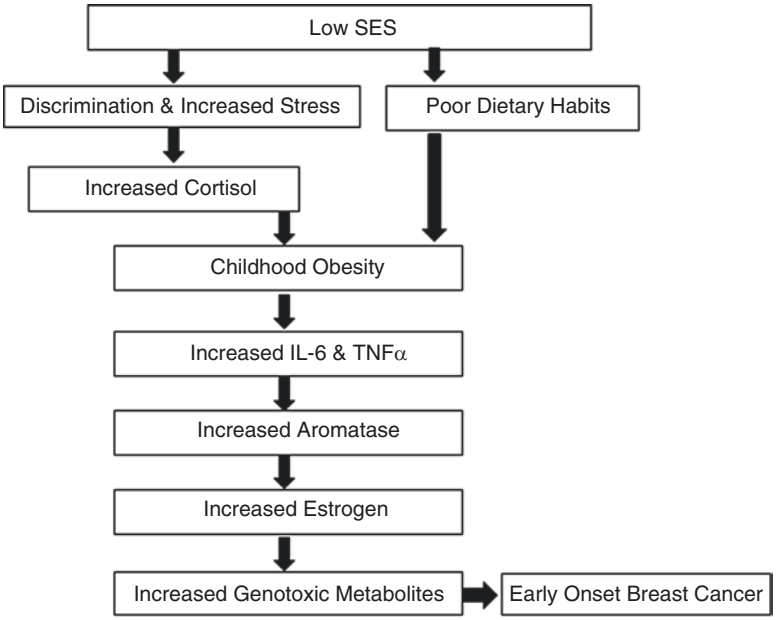

Fig. 9.1 Hispanic breast cancer outcome disparities are greatest in the early onset breast cancer subset. We speculate that this is likely a result of genetic factors and disparities in the prevalence of obesity among low SES Hispanics with its effects on estrogen metabolism

Childhood Obesity: A Likely Contributor to Breast Cancer Disparities

The prevalence of obesity in US children and adolescents has tripled over the last 30 years [4, 10]. The prevalence of childhood obesity is highest in non-White children with 30% AA children and 20% Mexican American children being obese as compared to 11% NHW [4]. Recent data also shows that obesity in childhood predicts for adult obesity. Among 2400 obese 5–14 year olds followed for 17 years, 83% AA vs. 68% NHW were obese as adults [11]. Finally, low income is associated with higher obesity and with a higher consumption of fast foods, snacks, and soft drinks [4].

Possible Linkage of Childhood Obesity with Breast Cancer: The Third Harvard Growth Study

The Third Harvard Growth Study was a longitudinal study of more than 3000 school children performed by the Harvard School of Education from 1922 to 1935 [12]. The subjects were first- and second-grade public school students enrolled in 1922–1923 from three middle-class cities in the north of Boston. Subjects were measured annually through high school, and those with at least eight height and weight

measurements were included in this study. Subjects were contacted in 1968 and 1988. A total of 1877 subjects were included in the analysis, including 858 women. Ever been overweight before puberty was associated with a 2.7 times risk of breast cancer mortality in females. Previous studies had yielded conflicting results regarding the risk of breast cancer associated with childhood obesity, but these studies were dependent on patients' recollection of their childhood weights [12].

Childhood Obesity: A Proinflammatory State with High Estrogen and Genotoxic Estrogen Levels

Mauras et al. evaluated a cohort of obese and lean pre-pubertal girls. In the obese girls, they found a significant increase in levels of proinflammatory cytokines, including IL-6 as well as evidence of elevated prothrombotic proteins (PAI-1 and fibrinogen) [13]. These findings show that obesity in childhood, prior to the onset of clinically evident metabolic syndrome, is associated with a significant proinflammatory and prothrombotic state. In addition, using the same cohort of patients, they showed that childhood obesity is associated with significantly higher levels of estradiol and its genotoxic metabolites (16-OH-E1, 2-OH-E1, 2-OH-E2, 4-OH-E1 and 4-OH-E2) with greatest elevations in the 16-OH-E1 levels and a significantly lower ratio of 2-OH-E1/16-OH-E1, values that had been directly and reciprocally related to the subsequent risk of breast cancer in postmenopausal women by Fuhrman et al. [14]. The elevations of estradiol and its metabolites in the obese group correlated with the elevation of IL-6.

Contemporary Hormonal Contraception Is Associated with a Higher Risk of Breast Cancer

Morch et al. recently reported a detailed epidemiologic analysis of the effects of hormonal contraceptive use on the prevalence of breast cancer. This was a prospective study of 1.8 million Danish women aged 15–49 years followed for an average of 10.9 years [15]. More than 10 years of hormonal contraceptive use was associated with a 1.38 RR for breast cancer in this population.

Oral Versus Transdermal Estrogen Replacement and Its Effects on Estrogen Metabolism

Estrogen is converted into its oxidative metabolites in the liver, and it is conceivable that oral estrogens may be associated with a greater generation of these metabolites than the transdermal estrogens. In a prospective randomized study of hypogonadal

girls with Turner syndrome, Dr. Mauras' team administered estradiol orally versus transdermally at doses that resulted in similar serum-free estradiol levels [12]. Measurements of total estradiol and its metabolites after 12 months of therapy were obtained. The oral estradiol group was associated with higher generation of genotoxic estrogen metabolites than normal post-pubertal girls and the transdermal estradiol group [16]. This may explain the higher risks of breast cancer associated with oral hormonal contraception reported by Morch et al. [15] and suggests that a switch from oral estrogen to transdermal estrogen contraception could potentially decrease breast cancer and ameliorate breast cancer disparities.

Future Research on Genotoxic Estrogen Metabolites and Breast Cancer Disparities

Additional studies aimed at determining if obesity in Hispanic young women is associated with higher levels of genotoxic estrogen metabolites will be of interest. Evaluating possible interactions between BRCA mutations (or other pathogenic DNA repair mutations) and genotoxic estrogen metabolism in Hispanics may identify mechanisms involved in early onset breast cancer. Short-term diet and exercise interventions may alter genotoxic estrogen metabolite generation in pre-pubertal obese girls, and measuring the effects of dietary manipulations on these metabolites may be of clinical value.

Conclusions

In summary, Hispanic women overall have lower prevalence and mortality from breast cancer than NHW. On the other hand, breast cancer in Hispanics develops at a younger age, is more likely triple-negative or HER2-positive, presents in advanced stage and has a worse prognosis. Data is emerging on the potential roles of stress from low SES status, childhood obesity, genotoxic estrogen metabolites, exogenous oral estrogens, and genetics on breast cancer, particularly early onset breast cancer and its associated disparities in Latinas. Further studies are needed to elucidate the biological factors accounting for disparities in outcome among Latinas with breast cancer.

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Chapter 10
Molecular Profiles of Breast Cancer in Hispanic/Latina

Silvia J. Serrano-Gómez, Maria C. Sanabria, Jone Garai, Li Li, Melody Baddoo, Lucio Miele, Laura Fejerman, and Jovanny Zabaleta

Introduction

Breast cancer is the most common cancer in women worldwide and is the second leading cause of cancer death among women in the United States [1]. Although it is the most incident cancer at the global level, its incidence and mortality rates vary among the population groups in the United States [2]. African American (AA) and Hispanic/Latina (H/L) women have a lower incidence of breast cancer (125.5 per 100,000 and 91.9 per 100,000, respectively) compared to non-Hispanic White (NHW) women (128.7 per 100,000) [2]. Mortality rates for breast cancer are higher

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in AA women (29.5 per 100,000) and lower in H/L women (14.2 per 100,000) when compared to NHW women (20.8 per 100,000) [2].

Breast Cancer Intrinsic Subtypes

Breast cancer is a complex and heterogeneous disease in terms of histology, therapeutic response, metastatic patterns, and outcomes [3]. In 2000, Perou et al. published the first classification of breast cancer into intrinsic subtypes based on data from gene expression microarrays [4]. They used complementary DNA (cDNA) microarrays to analyze breast cancer tissue from 65 surgical specimens of human breast tumors from 42 different patients. These samples were collected at Stanford University California, or at the Haukeland University Hospital in Bergen, Norway, so presumably included women of mostly European descent. Gene expression analysis separated intrinsic subtypes of breast cancer into two main groups based on the expression of estrogen receptor (ER). Within these two groups, four intrinsic subtypes were identified: luminal A and luminal B subtypes, which are positive for the ER expression (ER+); and HER2-enriched and basal-like, both ER negative (ER−) [5, 6]. One year later, Sorlie et al. [7] analyzed the clinical implications of this new classification of breast cancer [8] and reported differences in breast cancer outcomes between the intrinsic subtypes [7].

Genetic Ancestry and Breast Cancer Characteristics

Each Latin American country shows variations in the proportions of European, African, and Native American ancestries, and countries such as Mexico, Peru, and Bolivia are predominantly indigenous while Argentina and Uruguay are predominantly European [9]; there are differences not only in genetic ancestry but also in lifestyles and exposures of breast cancer [10].

Increasing evidence shows that breast cancer characteristics differ according to genetic ancestry. European ancestry in H/L women has been associated with an increased risk for breast cancer in women from the San Francisco Bay area [11], and this finding was replicated in women from Mexico [12]. Also, Fejerman et al. [11] did not find any associations between genetic ancestry and tumor characteristics such as hormone receptor status. Al-Alem et al. [13], however, studied the association between genetic ancestry and breast cancer characteristics in a group of 656 women (255 NHW, 277 AA, and 124 H/L) from the "Breast Cancer Care in Chicago" study and found that higher European ancestry was protective for later stage at diagnosis in H/L women (OR 0.70, 95% CI 0.54–0.92) and that Indigenous American ancestry (IAA) was associated with later stage at diagnosis (OR 1.36, 95% CI 1.04–1.79). The lack of concordance between the last two studies can be explained by the

variation in the case populations. The study by Fejerman et al. [12] included women from the San Francisco Bay area, presumably of Mexican origin while the Al-Alem et al. study [13] included a larger proportion of women from the Caribbean. This highlights and reinforces the idea that results found in one Hispanic population cannot be generalized for all Latinos and that there is a need to include genetic ancestry in the studies [13].

Growing evidence suggests that differences in gene expression profiles of breast cancer can be influenced by the genetic architecture of the individual's genome [14–17]. These studies have compared gene expression profiles from NHW and AA women with breast cancer in an effort to explain health disparities in the tumor biology context. Martin et al. [16] compared breast tumors from 18 AA and 17 NHW women, and over the 400 differentially expressed genes, they found two genes that could distinguish between the two population groups, *CRYBB2* and *PSPHL*. Similar findings were reported by Field et al. [14] who analyzed 52 matched patients (26 AA and 26 NHW) and compared the gene expression profile between the two population groups. They found 22 differentially expressed genes, including *CRYBB2* and *PSPHL*. Stewart et al. [17], using data from The Cancer Genome Atlas (TCGA) compared gene expression profiles of 574 NHW and 53 AA patients and found 674 differentially expressed genes. Among those, resistin (*RETN*), a gene associated with obesity and diabetes [18], was the most changed. *CRYBB2* was also found to be overexpressed in AA patients [17]. Grunda et al. [15] analyzed the expression of 84 genes involved in breast cancer prognosis associated with therapy, estrogen signaling, and tumor aggressiveness in 11 AA and 11 NHW patients and identified 20 genes that participate in regulatory processes such as G1/S transition, cell adhesion, and estrogen pathway targets. The results suggest that there may be some differences in the gene expression profile as a consequence of ancestry. None of these studies included H/L women in the analysis. More importantly, ancestry was assessed by self-identification, and genetic ancestry was not analyzed.

There is one study from Chavez-MacGregor et al. [19] that investigated the differences in gene and protein expression within each molecular subtype as a consequence of ancestry. They analyzed a group of 376 women belonging to different racial groups (AA, NHW, H/L, and others) and did not find differences in gene and protein expression between racial/ethnic groups. As they discuss in the paper, to perform a more accurate analysis in an admixed population, it is important to analyze their genetic ancestry, as it could lead to misclassification of the population. Even though the latter work did not find ancestry-modulated genes in breast cancer, more studies are needed to answer that question.

Few studies have explored genetic ancestry to assess gene expression differences. Huo et al. [20] analyzed genetic ancestry in 930 patients with breast cancer who were grouped into the categories genomic black (≥50% African ancestry) or genomic white (≥90% European ancestry). After adjusting for intrinsic subtypes, they found 142 differentially expressed genes, with *LOC90784* and *CRYBB2* being the top two most differentially expressed. This result is consistent with previous studies where genetic ancestry was not analyzed [14, 16, 17]. This finding can be

explained by the fact that the genetic ancestry in patients who self-identify as NHW and AA is more uniform, with dominant ancestries being European and African, respectively [20].

Our recent work identified luminal B as the most prevalent subtype in Colombian women with breast cancer [21]. In the context of genetic ancestry, we analyzed gene expression profiles of 42 Colombian women with breast cancer (21 luminal A and 21 luminal B) based on 80 ancestry-informative markers (AIMs) [22]. The patients were categorized according to luminal subtype and to the proportion of European or Native American ancestry. Differential expression analysis was performed according to intrinsic subtype and by ancestry category. We found five genes potentially modulated by genetic ancestry: *ERBB2*, *GRB7*, *GSDMB*, *MIEN1*, and *ONECUT2*. Further studies are needed to explore the prognostic value of this finding and to replicate it in other Latin-American patients.

Other studies have analyzed gene expression profile in H/L women without determining genetic ancestry. DNA repair capacity (DRC) has been previously described as a breast cancer risk factor [23, 24]. DRC can be measured by the host-cell reactivation (HCR) assay that quantifies the capacity of a lymphocyte to repair exogenous DNA [25, 26]. Ramos et al. [27] reported that a low DRC is a breast cancer risk factor in H/L. They compared the DRC in 33 breast cancer patients and 47 healthy controls from Puerto Rico and found that for every 1% decrease in the DRC, there was a 22% increase in breast cancer risk. Matta et al. in 2012 [28] analyzed the DRC from 824 women (285 breast cancer patients and 539 controls) and also found that the DRC was lower in breast cancer patients. One year later, the same group [29] performed microarrays to analyze the expression level of DNA repair genes in women with breast cancer from Puerto Rico compared to controls to explore how DNA repair was dysregulated in breast cancer. They found 21 genes differentially expressed between breast cancer patients and controls: *CHEK2*, *EME1* (*MMS4L*), *ERCC3* (*XPB*), *FANCM*, *H2AFX* (*H2AX*), *HMGB1*, *HUS1*, *MBD4*, *NEIL3*, *PCNA*, *RAD1*, *RAD23B*, *RAD51*, *RAD54B*, *RDM1* (*RAD52B*), *SHFM1* (*DSS1*), *TP1*, *UBE2N* (*UBC13*), and *XRCC5* (*Ku80*). Moreover, they analyzed DRC using the HCR test and found three genes positively associated with the DRC level, *RAD51*, *FANCB*, and *FANCA*. This study is important because the use of inhibitors of DNA repair pathways can interfere with the ability of the cells to survive DNA damage induced by chemotherapeutic agents [27, 30, 31]. The results in Matta et al. [29] and Ramos et al. [27] provide evidence regarding dysregulation of DNA repair capacity at the gene expression level in H/L women with breast cancer. Similar results have been reported in NHW women [32, 33].

Analysis of gene expression profiling has also been used to develop gene signatures to estimate recurrence risk and to better select patients who will benefit from chemotherapy [34–37]. These signatures have been developed and validated in samples of NHW women and have been used in H/L patients with the assumption that the molecular profile would be similar. Kalinsky et al. [38] compared the proliferation index of ER(+)/HER2(−) early stage tumors based on the Oncotype DX gene expression signature in H/L and NHW women and found that tumors from H/L women showed higher proliferation scores than tumors from NHW women.

Conclusions

Hispanic/Latinas are underrepresented in breast cancer studies and usually are analyzed as a whole group. However, the genetic make-up of H/L women may create a bias in genetic association studies and generate false-positive or false-negative associations. It is thus advisable to properly classify genetic ancestry in admixed populations, like Hispanic/Latinos, to better understand the real contribution of genetics to disease susceptibility and to provide this ethnic group the benefits of recent treatment advances.

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Part V
Advances in Cancer Therapy and Clinical Trials

Chapter 11
Biomarkers and Precision Medicine in Oncology Practice and Clinical Trials

Edith A. Perez

Introduction: Biomarkers in Clinical Care and Research

Biomarker-Based Precision Medicine

Biomarker-based precision medicine is now often the standard of care for patients diagnosed with cancer. Industry and government have invested heavily in the development of precision medicine, and as improved diagnostics, testing, and biomarkers become more common, existing barriers to the use of precision medicine will be eliminated. To make this happen, there must be clear scientific communication that enhances understanding and influences clinical practice. One concern is the high cost of new precision medicines available for patients, which should be offset by efficiency and overall value provided to patients with cancer. Additionally, rather than testing tumor specimens just once, there will be increased reliance on dynamic biomarkers in the continuum of cancer care. This will influence existing guidelines and procedures in many hospitals, clinical practices, and insurance companies, so that patients can access the best medicine for them.

Biomarkers for Decision Support

It is increasingly evident that the introduction of targeted therapies has revolutionized the management of patients with cancer. Integration of biomarkers, in the tumor and stroma, in addition to clinical characteristics, helps healthcare professionals optimize diagnosis and treatment recommendations. However, when should

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a physician consider the use of biomarkers for decision support in the continuum of cancer care? Biomarker testing can be used to help assess cancer risk, best diagnose a particular malignancy, select treatment, and/or assess the treatment response. There are many decisions that physicians must make when they use biomarker testing, not the least of which is what tests to choose from the many now available. And once the results are in, how does the physician interpret the sometimes massive amount of information and report them in an understandable way? How should the results be applied to patient care? Will patients be reimbursed for this selected therapy? Ultimately, physicians are increasingly expected to consider these issues in the context of biomarker testing in the continuum of cancer care.

Biomarker Properties

Biomarkers, which are measureable indicators of biological processes, may be prognostic or predictive. A prognostic biomarker demonstrates the relationship between the biomarker and response in a control group (patients receiving standard of care); it predicts disease aggressiveness regardless of the experimental study treatment. A prognostic biomarker can be evaluated by comparing a control group response in patients who have the positive biomarker (Dx^+) with patients who do not have the positive biomarker (Dx^-). A predictive biomarker demonstrates the relationship between the biomarker and treatment effect; it differentiates between patients who are likely to benefit from a particular treatment (relative to those in a control) and patients who are not. Sometimes a predictive biomarker helps identify patients who will benefit the most from a treatment; however, it does not necessarily preclude patients without the biomarker from also receiving treatment benefits. This scenario often occurs in the context of new cancer immunotherapies and the use of PD-L1 testing or tumor mutational burden biomarker analyses. These concepts are further clarified in Figs. 11.1, 11.2, 11.3, and 11.4; note that depending upon the circumstance, biomarkers may be both prognostic and predictive.

Considerations in Biomarker-Driven Trial Design

Because the analysis of biomarker studies can be complex and challenging, it is recommended that a knowledgeable statistician be consulted for high-level biostatistics guidance. When designing a trial, it is best if all hypotheses are prespecified and ranked to guide interpretation and that appropriate analytical strategies are used to minimize bias. Also, it is best if the experimental design does not have a large number of analytical covariates, because it can decrease confidence in the results. An additional general consideration in trial design is having respect for the patients participating in the study and understanding that their time is valuable. Thus, it is critical to develop the best clinical or translational trial possible. Obviously, one size design

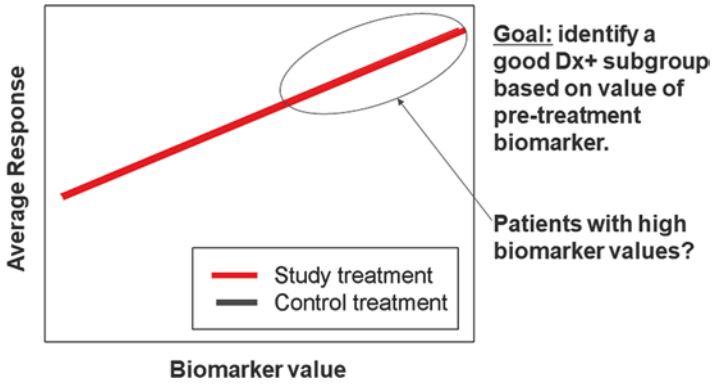

Fig. 11.1 Average patient response versus the value of a pretreatment personalized healthcare biomarker (PHC) in a single arm trial. While there appears to be a correlation between response and biomarker value, it is not possible to determine whether the biomarker is prognostic or predictive without a control group for comparison

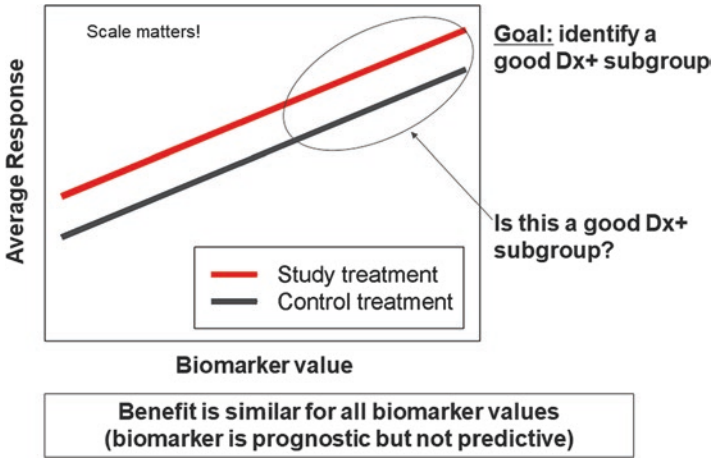

Fig. 11.2 Average patient response versus biomarker value in a randomized trial. The biomarker is prognostic, because the benefit is similar for all biomarker values irrespective of the treatment

strategy does not fit all, but strategies based on the three pillars of time, cost, and risk still serve as a good guiding principle for biomarker-driven drug development.

There are some unique challenges in biomarker research that require special consideration in trial design. Sometimes there is a need to shorten the timeline from specimen collection to having the biomarker report available for clinical decisions, because patients are waiting for the information needed to improve (as well as lengthen) their lives. In this case, it is possible to use a clinical trial design that is adaptive—having the ability to change the design or hypotheses in an ongoing study based on early results from the same study or on biomarker data from other studies.

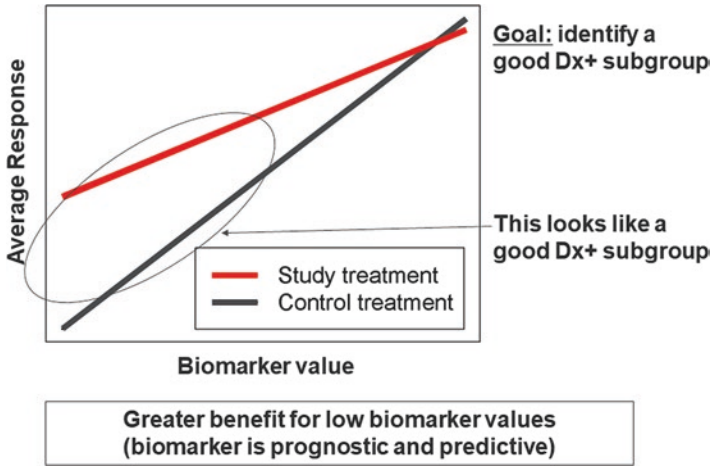

Fig. 11.3 Average patient response versus biomarker value. This example shows a biomarker that is both prognostic and predictive. Patients in the treatment group (red line) with higher biomarker values showed a better response. For the control group (blue line), the biomarker gives some prognostic information and shows that patients with lower biomarker values receive the greatest benefit of treatment

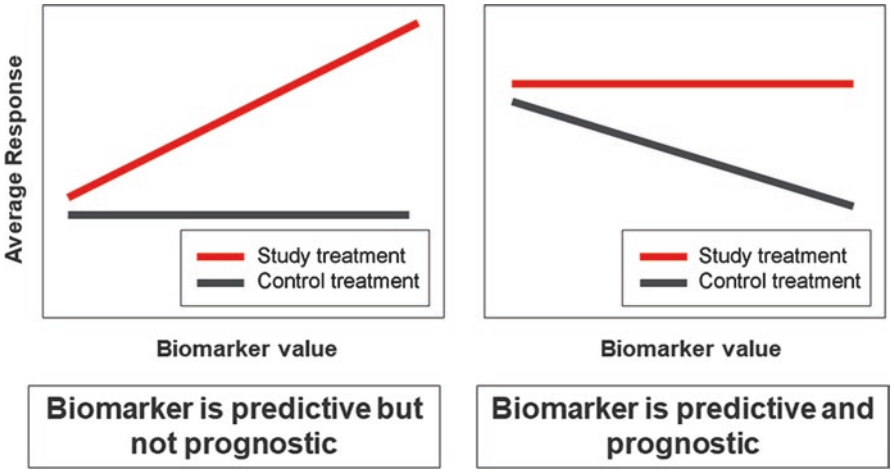

Fig. 11.4 Further examples clarifying the difference between prognostic and predictive biomarkers

For example, when phase II and III studies run in parallel, the data from phase II may be used to adjust the phase III study design while the study is still ongoing, thus shortening the time it takes to get results. The opportunities or triggers for adaptation are prespecified in the initial design to protect the integrity of the phase III study.

Tumor Sequencing for the Near Future

Looking to the future, one projection is that tumor sequencing will become standard clinical practice in the next few years, and the question is when should this tumor sequencing occur? Should it occur right after initial diagnosis? Should it occur after patients have received initial therapy and then develop refractory disease for us to identify potential biomarkers or to think about novel approaches?

It is also likely that liquid biopsy technology will be developed. Blood tests used to follow patients in the past are based on single proteins, such as CEA, CA 125, CA 19-9, but in the last few years there has been much interest in new technology to sample circulating cell-free tumor DNA (ctDNA). The ability to detect mutations in tumor DNA from a blood sample rather than from multiple tumor biopsies would be a huge improvement for patients. The isolation and subsequent analysis of ctDNA is viewed as a powerful tool with considerable potential to facilitate and improve clinical outcomes across multiple cancer types. This technology is promising, but still has limitations such as its inability to examine a large number of genes. Accurate blood sample collection, handling, and storage procedures are essential for reliable ctDNA extraction and molecular analyses. The conditions in which the blood samples are stored and shipped, as well as the amount of time that elapses between blood drawing and plasma extraction, are just some of the factors that may influence the accuracy of ctDNA analysis. Both clinical practitioners and researchers should be particularly attuned to these steps to maximize progress. In addition to screening for cancer, circulating tumor DNA technology can become part of the assessment of patients receiving cancer therapy. A positive finding of an actionable mutation in ctDNA (if using valid procedures and assays) could represent sufficient evidence to initiate targeted therapies. If the patient, for example, has had mutations detected in their tumor with next-generation gene sequencing, the physician can sample circulating tumor DNA during and after treatment to follow these mutations and other molecular changes over time—and do so without performing invasive tumor biopsies. The role of sensitivity, specificity, and concordance rates among various techniques will be important to elucidate in the next few years.

Cancer taxonomy is expected to become molecular-based; however, it is likely that tumor classification is going to be based on a combination of tumor location and molecular diagnosis. This field is evolving quickly, for example, there are therapies that have been approved for patients with melanoma whose tumors have the BRAF mutation. Many of these medicines have already been approved by the FDA including some combinations such as a BRAF inhibitor and a MEK inhibitor that work better than monotherapy. The future may be for an increasing tumor-agnostic biomarker strategy to manage patients. Two of these approvals have been recently granted by the FDA and other regulatory agencies, based on the analysis of somatic microsatellite instability (MSI) and the other NTRK fusion alterations. Basket trials and biomarker testing in various tumor types will help us gain more insights that will be relevant to the inclusion of new therapeutic strategies by the FDA, guideline, and pathway development groups. As an example of a recent development, the

Southwest Oncology Group conducted a study in which they used a BRAF inhibitor (which had only been approved by the FDA for melanoma) in patients with refractory colon cancer whose tumors have the BRAF mutation. The impressive results of that trial led to an NCCN (National Comprehensive Cancer Network) designation, so that patients with colorectal cancer whose tumors have the BRAF mutation, may gain access to BRAF treatment, even though not yet approved by the FDA for the treatment of colorectal cancer. Another type of biomarker testing is the one of germline alterations, or alterations of homologous recombination, with therapies such as PARP inhibitors being either approved or under study. For clinicians and healthcare professionals, it is significant that this type of research is being done, because of its impact to improve options for patients.

Finally, clinical trials in oncology will increasingly use sequencing at enrollment and follow-up. This is already the standard of care for many current research studies. Earlier intervention and prevention strategies will facilitate adoption of gene and protein testing and will require better trial designs and statistical plans. As a consequence, people will have more access to these genomic technologies, regulatory approval will become adaptive, and early phase clinical trials will reflect a genomic approach.

FDA Approvals of Next-Generation Gene Sequencing (NGS) Panels and In Vitro Diagnostics (IVDs)

Many companies offer next-generation gene sequencing, but in addition, many healthcare facilities have developed their own panels. There are probably about 20,000 genes in our genome, but only a portion of those actually encode protein. In the context of cancer, the question is how many genes should be tested for clinical practice versus clinical research, because they have different purposes. For example, some hospitals have a 46-gene panel, 50-gene panel, and 200-gene panel, and it is not known which is best.

The FDA now considers not only safety but also efficacy as a way to regulate approvals, and the good news is that the FDA has given regulatory approval and clearance for some next-generation sequence, multigene marker tests. On June 23, 2017, the FDA approved the Oncomine Diagnostic Target Test, a 23-gene next-generation assay for patients with non-small cell lung cancer. On November 15, 2017, the FDA gave clearance (not approval) to the Memorial Sloan Kettering Cancer Center (MSKCC) for IMPACT—a tumor profiling test based on next-generation gene sequencing. To do this, the FDA developed a mechanism to approve diagnostic tests in addition to medicines. In this case, they accredited the New York State Department of Health (NYSDOH) as an FDA third party reviewer of in vitro diagnostic (IVD) tests. This resulted in the establishment of a Class II regulatory pathway for the review of other NGS-based tumor profiling tests, making these tests eligible for the 510(k) clearance process by applying either to the FDA directly or

through an accredited third party reviewer like the NYSDOH. The cleared IMPACT test analyzes 468 genes and captures somatic mutations (e.g., point mutations, insertions, deletions) and microsatellite instability. This test, however, does not detect gene copy number alterations or rearrangements.

On November 30, 2017, the FDA and the Center for Medicare approved another multigene marker test, FoundationOne from Foundation Medicine (FMI). The approval was somewhat different from the other diagnostic tests, because it is a companion diagnostic (CDx) used to predict and inform therapy decisions. This is the first time there has been an FDA approval of a test that also considers what therapeutic drug can be used based on the patient's test results. This test analyzes 324 genes and can be used for any tumor; it detects four genomic alterations (base pair substitutions, insertions and deletions, copy number alterations, and rearrangements), tumor mutational burden, and microsatellite instability. Other tumor sequencing platforms and the so-called liquid biopsies, such as the Guardant test, have more recently received regulatory approval.

A new type of test that is available for clinical testing is tumor mutational burden (TMB)—a genomic biomarker for cancer immunotherapy that measures the number of mutations in a tumor's genome. There is research evidence that there is a correlation between the amount of tumor mutational burden and responsiveness to checkpoint inhibitors, a fairly new class of immunotherapies for patients with cancer. Thus, TMB may be an important predictive marker for patients who are being considered for this new type of immunotherapy. In addition to strengthening the correlation between TMB and benefit to checkpoint inhibitors, further research must answer two questions. One, who can do the most accurate and reliable test? And second, what should be the cutoff for tumor mutation burden and decision for patient treatment? Most recently, tests that allow for comprehensive genomic results from a blood draw have started gaining FDA approval, which could be instrumental to help move beyond the limitations of tissue biopsies to match patients to best personalized treatments.

Designing Clinical Trials to Support FDA Approval

Suggestions for designing biomarker trials that support FDA approval include design trials that make sense in the context of the United States; ask clinically meaningful questions; select and refine drug dose; think about biomarkers early and often; and include more patient-related outcomes and do them well. What is an ideal biomarker trial? It should inform about the in vitro diagnostic (IVD), the drug, and their interaction. To determine whether an IVD can be used to select a therapy, there must be knowledge about sensitivity determined by the fraction of responders that are marker-positive; specificity determined by the fraction of non-responders that are marker-negative; positive predictive value (PPV) based on the fraction of marker-positive patients who respond; negative predictive value (NPV) determined

by the fraction of marker-negative patients who do not respond; and cutoff point for positivity.

A further consideration when designing biomarker trials is to include diverse ethnic patient participation, because it provides the most comprehensive ability to apply data to the general population. The issue is what is a sufficient number of diverse patients to adequately do the analysis? Finally, one additional caveat is that limiting a study to marker-positive patients may characterize the drug/diagnostic poorly. Sometimes researchers incorrectly assume that a biomarker is required for a response and may thus deny effective therapy to marker-negative patients.

Cancer Immunotherapy (CIT) Biomarkers

General Concepts

The use of cancer immunotherapy (CIT) biomarkers for a variety of malignancies is revolutionizing oncology. The number of drugs approved by the FDA is rapidly growing, added to unprecedented opportunities to better understand biology and offer better treatments for patients with various malignancies.

Many different types of cells and molecules are necessary for the immune system to work properly. These include T-cell lymphocytes such as $CD4^+$ and $CD8^+$ T cells, natural killer (NK) cells, dendritic cells, macrophages, and a myriad of regulatory cells and proteins that influence immune mechanisms. Because the immune response is so complex and each individual's response unique, there are many challenges to develop effective CIT biomarkers. For example, researchers must first be able to answer some fundamental questions such as which cells are important for the immune system, how to test whether cells are functioning properly, and how to test whether they are activated or not. It is also critical to know specifically which of the many proteins (and their spatial localization) are important for elucidating the role of biomarkers as predictors for immunotherapy, as well as how to identify patients who are most likely to benefit from these cancer immunotherapies.

There are a variety of immunotherapy biomarkers currently being researched and used in cancer management. One is a measure of tumor infiltrating lymphocytes (TILs); in many tumors, there is a correlation between infiltration of T cells into the tumor (e.g., $CD8^+$ T cells) and patient outcome. However, validation studies are still required before incorporation for therapeutic decisions. The biomarker most advanced to help predict the likelihood of benefit to checkpoint inhibition is the expression of an immune checkpoint protein, programmed death ligand (PD-L1); although it is not a binary marker (in other words, high expression predicts for greater likelihood of response), it does not mean that responses will not be seen in patients whose tumors do not express the protein. Combined expression patterns of multiple genes such as T-effector gene expression signatures as well as mutational

load across targeted genes may be used to evaluate the predictability of clinical benefit to immune therapies. One promising note is that, in the past, mutational burden was measured from tumor biopsies, but now there is the potential to measure it from blood (liquid biopsy). A future goal is to identify neoantigens—tumor-specific antigens that may be detected and targeted by T cells (e.g., $CD4^+$ and $CD8^+$). Whole transcriptome sequencing can now be used to identify neoantigens and T-specific subsets in a given patient. One current avenue for research is to identify neoantigens that may help predict benefit to therapy and those that may be helpful to develop new vaccines. There are multiple companies worldwide that are developing vaccines for patients with cancer, and this neoantigen approach is one of the most promising (added to focused trials using protein-based vaccine approaches).

Program for Accelerated Cancer Therapies (PACT): An Example of Multidisciplinary Collaboration to Elucidate Relevant Biomarkers in Oncology

A new Program for Accelerated Cancer Therapies (PACT) has been initiated in collaboration with NIH, NCI, and biopharma. It emerged from the importance of working together to solve the problem of understanding biomarkers in the area of cancer immunotherapy. The overall goal is to provide a systematic approach to immune and related oncology biomarker investigation in clinical trials by supporting the development of standardized biomarkers and assays. This project will leverage NCI investments in its Cancer Immune Monitoring and Analysis Centers (CIMACs) and Cancer Immunologic Data Commons (CIDC) Network to select biomarkers for uniform clinical applications, to validate and standardize biomarker assays, to incorporate biomarkers as standards in clinical trials, and to create a comprehensive database, integrating biomarker, and clinical data to enable pre-competitive correlative biomarker analyses. Also, PACT will engage the FDA in its biomarker standardization and harmonization efforts in order to enhance regulatory decision making. This important project will help develop standardized biomarkers for immunoprofiling and exploratory biomarkers of high relevance to patient care.

Challenges and Opportunities to Improve Biomarker-Based Trials

There is growing pressure on many fronts to accelerate the pace at which new medicines are launched and made available for patients, but bringing biomarker-based trials to patients is challenging. A major hurdle is that investigators are reluctant to run extensive molecular profiling panels if only a small fraction of patients will be eligible to participate in their clinical trial. Thus, there is a need for a more efficient

way to connect patients with genomic information to a clinical study, because high screen failure rates make trials more costly and time consuming. For example, if a marker is present perhaps in one out of 500 patients, it is really difficult for a clinician or institution to order 500 tests to find only one patient who might be enrolled in that particular clinical trial. This has slowed down the progress. Thinking about this scenario in more detail brings to light another issue—accountability to the patient. Increasing screen fail rate in clinical trials not only makes a large number of screenings necessary but also leaves many patients with no accountability. For example, imagine a patient with refractory ovarian cancer who wants to join a clinical trial testing a promising new drug for a particular alteration, and the patient is screened only to find that her tumor is negative for the marker. This is very tough on the patient who at this point wants to try everything that might help.

One way to address both of these issues is to link patient screening to a set of trials with an algorithm that assigns patients to the most relevant study. For example, consider a scenario with five trials A through E. If it is found on screening that a patient has a particular abnormality based on the biomarker A, the patient can enroll in trial A. If a patient does not have the biomarker for trial A, the patient can be considered for one of the other trials (B, C, D, or E) with one screening and patient consent. If screened patients do not have any of the abnormalities for the five trials, they can be enrolled in an all-comer trial. Thus, this theoretical initiative is a win-win scenario because patients will always have access to a clinical trial with new options, and cancer centers and institutions will have more efficient recruitment into their clinical trials. This type of solution requires both collaboration and the analysis of thousands of annotated biospecimens. There are many of these projects in the United States, such as PACT and the GENIE program sponsored by AACR that now have data on more than 100,000 patients. A collaborative strategy will catalyze biomarker precision medicine and precision oncology by linking clinical retrospective and prospective cancer genomic and proteomic data with longitudinal clinical outcomes. Data aggregation will benefit patients through the validation of biomarkers; drug repositioning or repurposing; addition of new mutations to existing drug labels; and identification of new targets and new biomarkers enabling the development of better therapies for patients.

In summary, cancer is composed of a broad spectrum of biologically distinct subtypes with overlapping or unique molecular alterations. We will need to increasingly expand biomarker development in various populations, incorporate biomarker testing, as well as consider clinical, ethnic, and socioeconomic factors to optimize patients' lives. We are on this path.

Chapter 12
Overcoming Barriers for Latinos on Cancer Clinical Trials

Ruben A. Mesa and Amelie G. Ramirez

Increasing Complexity of Accrual in Clinical Trials for All Populations

The concept of clinical trials has expanded over the years from straightforward drug-based interventional studies to those that recognize the breadth of the human experience. We are now focusing on preventing cancer, expanding research into screening, primary prevention, active prevention, and behavioral modification in ways that would not have been done before. Still clearly concerned about treatment, we are also concerned about symptom control and how to deliver the care itself, as well as with issues of health economics and survivorship such as healthcare outcomes and post-therapy care. Now, with the complexity of clinical trials, testing whether interventions can make a difference relies on rigorous, well-conducted clinical trials to either support the case or, sometimes just as importantly, demonstrate that the intervention does not work.

In the era of individualized medicine, enrolling patients in clinical trials has become much more difficult because of narrowed eligibility criteria, such as the case where patients must have a particular mutation before they can be enrolled. Another issue is the requirement for randomization. The enthusiasm of patients to be randomized has clearly decreased. Availability of information on the Internet means that individuals learn and question more, and for some, the concept of not being able to select their therapy is very uncomfortable. Being in the placebo group is a frightening thought for most patients; if included, it typically has to be for a finite amount of time, with a fair amount of confidence that they will then be able to receive the

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therapy they seek. Another hurdle to recruitment is that there are now many nonexperimental treatment options, so the patient has to weigh the benefits of standard care against the inconvenience of entering a trial. Other barriers to recruitment are that patients may be wary of becoming a guinea pig for research or of taking experimental drugs they fear will have greater toxicity and adverse effects. Also, patients receive a river of information and misinformation daily from the Internet, television, and the lay press that may give them unrealistic expectations for miracle cancer cures.

There is also the issue of expense of participating in a clinical trial. There is the direct standard of care expense, but there are also expenses that are often not considered. For example, is the experimental drug going to be more expensive? Usually the answer is no, but it may be more expensive to be in a clinical trial in other ways. There may be more travel, more time away from work, and more standard of care expenses. A significant barrier may not be a new experimental therapy, but rather the use of standard of care therapies that are in the control arm and would have to be covered. There are clearly also barriers of third-party payers having significant concerns around trials. Some of that is protected through healthcare policy, but not completely.

There are additional barriers to recruiting racial and ethnic minorities from underserved populations. In 2013, Brown et al. conducted semi-structured audio interviews with 22 African American patients who refused to participate in clinical trials in order to gain insights into their perceptions of clinical trials and reasons for refusal [1]. Most participants refused because of fear of treatment-related burdens and fear of adverse effects. Some refused out of mistrust. Many patients and family members misunderstood the purpose and benefits of the clinical trial, and family members were mostly against participation. However, most patients indicated that they would participate if given access to a decision aid and the ability to discuss their concerns with a provider. In other interventions, these researchers found that with sufficient information, patients felt they could overcome some of these barriers. Other barriers they identified include additional patient burden; in addition to the burden of the disease itself, patients reported their reluctance to undergo more testing and more office visits. Lost time at work and trouble finding transportation were cited most often. Also, patients expressed the fear of participating in an "experiment." Frequently, there was a lack of understanding about the benefits of clinical trials; many patients did not understand that they would continue to treat their cancer and receive high-quality care throughout the clinical trial. Also, most patients were frightened about possible side effects from clinical trials, though, in some cases, the effects were the same as those associated with the standard of care.

Barriers That May Disproportionately Impact Latino Patient Enrollment

What are some barriers that may disproportionately affect Latino patient enrollment in clinical trials? In an effort to answer that question, scientists from the Institute for Health Promotion Research and the Mays Cancer Center at UT

Health San Antonio interviewed patients from south Texas who were receiving treatment at the cancer center. This study explored, from the patients' perspective, both promoting factors and barriers to participation in early phase clinical trials [2]. They found that more Latinos than non-Hispanic whites decline early phase clinical trials and were more likely to be concerned with symptom improvement. On the positive side, Latinos surveyed were more concerned that treatment would improve symptoms, decrease hospitalizations, and have the potential for better outcomes than standard of care. Barriers to participation included greater fear of uncertainty over experimental treatment efficacy and poor communication with their doctor and poor understanding of the purpose of the clinical trial. Exploring this further, Ramirez et al. examined if there was an association between the attitudes and practices of Latino physicians and clinical trial participation [3]. They found that Latino physicians were less connected to and saw less value in clinical trials. The authors identified this as an opportunity for education and engagement with physicians to better promote clinical trial recruitment among Latinos. Langford et al. examined eligibility, refusal rates, and clinical trial participation among patients at sites in the National Cancer Institute's Community Cancer Centers Program [4]. One question they asked was whether minorities have a lower rate of enrollment because they have more comorbidities, such as diabetes, obesity, and hypertension. They found that the odds of comorbidity were higher with older age, males, and non-Hispanic blacks, but not for Hispanics. They also found that consent readability was a factor for refusal across the board and that in this community center setting, there were no racial/ethnic differences in clinical trial enrollment.

One recent study examined underrepresentation of Hispanics in clinical trials from the perspective of clinical trial recruiters [5]. They conducted focus groups with professional recruiters and described how to adapt to potential participants' language competency and literacy levels. One issue that emerged is the consent form, the legal document designed to protect the institution but not necessarily to communicate clearly. Additionally, translating the form from English to Spanish does not necessarily enhance understanding; communicating the general concepts is what is needed. It is also important for recruiters to engage in culturally appropriate verbal and non-verbal communication; establish a sense of connection between recruiters and patients; accommodate socioeconomic concerns; adapt to contextual factors; and respond to potential participants' mistrust of medical research.

Are there differences between urban and rural residents in their willingness to participate in a clinical trial? The results of a telephone survey of South Carolina residents showed no significant differences between the two groups [6]. The researchers who performed the study found that distrust and fear of clinical trials were barriers in both groups. However, clinical trial participation is lower among the rural population, and they attribute this to perceive limited access to clinical trials and a greater lack of knowledge about clinical trials.

Strategies to Facilitate Clinical Trial Participation

How do we augment the enrollment of Latinos into cancer clinical trials? And why do we want to do so? The answer is that cancer clinical trials must reflect the population that we are studying, so that we can capture differences among ethnic groups and make inferences that are generalizable. We (Hispanics/Latinos) may be different in how we process drugs, the genetic profile of disease, or the risk factors we possess. For example, Hispanics/Latinos in the United States have a higher rate and worse outcomes of acute lymphoblastic leukemia than the general population. Why is this so? Do they have a worse molecular profile? Do they have worse cytogenetics? Are they more likely to develop neutropenic fever? If they develop neutropenic fever, are they more likely to take longer to go into the hospital? Do they have more port infections because they do not have family members who are able to assist them with their port? Really delving into these issues is the key to understanding.

An active area of research is determining how to improve accrual into clinical trials. Drs. Iruku and Kaklamani from UC Health Colorado Springs and UT Health San Antonio, respectively, are developing a predictive model of trial accrual. Based on an analysis of 297 trials carried out at the Mays Cancer Center in San Antonio (formerly the CTRC), they found that certain variables—the type of sponsor, author of the trial, and the type of intervention—were significantly associated with accrual. Trials that were observational, interventional, industry-sponsored, and authored by the local PI were more likely to meet accrual goals.

Experience has taught us that it is important for staff involved in clinical trials to be knowledgeable about the study and to have a strong stake in the trial. Having staff such as the nurses, cancer navigators, or clinical trial coordinators who understand the settings around the studies is incredibly important. Dr. Vanessa Sheppard reports a similar approach used at the Massey Cancer Center at Virginia Commonwealth University. Their strategy to improve trial accrual includes using dedicated resource specialists; clinical social workers help patients identify resources, including alternative transportation grants, childcare, or legal assistance, freeing the clinical research nurses to better focus on patient care and treatment. There is also a dedicated insurance authorization coordinator who explains insurance policies to determine coverage and financial obligations. Further, Massey offers communications training not only to physicians but also to nurses. Our experience has been that appropriate communications are important even in terms of the discussion between the infusion nurses or the pharmacy and the patients as well. How one phrases something might have a very significant impact on patients. Finally, another strategy that Massey uses to improve accrual is to build awareness of clinical trials through marketing; it actively promotes its trials in clinics, at community events and within the larger health system.

Enhancing accrual and addressing underrepresentation in clinical trials begin with the process of matching patients with appropriate trials. Our experience is that we are much more likely to have a successful discussion around trials if patients have the preconceived notion that a clinical trial is something positive and that the

physician is someone who might be able to connect them with a study that helps. Determining eligibility is a necessary step to minimize bias in the results from the clinical trial, but it can be a tedious, slow process. Penberthy et al. from the Massey Cancer Center at Virginia Commonwealth University have attempted to automate the process by using matching software; when patients register they can be potentially matched up with a clinical trial [7]. Not only does the automated process reduce the time for eligibility screening, but it also assures patients that there might be a clinical trial for them. The earlier in the process patients become aware that clinical trials are available and might be beneficial, the more likely they are to participate.

At the Mays Cancer Center, we have the mandate to decrease the burden of cancer in our catchment area, which is from San Antonio down to the border. It is a sizable area that is 69% Hispanic, 24% non-Hispanic white, 4% African-American, and 3% other. Our collective efforts reflect this largely Hispanic population, which includes developing a minority recruitment plan for cancer clinical trials. How did we do this? Our first step was to identify the potential resources. A Minority Clinical Trial Accrual Committee was established to try to reduce barriers for accrual and to implement strategies to enhance minority recruitment. A Coordinator of Minority Programs was hired to oversee these activities, which included developing a minority accrual plan required for all clinical trials. As part of this effort, Trevino et al. developed a toolbox to help investigators create a minority recruitment plan and meet those goals [8]. Barriers to minority enrollment were identified through research, focus groups, interviews, and physician outreach. Strategies and materials were then developed including virtual connections with physicians in remote areas in South Texas; Spanish translations of signs, brochures, and consent forms; and expanded media outreach with Spanish-language television (Univision), a Spanish-language daily newspaper in San Antonio (La Prensa), and others. The minority accrual plan (MAP) toolbox thus includes activities that build awareness and improve health literacy. Since its inception in 2013, this group has helped at least 50 clinical trials per year with the goal of improving enrollment in cancer clinical trials. Prior to its implementation, the enrollment of Hispanics into our interventional studies was 46%; now it is 56%. Accrual of Hispanics into interventional non-treatment studies has fluctuated over the years, but in 2017 it was 59%. If we look at non-intervention, observational ancillary-correlative studies, the accrual numbers are lower (37% in 2017). Even within our own Latino communities, when therapy is taken out of the equation, interest in participation wanes. We must communicate better how important the biospecimen study is to inform future research, even though it does not center on immediate therapy.

A research team from the Institute for Health Promotion Research and the Mays Cancer Center at UT Health San Antonio conducted a pilot study to test whether CHOICES, a bilingual multi-component intervention, would empower Latina patients with breast cancer to make informed decisions about clinical trials [9]. The CHOICES intervention included an educational interactive video, a low-literacy booklet, and care coordination by a patient navigator. This randomized controlled study compared the CHOICES intervention group with a control group that received

general clinical trial information. They found that the intervention was more effective than the control in increasing patients' perception of understanding clinical trials and their consideration of a clinical trial as a treatment option.

Next Steps

In conclusion, key opportunities for increasing accrual of Hispanics/Latinos in clinical trials include the education of registering physicians to better promote enrollment in clinical trials. It also includes building general awareness among Hispanic/Latino populations of the role of clinical trials in improving cancer care. The more that it becomes the collective impression, the more successful accrual will be. For example, only a minority of adult patients with cancer goes into clinical trials, but there is a very different experience that exists with pediatric patients. In the pediatric world, it has become by culture, from physicians, staff, and parents that clinical trials are the standard of care for their disease. Almost all patients go into clinical trials; they have been incredibly successful, making great advances in pediatric cancer research. If we can accomplish a similar culture among Hispanic/Latino patients that clinical trials are considered to be a good thing, accrual should improve. Another opportunity to increase accrual is enhancing care navigation to better support the role of cancer clinical trials in treatment planning, including matching up the right patient with the right study. Clearly the issue of language and culture cannot be overstated; there must be language- and culture-appropriate materials, education, and clinical trial coordination. Finally, a key opportunity exists in the sharing of lessons learned between centers and investigators committed to this mission.

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Part VI
Cancer in the Era of Precision Medicine

Chapter 13
Breast Cancer Precision Medicine in Hispanics/Latinas: Focus on Luminal B Tumors

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Introduction

Breast cancer risk assessment and treatment are increasingly guided by genetic and transcriptomic information. In addition to the few well-known genes associated with high risk of breast cancer that are routinely tested in the clinic [1], the recent description of polygenic risk scores [2, 3] has further complicated the picture of genetic risk evaluation for breast cancer. Gene expression-based tests such as Oncotype DX [4] and MammaPrint/BluePrint [5] have demonstrated clinical value in predicting the risk of recurrence for early stage breast cancers. Among these, PAM50 [6] and BluePrint [5] can be used to assign breast cancers to one of the most common molecular subtypes.

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The first molecular classification of breast cancer based on gene expression profiling was proposed in 2000 by Perou et al. [7]. This classification has been subsequently refined, and the most commonly accepted subtypes today include luminal A and B, both estrogen receptor alpha (ER)-positive, as well as Her2-enriched, basal-like and "non-basal triple-negative" ("normal-like" in some classifications) [8, 9]. Luminal A tumors are the most common among non-Hispanic Whites, and they typically carry a better prognosis than luminal B or non-luminal tumors, particularly when diagnosed and treated early. "Triple-negative" tumors, immunohistochemically "negative" by standardized pathological criteria for ER and progesterone receptor (PR) and not carrying Her2 amplification, are often conflated with the basal-like molecular subtype. However, not all basal-like tumors are triple-negative and not all triple-negative tumors are basal-like. Indeed, triple-negative tumors may include as many as four molecular subtypes (basal-like 1 and 2, mesenchymal, and androgen receptor luminal-like) with different biology and prognosis [10]. Significant molecular heterogeneity exists even within the recognized subgroups, with a variety of low-frequency driver mutations [11]. Higher-dimension classifications including mutations, copy number variations, and gene expression profiling are being developed [12].

Despite nearly 20 years of genomic and transcriptomic studies of breast cancer, our understanding of the molecular portraits of breast cancer remains based on tumors overwhelmingly derived from European or European-American (non-Hispanic White) patients. The representation of patients of non-European ethnicity in public molecular datasets remains limited. As of December 2018, only 37 out of 3650 cases of breast cancer whose molecular portraits are available through The Cancer Genome Atlas (TCGA) portal are from women who declared a Hispanic/Latina ethnicity. Hence, it is fair to assume that we currently do not know to what extent the information gathered to date on the genetics and transcriptomics of breast cancer applies to Hispanic/Latina patients.

Hispanic/Latinos share a broad linguistic identity, but they are culturally diverse and genetically highly heterogeneous, with ancestry mixtures that vary among and within different countries. This makes the study of gene–environment and gene–gene interactions particularly challenging. Most of the populations commonly referred to as ethnically "Hispanic" are the result of admixture of three ancestral populations: European, Indigenous American, and African. Yet, there is considerable variability in the proportion of each ancestral genetic background within and across those populations [13]. A recent seminal paper by Conomos et al. [14] explored the genetic diversity of a large cohort (12,803 individuals genotyped using a high-density SNP chip) from four US metropolitan areas, the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). Using principal component analysis (PCA), this group identified substantial genetic differentiation within and among six self-identified background groups (Cuban, Dominican, Puerto Rican, Mexican, and Central and South American). These authors used a multidimensional clustering method to define "genetic-analysis groups" that retain many properties of self-identified background groups while achieving substantially greater within-group genetic homogeneity. Remarkably, these "genetic-analysis groups" accounted for

significant trait variation in 8 of 22 clinically measurable phenotypic traits. These authors argue that "genetic analysis groups" are a more useful covariate for genetic association studies than self-identified ethnic background groups. This underlying genetic complexity highlights the inadequacy of using self-reported "Hispanic" ethnicity for genetic and genomic studies.

Hispanics/Latinas and Breast Cancer: A Complex Relationship

Age-adjusted breast cancer incidence in the United States is approximately 25% lower in Hispanic/Latina women than among non-Hispanic Whites [15]. The reasons for this "Hispanic Paradox" are most likely multifactorial and may include lifestyle (e.g., number and timing of pregnancies, diet), socioeconomic factors, and genetic factors. It is well established that high Indigenous American (IA) ancestry correlates with reduced risk of breast cancer, and at least one protective variant only found in high IA ancestry individuals has been identified [16]. That said, breast cancer risk varies among Hispanics/Latinas of different geographic origins and between US-born and foreign-born Hispanics/Latinas. This lower risk does not necessarily translate into better outcomes for patients who do develop breast cancer [17]. In fact, California Hispanics/Latinas with over 50% IA ancestry have a risk of breast cancer mortality that is twice as high as that of California Hispanics/Latinas with less than 50% IA ancestry. This may be because of socioeconomic factors, access to health care, late stage at diagnosis, and hitherto unknown biological factors. To our knowledge, the "genetic analysis groups" proposed by Conomos et al. [14] have not yet been studied as covariates for breast cancer risk. The interpretation of epidemiological studies is complicated by the fact that in most studies not only are Hispanics/Latinas considered a single group but "breast cancer" is treated as a single disease. Given the remarkable molecular heterogeneity of breast cancer, it is possible that part of the increased mortality risk observed among Hispanics/Latinas, despite their overall lower risk of disease, may be due to differences in the prevalence of specific breast cancer subtypes or due to molecular differences within the subtypes themselves. For instance, the protective variant identified in individuals with high IA ancestry is near the *ESR1* gene, which encodes the estrogen receptor α [16]. We do not know whether it protects against all breast cancer molecular subtypes, including ER-negative ones. In a large molecular epidemiology study of the LACE/pathways combined cohort, Sweeney et al. [18] examined the distribution of breast cancer subtypes as determined by the *PAM50* gene expression test among racial and ethnic groups. This study confirmed that Basal-like tumors are far more common among African-Americans (AA) than among other ethnicities. Additionally, Hispanic/Latina patients had a lower incidence of luminal A tumors compared to non-Hispanic Whites (44.2% vs. 55.2%) and a correspondingly higher incidence of luminal B tumors (24% vs. 20.9%). Her2-enriched and Basal-like tumors were also slightly more common among Hispanic/Latina patients than among non-Hispanic

Whites. These differences did not reach statistical significance, given the relatively small number of Hispanics/Latinas in the combined cohort. Hispanics/Latinas in this study were not stratified by national origin, IA ancestry, or "genetic analysis group." If these findings are confirmed, it is possible that despite their overall lower incidence of breast cancer, Hispanic/Latina patients may suffer from higher-risk, non-luminal A breast cancer subtypes than non-Hispanic Whites.

Luminal B Breast Cancer in Colombians

Among luminal/ERα-positive tumors, luminal B cancers are a distinct biological entity compared to luminal A tumors. These tumors are clinically more aggressive, with worse prognosis than luminal A tumors, similar to the basal-like and Her2-enriched tumors. They tend to have lower expression of nuclear hormone receptors, higher expression of Her2/Neu and proliferation markers such as Ki67, and a lower likelihood of responding to endocrine therapy with aromatase inhibitors, selective estrogen receptor modulators (SERM) or selective estrogen receptor disruptors (SERD) [19]. Luminal B tumors have distinctive molecular characteristics from all other subtypes. In the METABRIC multiparameter molecular classification of breast cancers [12], luminal B tumors fall within four clusters (IntClusts 1, 2, 6, and 9). Among recurrent mutations in these tumors are loss of PPP2R2A (protein phosphatase 2 subunit), TP53 mutations, and a hypermethylated profile. Conversely, PIK3CA mutations are less common in this subtype than in luminal A tumors [19]. Moreover, luminal B tumors have higher risk of de novo resistance to endocrine therapies [6, 11]. At the transcriptomic level, they are characterized by increased expression of cell proliferation genes or cell cycle regulators such as MKI67 and AURKA [20]. Luminal B tumors are usually characterized by high recurrence scores based on the Oncotype DX gene expression signature and are more likely to benefit from cytotoxic chemotherapy, reaching higher percentages of pathologic complete response (pCR) compared to luminal A tumors [19]. Interestingly, in a study of 219 women with early stage luminal breast cancers who received an Oncotype DX test, Hispanic/Latina patients had a significantly higher Proliferation Axis score, driven by higher expression of CCNB1 (cyclin B1) and AURKA (Aurora Kinase A) [21]. These authors suggest that biological differences between luminal tumors in Hispanic/Latinas and non-Hispanic Whites may contribute to the higher mortality observed among Hispanics/Latinas. Limitations of this study included its relatively small size, which did not allow stratification of Hispanics/Latinas by ancestry, geographic origin or "genetic analysis group," and the limited number of informative genes in the Oncotype DX test. Studies using larger panels, such as the 150-gene MammaPrint/BluePrint combined test, and larger, well-characterized Hispanic/Latina populations would be highly informative.

To begin to address this knowledge gap, the Zabaleta group studied a cohort of 301 Colombian breast cancer patients diagnosed and treated at the same institution, the National Cancer Institute in Bogota [22]. Using immunohistochemical markers

and the 2013 St. Gallen consensus criteria for surrogate subtype assignment [23], Serrano-Gomez et al. found a higher prevalence of luminal B tumors than luminal A (40.86% vs. 22.59% or 37.21%, vs. 26.25%, using 14% and 20% cutoff values for Ki67, respectively). This result was confirmed using the 2011 St. Gallen criteria. Interestingly, when Ki67 was excluded from the analysis and subtype assignment was based on ER, PR, and Ki67 alone, the prevalence of luminal B tumors decreased dramatically to 15.95% versus 52.49% luminal A, a subtype distribution more typical of US-based non-Hispanic Whites. The difference in subtype breakdown among different immunohistochemical criteria may hold biological clues. The St. Gallen consensus criteria for surrogate subtype assignment include Ki67, a proliferation marker, in addition to ER, PR, and Her2/Neu. Hence, luminal tumors in Colombian patients appeared to be characterized by higher proliferative activity, consistent with the Oncotype DX findings reported by Kalinsky et al. [21]. The tumors classified as luminal B based on St. Gallen 2013 or 2011 tended to be of higher histological grade, larger size, and higher stage at diagnosis, similar to molecularly confirmed luminal B tumors in US-based patients (Table 13.1). No significant association was found in this study between genetic ancestries established using 80 Ancestry Informative Markers (AIMs) and St. Gallen subtype distribution. Similar results were obtained by Gomez et al. in an independent study of a Colombian cohort [24].

Following up on these intriguing observations, the same group performed whole-transcriptome RNASeq on 21 immunohistochemically defined luminal A and 21 luminal B tumors from the same 301-patient cohort. Serrano-Gomez et al. [25] found 67 differentially expressed genes ($p < 0.05$) from which 39 were upregulated and 28 downregulated in the luminal B subtype (Fig. 13.1). Unsupervised hierarchical clustering showed that using these genes, luminal B tumors clustered together and separated from luminal A tumors. Pathway analysis showed that top upregulated genes participate in biological processes such as mitosis and cell cycle regulation (CDK1, CDC6, CCNB2, BUB1, CENPF, ANLN, CENPE, CCNA2, ASPM, MKI67) and downregulated genes mostly encode phosphoproteins (KCND3, RALBP1, RCAN3, ABCA3, RBBP8, PAIP2B, STARD13, ELOVL5, HIPK2, NTRK2, KDM4B, BAI2, FGD3). Another upregulated gene in luminal B tumors was CYP19A1. This gene encodes aromatase, the enzyme that catalyzes the rate-limiting step in estrogen biosynthesis, aromatization of androstenedione and testosterone to estrone and estradiol, respectively. Aromatase is a major therapeutic target in luminal tumors. This result may suggest that these luminal B tumors can produce estradiol endogenously. Whether the CYP19A1 mRNA derived from tumor cells or tumor-associated adipocytes is unclear. Another gene overexpressed in luminal B compared to luminal A tumors in this study is TOP2A, the gene encoding DNA topoisomerase IIA. Sparano et al. [26] suggested that in breast cancer patients with ER-positive, Her2-normal (hence, luminal) tumors, high levels of TOP2A may be associated with resistance to anthracycline-based chemotherapy. Higher expression of TOP2A correlated with poor tumor grade and high recurrence score based on the Oncotype DX signature. Romero et al. [27] also found higher expression of TOP2A in luminal B, HER2-enriched and basal-like tumors when compared to Luminal A. Consistent with immunohistochemical results, several proliferation-associated

Table 13.1 Clinical and pathological characteristics of breast cancer patients from Colombian population according to breast cancer subtype

	Luminal A ($n = 72$)		Luminal B ($n = 143$)		HER2 ($n = 24$)		Basal ($n = 26$)		Non-basal triple negative ($n = 28$)		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*P*
Mean age	55.6		59.3		57		51.6		48.5		0.000276
Age at diagnosis											
20–40	3	4.2	5	3.5	1	4.2	4	15.4	4	14.3	
40–55	36	50.0	47	32.9	9	37.5	11	42.3	16	57.1	
>55	33	45.8	91	63.6	14	58.3	11	42.3	8	28.6	
Bloom-Richardson grade											1.56E−08
1/3	8	11.1	8	5.6	0	0.0	0	0.0	0	0.0	
2/3	50	69.4	83	58.0	6	25.0	6	23.1	7	25.0	
3/3	6	8.3	40	28.0	11	45.8	15	57.7	17	60.7	
Unknown	8	11.1	12	8.4	7	29.2	5	19.2	4	14.3	
Histological features											2.41E−07
Well differentiated	5	6.9	8	5.6	0	0.0	0	0.0	0	0.0	
Moderately differentiated	30	41.7	60	42.0	5	20.8	5	19.2	6	21.4	
Poorly differentiated	2	2.8	21	14.7	11	45.8	11	42.3	14	50.0	
Unknown	35	48.6	54	37.8	8	33.3	10	38.5	8	28.6	
Unknown	0	0.0	5	3.5	4	16.7	3	11.5	4	14.3	
Unknown	6	8.3	17	11.9	4	16.7	6	23.1	5	17.9	
Recurrence											0.00026
Local	0	0.0	0	0.0	0	0.0	1	3.8	0	0.0	
Local and systemic	2	2.8	2	1.4	0	37.5	4	15.4	1	3.6	
Regional	0	0.0	1	0.7	2	16.7	0	0.0	1	3.6	
Regional and systemic	0	0.0	0	0.0	0	34.8	0	0.0	1	3.6	
Systemic	4	5.6	15	10.5	3	43.1	4	15.4	2	7.1	
No recurrences	62	86.1	110	76.9	12	51.5	14	53.8	19	67.9	
Unknown	4	5.6	15	10.5	7	59.8	3	11.5	4	14.3	

Statistically significant variables are highlighted in bold. Modified from ref. [22]

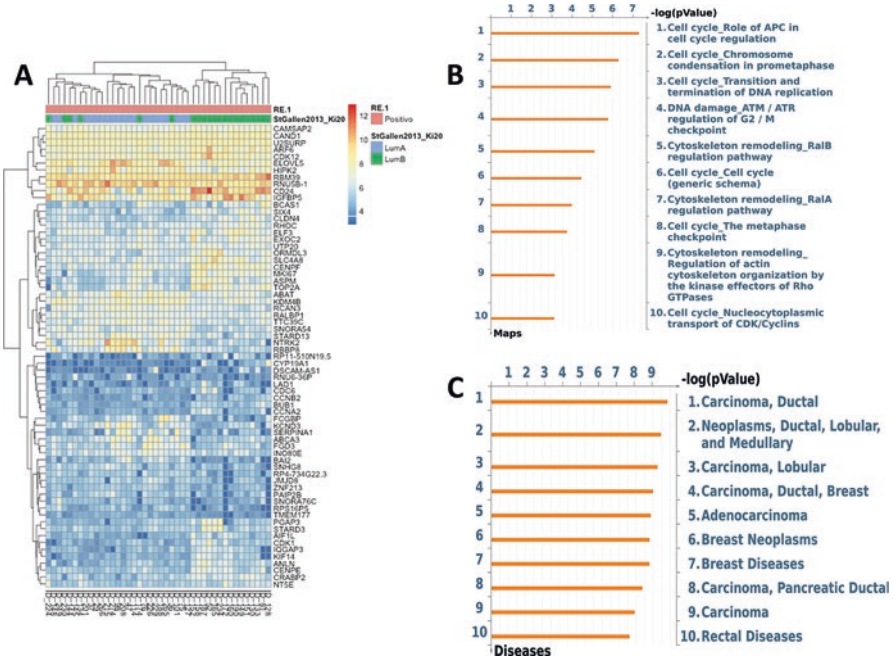

Fig. 13.1 Gene expression profile of 42 luminal breast cancer samples. (**a**) Unsupervised hierarchical clustering with 67 differentially expressed genes between IHC-defined luminal B and luminal A tumors. (**b**) Most relevant signaling pathways associated with 67 differentially expressed genes in luminal B tumors from Colombian women. (**c**) Diseases *associated* with differentially expressed genes in luminal B. Reproduced from Ref. [25]

genes, including CDK1, BUB1, CENPF, and MKI67 (the gene encoding Ki67) were overexpressed in luminal B versus luminal A tumors in this Colombian cohort. Taken together, these results support the hypothesis that, at least in this population of Hispanic/Latina patients, proliferative activity may be higher in luminal tumors compared to similar tumors occurring in non-Hispanic White patients.

When gene expression was correlated with ancestry, these authors identified five genes differentially expressed between luminal B and luminal A tumors that are potentially modulated by genetic ancestry: ERBB2 (log2FC = 2.367, padj < 0.01), GRB7 (log2FC = 2.327, padj < 0.01), GSDMB (log2FC = 1.723, padj < 0.01), MIEN1 (log2FC = 2.195, padj < 0.01), and ONECUT2 (log2FC = 2.204, padj < 0.01). These results were confirmed by RT-PCR. In the replication set, the authors found a statistically significant association between ERBB2 expression with IA ancestry ($p = 0.02$, $B = 3.11$) [25]. Again, these statistical correlations may reveal biological clues. ERBB2 (the gene encoding Her2/Neu, a clinically informative and therapeutically targetable gene), GRB7 (the gene encoding a molecular adaptor in the Her2/Neu pathway), and MIEN1 (a putative oncogene) are physically contiguous, occupying a region of approximately 60,000 bp on Chromosome 17q12. These genes are usually co-amplified in Her2-enriched tumors and are located near a common

enhancer. There are multiple possible explanations for an association of IA ancestry with high expression of these genes. Factors associated with IA ancestry may control the epigenetic regulation of the chromatin region encompassing these genes or the expression of transcription factors or non-coding RNAs regulating the transcription of this chromosomal region. Alternatively, the relatively high expression of Chromosome 17q12 transcripts may be due to the subclonal structure of the tumors; that is, to the presence of clonal populations within tumors containing copy number variants (CNV) in this chromosomal region. The appearance of these clones may be indirectly promoted by factors linked to IA ancestry. Ongoing investigations are exploring these potential mechanisms in other Hispanic/Latina populations.

Discussion

Our understanding of the "Hispanic Paradox" in breast cancer remains woefully inadequate. Lower risk of breast cancer, likely due to a combination of ancestry, socioeconomic, and lifestyle factors, contrasts with increased mortality, most likely due to a similarly multifactorial etiology. Hints emerging from the relatively few studies that have investigated the molecular portraits of breast cancer in Hispanic/Latinas suggest that the most common group of breast cancers, the luminal tumors, may be biologically different in Hispanic/Latinas than in other ethnic groups. Results from Oncotype-DX-based studies [21] and immunohistochemistry-based studies [22] suggest that genes associated with proliferation may be expressed at higher levels in breast cancers from Hispanics/Latinas. This putative difference does not appear to be associated with genetic ancestry and may be related to lifestyle, socioeconomic, hormonal, or dietary factors. Higher expression of Ki67 accounts for the higher prevalence of luminal B tumors among Colombian patients as defined by St. Gallen 2013 consensus immunohistochemical criteria. This is consistent with differences in gene expression profiling, which revealed differential expression of multiple genes linked to the cell cycle, including MKI67. The higher expression of aromatase in luminal B tumors suggests a possible role for endogenous estrogen in driving proliferation.

Conversely, the IA ancestry-associated expression of five genes, notably including ERBB2 and two of its genomic neighbors, may suggest that IA ancestry is associated with an ERBB2-driven phenotype in luminal tumors. ERBB2-encoded Her2/Neu signaling is among the several well-characterized mechanisms of endocrine resistance [28]. Whether these tumors might benefit from Her2/Neu-targeted treatment with trastuzumab, lapatinib, or other agents remains to be determined.

The studies we describe herein have significant limitations. The number of tumors molecularly profiled is still relatively small, as is the number of subjects studied. These findings must be replicated in larger population of Hispanics/Latinas of different geographic origin and ideally, in different "genetic analysis groups." Larger numbers of tumors need to be molecularly profiled, and the gene sets examined by clinically used gene expression-based molecular panels need to be examined in detail.

The possibility that luminal tumors in Hispanic/Latinas may have distinctive biology, due to non-genetic and/or ancestry-linked factors deserves further investigation. The interpretation of gene expression-based molecular tests, and thus the treatment choices made on the basis of gene expression results may have to take Hispanic/Latina ethnicity and/or genetic ancestry into consideration.

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Chapter 14
Is Precision Medicine Widening Cancer Care Disparities in Latino Populations? The Rutgers Cancer Institute of New Jersey Experience

Lorna Rodriguez-Rodriguez

Introduction

In 2016, people of Latino ancestry comprised 17.8% (57,398,719) of the total estimated US population (323,127,515) [1]. The states with the highest percentages of people of Latino ancestry include New Mexico, Texas, California, Arizona, and Nevada, with New Jersey ranking eighth. However, these data reflect an ethnicity that is far from homogenous. The term "Latino" encompasses a wide range of people from a large geographical area. Varying elements, such as culture, environment, and genetic makeup, foster diversity among people of Latino ancestry.

Precision medicine focuses on treating cancer based on the molecular alterations and dysfunctions within a tumor, not solely on the tumor type itself. It provides a more streamlined approach to cancer care, allowing an individual patient's tumor to be specifically targeted with available treatments, some of which may be FDA-approved for other diseases or tumors.

There is a great potential to treat cancer patients using precision medicine; however, research shows that its implementation in the Latino population is limited. For example, Latino representation in The Cancer Genome Atlas is <3%. In a 2016 analysis of genome-wide association studies, Popejoy and Fullerton showed that while nearly 20% of participants were of non-European descent, less than 1% were Latino [2]. While the data show that physicians have been less likely to offer genomic testing (including germline BRCA1/2 testing for breast cancer) to Latino versus white non-Latino women, there is evidence that Latino patients have positive

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attitudes and the willingness to participate in testing [3, 4]. The diversity among Latinos lends itself to the application of this targeted method of cancer care, but concern exists over whether a gap in the practice of precision medicine exists in this population.

Background

Latino Populations in the United States

Based on data from the US Census Bureau, 2016 American Community Survey (1-Year Estimates), the top 10 states with the highest percentages of people of Latino ancestry included New Mexico (48.5%), Texas (39.1%), California (38.9%), Arizona (30.9%), Nevada (28.5%), Florida (24.9%), Colorado (21.3%), New Jersey (20.0%), New York (19.0%), and Illinois (17.0%) [5]. Among these states, the most prevalent subpopulations of ethnicities varied from Mexican in New Mexico, Texas, California, Arizona, Nevada, Colorado, and Illinois to Cuban in Florida and to Puerto Rican in New Jersey and New York [5].

Latino Populations in New Jersey

Based on data from the US Census Bureau, 2016 American Community Survey (1-Year Estimates), ancestries within the Latino populations in New Jersey were 26.3% Puerto Rican, followed by Dominican (15.2%), Mexican (13.7%), Colombian (7.0%), Ecuadorian (6.7%), Peruvian (5.5%), Cuban (4.8%), and Salvadoran (4.6%) [6]. New Jersey is home to a diverse array of people of Latino ancestry, providing a unique opportunity for the Rutgers Cancer Institute of New Jersey (RCINJ), an NCI-designated comprehensive cancer center, to understand precision medicine and potential cancer-care disparities within the Latino population.

Targeted Therapies as Standard of Care

With a growing focus on cancer therapies that target dysregulated proteins along signaling pathways, guidelines for standard of care treatments for a wide array of cancer types have begun incorporating targeted agents into their clinical recommendations. For example, bevacizumab, a VEGF inhibitor has been recommended in National Comprehensive Cancer Network (NCCN) guidelines for some brain and CNS cancers, such as anaplastic gliomas and glioblastomas [7]. The NCCN guidelines have also incorporated targeted agents into their clinical guidelines for such cancer types as ovarian, thyroid, breast, and colorectal cancers [8–11].

Cancer Incidence and Mortality Rates Among Patients of Latino Ancestry

Among brain and CNS cancers, ovarian cancer, thyroid cancer, breast cancer, and colorectal cancer, data on 5-year (2010–2014), age-adjusted incidence rates (cases per 100,000) and death rates (deaths per 100,000) from the US Department of Health and Human Services on State Cancer Profiles show the following [12].

Brain and CNS Cancers The highest incidence rates of brain and CNS cancers among Latinos are reported in Florida (6.1), Connecticut (6.1), Rhode Island (6.0), and New Jersey (6.0). Nonetheless, the incidence rates of cancers of the brain and CNS in each of these states are higher in non-Latino whites who also suffer higher mortality rates for brain and CNS cancers than Latinos in these states.

Breast Cancer The highest incidence rates of breast cancer among Latinos are reported in Hawaii (151.6), Montana (134.3), Connecticut (127.5), and Oklahoma and Colorado (tied at 104.4). Of these five states, incidence rates of this cancer type in non-Latino whites are higher in Connecticut, Oklahoma, and Colorado. In each of the aforementioned states, non-Latino whites have higher mortality rates for breast cancer than Latinos.

Ovarian Cancer The highest incidence rates of ovarian cancer among Latinos are reported in Oklahoma (15.7), Colorado (12), Wisconsin (11.2), and Virginia and New Mexico (tied at 11.1). Of these five states, incidence rates of this cancer type in non-Latino whites are higher in Wisconsin, Virginia, and New Mexico. This population also has higher mortality rates for ovarian cancer than Latinos in each of the aforementioned states.

Colorectal Cancer The highest incidence rates of colorectal cancer among Latinos are reported in Hawaii (43.3), Connecticut (42.9), Montana (42), and New Jersey (38.9). Incidence rates of this cancer type in non-Latino whites are lower in each of these four states. In all of the aforementioned states except Hawaii, non-Latino whites have higher mortality rates for colorectal cancer than Latinos.

Thyroid Cancer The highest incidence rates of thyroid cancer among Latinos are reported in Connecticut (21.2), Utah (19.6), New Hampshire (18.7), and Montana (18.3). Of these four states, incidence rates of this cancer type in non-Latino whites are all lower. In each of the four aforementioned states, the mortality rates are higher among non-Latino whites.

Our Experience

At the Rutgers Cancer Institute of New Jersey (RCINJ), we designed a protocol that longitudinally follows patients with rare or refractory tumors who underwent tumor genomic profiling (NCT02688517). Patients provided their informed consent to

participate in this study, which was approved by the Rutgers University New Brunswick Health Sciences IRB (Pro2012002075).

Using precision medicine at RCINJ, we analyzed readily available data from selected tumor groups to determine if disparities exist between Latino patients and non-Latino whites. Initial analysis of 93 patients shows that 43 patients were of Latino ancestry, while 50 patients were non-Latino white (Table 14.1). Cancer groups included breast, central nervous system (CNS), colorectal, gastrointestinal, genitourinary, gynecologic, thyroid, pulmonary, skin, unknown primary, and other cancers. The median ages for Latino patients and non-Latino white patients were 50 and 60.5 years, respectively.

Next-Generation Sequencing (NGS)

Formalin-fixed, paraffin-embedded tumor specimens were sent to a Clinical Laboratory Improvement Amendments (CLIA)-approved, laboratory for next-generation sequencing. Sequencing included the entire coding regions of cancer-related genes as well as introns of genes involved in fusions.

Results

Thirty-three percent of Latino ancestry patients and 30% of non-Latino white patients received targeted therapy. Interestingly, patients of Latino ancestry who received targeted therapy survived an average of 10 months longer than their white counterparts. In addition, Latino ancestry patients who did not receive targeted therapy survived an average of 4 months longer than their non-Latino white counterparts. Paradoxically, the Latino ancestry patients had more advanced disease (higher stage) at the time of diagnosis.

Discussion

Precision medicine in cancer care provides physicians with the ability to offer targeted treatment options to patients based on the molecular makeup of the individuals' tumor. Given disparities in cancer healthcare in Latino populations and the cost and effort involved in genomic testing, we hypothesized that precision medicine has the potential to increase disparities in care for Latino ancestry patients and may hinder the progress of precision-based medicine in this population. In this study, we found that, at our institution, there may not be a disparity between Latino ancestry patients and non-Latino white patients with regard to the implementation of precision medicine in their clinical care. A limitation to our study is the small sample

Table 14.1 Demographics

	Latinos	Non-Latino whites
Total number of patients, *n*	43	50
Age (years)		
Median	50	60.5
Mean	43	60
Range	(5–80)	(16–79)
Gender		
Female	34	29
Male	9	17
Cancer groups	*Histologies*	
Breast	11	9
Stage II–IV cases	6	6
Mean age	51	57
CNS	11	6
Stage II–IV—WHO grade case	8	3
Mean age	35	49
Colorectal	2	3
Stage III cases	2	–
Stage IV cases	–	2
Mean age	64	46
CUP	[a]	2
Stage IV cases	–	1
Mean age	–	48
Genitourinary	[a]	9
Stage I–IV cases	–	5
Mean age	–	66
GI	4	[a]
Stage IV cases	2	–
Mean age	56	–
GYN	4	10
Stage I–IV cases	–	10
Stage II–IV cases	4	–
Mean age	50	63
Thyroid	5	[a]
Stage II–IV cases	5	–
Mean age	51	–
Other	6	5
Stage I cases	–	1
Stage III–IV cases	3	–
Mean age	42	69
Pulmonary	[a]	3
Stage I–III cases	–	2
Mean age	–	65
Skin	[a]	3
Stage II cases	–	3
Mean age	–	65

[a]Low number of patients, counted in other

size. Having a larger sample size may affect the outcome of our analysis, and an ongoing analysis will contribute to our final conclusions.

The Cancer Genome Atlas (TCGA) provides a large repository for data on genomic characteristics of tumors, which have been de-identified but made publicly available [13, 14]. Hispanics were recently shown to represent <3% (N = 5729, n = 149) of the patients included in the TCGA database [15]. This finding reflects the underrepresentation of Latinos on larger and broader genome studies.

Targeted treatments are being recommended as standard of care for many cancer types. For example, the guidelines of the National Comprehensive Cancer Network (NCCN) recommend the immune checkpoint inhibitors, nivolumab or pembrolizumab, for colon and rectal cancers that are mismatch repair deficient or have microsatellite instability, and agents targeting receptor tyrosine kinases (e.g., vandetanib, cabozantinib, lenvatinib, and sorafenib) in some thyroid cancer types [8, 9]. Given the higher incidence rates of these two cancers in Latinos, it is crucial to ensure that this population has access to tumor molecular analysis.

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Ethics Statement: The patients provided informed consent to participate in the Rutgers CINJ genomic tumor profiling protocol (NCT02688517), which was approved by the Institutional Review Board (IRB) of Rutgers University New Brunswick Health Sciences (Pro2012002075).

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Part VII
Cancer Outcomes and Survivorship in Latinos

Chapter 15
A Vision for Improving Quality of Life Among Spanish-Speaking Latina Breast Cancer Survivors

Anna María Nápoles

Introduction

Latinas are at higher risk than non-Latino white women of psychosocial and physical sequelae of breast cancer. Latinas report higher rates of anxiety, depression, fear of recurrence, fatigue, and pain; they also have worse health-related quality of life (HrQoL) and shorter disease-free survival [1–3]. Spanish-speaking Latina immigrant breast cancer survivors, in particular, experience worse quality of life and emotional well-being than their English-speaking and White counterparts [2]. Multiple synergistic factors place many Latinas with breast cancer at increased risk of chronic elevated stress; these factors include limited English proficiency (LEP), 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 [4–6]. Compared to White, African American, and English-speaking Latinas, Spanish-speaking Latinas are significantly more likely to report difficulty understanding treatment information and to need help with written materials they receive from their treatment team [5].

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State of the Science on Behavioral Interventions to Improve Health-Related Quality of Life Among Latino Cancer Survivors

Among White women with breast cancer, stress management interventions improve health-related quality-of-life (HrQoL), reduce stress and anxiety [7], and may reduce chances of recurrence by decreasing inflammation and improving immune responses [7, 8]. However, a limited number of studies of the effectiveness of stress management programs have included Latinas with breast cancer and rural populations. Furthermore, stress management programs for cancer patients are primarily delivered by mental health professionals in large cancer centers. Widespread adoption of stress management programs could be enhanced if they were translated for more vulnerable, ethnically diverse patient groups and for delivery in community settings by trained peers. Similarly, physical activity interventions have resulted in improved mood among women with breast cancer [9].

A comprehensive systematic review identified 15 intervention studies designed to improve HrQoL among Latino cancer survivors; most of these studies were pilot or feasibility studies, and nine were randomized controlled trials (RCTs) [3]. Half of these studies involved mixed ethnic groups and, thus, were not specifically tailored for Latinos, and very few engaged community partners. Interventions were largely psychosocial (6), followed by educational (4), exercise/dietary (4), and navigational (1). The authors concluded that the science of interventions among Latino cancer survivors is nascent and in great need of further development. Although this review found that interventions are feasible and acceptable among Latinos and that early results are promising, there is insufficient evidence on which to base further translation and dissemination efforts to reduce psychosocial health disparities and improve HrQoL among Latinas with breast cancer.

The Nuevo Amanecer Program and Translation Methods

Rationale

Our research program focuses on developing community-based interventions to equip Spanish-speaking Latina breast cancer survivors with the information and tools to manage their disease. This research aims to reduce psychosocial and symptom disparities experienced by underserved cancer survivors. We focus on community-based self-care approaches for several reasons. First, many underserved communities have limited access to cancer support services and oncology specialists, especially in rural areas [10]. Second, a shortage of cancer specialists, including psycho-oncologists, is projected to worsen with the growth of the older population [11]. Third, two influential reports by the National Academy of Sciences have led to recommendations by several regulatory and advocacy bodies that cancer

care address survivors' comprehensive needs including surveillance, late effects of treatment, distress screening, psychosocial care, and healthy lifestyles, as well as attention to the transition from active treatment to survivorship [12, 13]. Fourth, over 75% of cancer patients are followed up in primary care, but primary care physicians often lack the necessary training and confidence that they possess the specific expertise required to manage the health care needs of cancer survivors [14]. Finally, as health care in this country moves to accountable care organizations responsible for managing the health of populations, integration of cancer support services with health care systems will be critical, including establishing linkages among oncologists, primary care providers, and community-based cancer support services.

Translation of the Nuevo Amanecer Program

Working with community partners, we developed an extensive research program to address these gaps. We conducted extensive formative research and developed Nuevo Amanecer (A New Dawn), a new 8-week, peer-delivered cognitive-behavioral stress management (CBSM) program for Spanish-speaking Latinas. Using community-based participatory research methods, we applied an innovative translational process model appropriate for minority and underserved populations (we integrated an evidence-based intervention, a community best-practices program, and formative research results) resulting in a program that could be delivered by trained breast cancer survivors (peers) [15]. We tested Nuevo Amanecer in a randomized controlled trial (RCT) of urban Latinas who were newly diagnosed with breast cancer; results indicate that it effectively improved several quality-of-life domains and decreased breast cancer concerns and depressive and bodily symptoms [16]. In the words of a participant, "The program changed me. It made me happier and helped me think positive thoughts so I could push forward and fight."

Cognitive-behavioral stress management interventions such as Nuevo Amanecer and culturally tailored physical activity interventions have tremendous value for giving disenfranchised patient populations the tools to help manage their cancer and gain control over what many perceive as an untenable situation. CBSM skills training delivered early in the cancer care trajectory can reduce the most common symptoms experienced by Latinas with limited access to culturally and linguistically appropriate psychosocial services [16].

Throughout rural California, Latinos are concentrated in communities with agricultural jobs; in these communities, we find more Latinos living in poverty, fewer with a high school degree or some college, and lower per capita community revenues and expenditures [17]. Cancer patients in rural areas suffer greater disparities related to lack of access to cancer supportive services, including informational and psychosocial support [18]. Barriers to cancer support services among rural women with breast cancer include distance, lack of transportation, low income, and low literacy. In the Central Valley of California, geographic isolation, distance to health care providers, and language barriers are risk factors for poor health [19]. Effective

psychosocial health programs for rural Latinas with breast cancer could reduce these disparities. Because the broader Latina population in California includes many in rural settings and with limited literacy, a necessary step prior to full-scale dissemination is to adapt Nuevo Amanecer for more vulnerable subgroups and test it in these new populations. In addition, community organizations need resources to facilitate incorporating such programs into their settings. Thus, we embarked on Nuevo Amanecer-II, a study in which we are translating and testing the program in three rural, low-income communities in California. We trained a new set of community health workers (CHWs) to deliver the program. Recruitment for the study has closed, and intervention delivery and follow-up assessments should be completed by September 2018.

Baseline breast cancer-specific quality-of-life data from our Nuevo Amanecer and Nuevo Amanecer-II RCTs demonstrate that compared to norms based on white breast cancer survivors, Latinas do worse on every domain. Using the Functional Assessment of Cancer Therapy measures that include a subscale on breast cancer concerns (FACT-B), we found that urban and rural Spanish-speaking Latinas reported worse overall quality of life, physical well-being, emotional well-being, social/family well-being, and functional well-being compared to norms from a sample of 400 White women with breast cancer. Spanish-speaking Latinas scored about 60% lower (indicating poor quality of life). These results are consistent with prior studies, although these studies are few in number [1, 2].

Development of these programs occurs in partnership with community organizations, Latina breast cancer survivors, and clinicians using an integrative approach that synthesizes scientific evidence with community knowledge, while taking into account the local context [15]. We utilize mixed methods to obtain data that informs program development (e.g., semi-structured interviews and surveys with survivors, clinicians, and social service providers). We embed these programs in the community by training community-based organizations to deliver them in a fashion that they have determined works with the populations they serve. We have described this implementation model and the features that make it especially suitable for translation of programs for delivery in health disparity communities [15].

A Conceptual Framework to Guide Research on Behavioral Interventions for Latino Cancer Survivors

Based on this program of community-based participatory research (CBPR), we developed a conceptual framework of survivorship needs, types of programs that would address these needs, and the hypothesized mediators and outcomes that would be affected by these programs [20]. According to Spanish-speaking breast cancer survivors, their needs focus on four general areas: symptom management, psychosocial health, coordination of post-treatment care including the transition from immediate diagnosis to survivorship, and healthy lifestyles. Based on the

literature, the types of interventions that help include (1) skills training on symptoms, stress management, and communication with family and clinicians; (2) information on symptoms and treatment side effects, recommended follow-up care, signs of recurrence, healthy lifestyles (physical activity and nutrition), and community resources; and (3) social support. These types of interventions have been shown to improve self-efficacy for managing symptoms, stress, and communication; improve knowledge; and increase perceptions of social support. Improvements in these mediators lead to decreased stress and distress and improved health-related quality of life [20].

Spanish-speaking Latinas experience limited access to culturally and linguistically appropriate cancer survivorship care. Cancer centers are often ill-equipped to meet the needs of cancer patients who are limited-English proficient and low income, especially in rural areas. Such women often fall through the cracks and may not receive high quality care for breast cancer into the acute and survivorship phases. Community-based models that utilize CHWs and peers are proven methods for reaching underserved populations, resulting in improved health outcomes [21]. CHW-delivered cancer support programs could be a low-cost, effective method for meeting the psychosocial needs of underserved Spanish-speaking cancer survivors.

Gaps and Opportunities for Future Research

Clearly, we need stronger evidence for the effectiveness of behavioral interventions for improving the HrQoL of Latino cancer survivors. Once culturally appropriate cancer support programs are found to be effective in diverse populations, we will need effective methods for disseminating these evidence-based programs. Although there are platforms for dissemination of evidence-based behavioral interventions, including cancer-related programs, these are largely only known to and used by researchers. Researchers can address such service delivery gaps by developing an integrated program of research focused on translation and dissemination of evidence-based behavioral interventions for underserved cancer survivors.

Importantly, in our Nuevo Amanecer-II study, we added the collection of biospecimens (hair and saliva samples) to examine the effects of the program on cortisol levels (a biomarker of stress). Minority populations in the United States are less likely than Whites to donate biospecimens [22], and there is almost no evidence on the effectiveness of methods employed by researchers to collect biospecimens among Latinos. In the context of this study, our CHWs successfully collected the biospecimens. However, we were unable to secure the cooperation from one partner community-based organization; thus, we were not able to offer women from that community the choice of providing saliva and hair samples. To inform future efforts, we will report on the unique issues we have faced with collection of biospecimens among Spanish-speaking Latina breast cancer survivors. Such evidence is critical so that vulnerable populations can accrue the benefits of precision medicine. Deployment of targeted resources will be necessary to include minority populations

in large, multicomponent cohort studies that require biospecimens, such as the "All of Us" program, a national initiative to enroll a diverse and representative cohort of one million Americans to advance precision medicine for all diseases [23]. Inclusion of vulnerable populations in all phases of this research is imperative, if we are to reduce health disparities and assure communities that the results will be relevant for and accessible to them.

A promising avenue for delivering behavioral interventions to minority communities, including Latinos, is technology-assisted community health worker interventions. In other translation efforts, we recently developed and conducted a pilot test of a Spanish-language mobile phone application to provide women with breast cancer survivorship planning and physical activity promotion tools. We combined the mobile phone application with telephone-delivered health coaching. Data analyses are in process, but preliminary results suggest that the tool was acceptable to women, increased their self-efficacy to manage their illness, and increased their daily average steps. In another study, we developed a prototype of an English and Spanish mobile phone application that adapted the core stress management components of the Nuevo Amanecer program for use among low-income women undergoing chemotherapy for breast cancer. We hope to test this mobile phone application in a future RCT that will incorporate telephone health coaching as well. Finally, we are providing technical assistance to another investigator-community stakeholder research team on a project that is translating our program for use among underserved, rural white women using a telehealth modality delivered by peers (rural breast cancer survivors). Thus, we are translating effective programs for new populations and delivery methods that have potential for broad-based dissemination.

Conclusions

As cancer centers strain to meet the needs of the burgeoning cancer survivor population, alternative service models that capitalize on community resources and integrate CHWs and families into the health care delivery system will be needed. Working with disparities communities, investigators can integrate evidence-based programs with community knowledge and best practices to test and disseminate co-developed programs to meet the needs of vulnerable cancer survivors. Working together, academic-community partners can develop acceptable, effective, and potentially more sustainable programs to reduce disparities. With such an approach, the intervention development process is incomplete "until an intervention is optimally efficacious and implementable with fidelity by practitioners in the community" [24].

Through Nuevo Amanecer-II we are testing whether the program meets the needs of vulnerable and low literacy Latinas in rural areas. This will ensure that the program is appropriate for rural and urban Latinas and results in a transportable program and implementation guide for community-based organizations prior to widespread dissemination. Because of the extensive involvement of community

advocates, survivors, and cancer care providers throughout translation, broad program dissemination should reduce ethnic disparities in psychosocial health. Our Nuevo Amanecer process evaluation indicates that it was precisely this careful integration of community input that resulted in a program that effectively reduced disparities in the psychosocial health of vulnerable Latinas in the study by meeting their needs and anticipating implementation barriers [25]. On study completion, we will post our program products on Internet sites to further disseminate them and to maximize the community benefit derived from these studies. Our vision is to see this practical, culturally relevant program widely adopted to eliminate psychosocial health disparities in vulnerable Latinas with breast cancer.

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Chapter 16
Research Democracy in a Randomized Controlled Trial: Engaging Multiple Stakeholders in Patient-Centered Outcomes Research

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Introduction

Patient-centered outcomes research (PCOR) addresses issues and measures outcomes that are meaningful to patients and other stakeholders. PCOR emphasizes involving patients and other interested stakeholder groups such as clinicians, advocates and caregivers in the research process [1–4]. Some funding agencies, such as the Patient-Centered Outcomes Research Institute (PCORI), require the "active incorporation of perspectives beyond those of the researchers" throughout the entire project [1]. Understanding factors that contribute to successful collaborations is a critical component to better serve our patient populations and forge stronger partnerships in PCOR. The involvement of engaged and enthusiastic team members with diverse perspectives is one of the factors important for PCOR.

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The benefits of engagement are demonstrated through the effective management of partnerships concerned with health and social welfare [4, 5]. True engagement yields better work performance among team members. Improved work performance among teams is supported by creating an environment in which team members can fulfill and exceed expected roles and apply creativity to problem-solving to achieve or exceed the desired outcomes [4]. Similar contexts among health care teams can increase patient-centered care [6].

For teams conducting PCOR, one approach that may work to promote involvement among stakeholders with diverse perspectives and experiences is research democracy—a process in which individuals involved in research (e.g., team members, participants, advisors) have a vote and a voice in the decisions that are made and the procedures that are used to conduct the research. Elements of research democracy include opportunities for sharing opinions, casting votes, discussing outcomes, and identifying areas for improvement. We expand upon ideas presented in the limited literature on team engagement in PCOR [7–9] and provide examples of effective communication to keep each member updated and informed [9–11]. Research democracy can also provide a process for fostering creativity, innovation, and synergy among team members [9, 12, 13].

The purpose of this chapter is to describe research democracy in a PCORI-sponsored project, the Nueva Vida Intervention, and illustrate how such research democracy may promote PCOR. The literature on team engagement in research and public health interventions is limited [7–9]. To address these gaps, we present research democracy applications (Table 16.1), team member satisfaction (Table 16.2), barriers (Table 16.3), and benefits (Table 16.4) to conducting research in a PCOR context.

Methods

The Nueva Vida Intervention is a dyadic intervention that aimed to improve quality of life outcomes among Latina breast cancer survivors and their caregivers (PCORI AD12-11-5365) [14]. The Nueva Vida Intervention was evaluated in a randomized controlled trial, and the study team was composed of four community-based organizations (CBOs), scientific investigators from the Lombardi Comprehensive Cancer Center at Georgetown University, clinical and research consultants, an advisory board that included Latina cancer survivors and caregivers, and a data safety and monitoring board [14]. The intervention consisted of eight group-based sessions in which survivors and caregivers learned coping and communication skills in separate rooms and then joined together for discussion and a meal [14]. Throughout the process of study design, intervention refinement, protocol implementation, and follow-up, we collected data on team engagement through informal observations, direct discussions during team meetings, and survey assessments.

Table 16.1 PCOR elements and research democracy approaches in the Nueva Vida Intervention project

PCOR element	Research Democracy Approaches in the Nueva Vida Intervention
Clear expectations [9, 11]	• Maintained detailed records of every phone call and meeting • Set a goal and deadline for each (new) action item • Reiterated expected deliverables from team members for each deadline • Followed up with one another as deadlines approached • Allowed time for expression of differences of opinion related to identified goals
Delegation [9]	• Each site recognized and understood their responsibilities to meet their own goals as well as the larger overall team goals. Individual team members were tasked with different responsibilities as appropriate for each site. • Newsletter writing was divided so that each Community Based Organization (CBO) authored one newsletter and the Georgetown University Medical Center team edited each issue • New tasks were assigned based on the consultants' and advisory board members' interest
Effective communication [9, 12]	*Structural elements of communication*
	• Team members were invited to specific telephone calls based on their tasks. Most calls were open to all members, including bi-weekly phone calls between the principal investigator and project directors at each CBO, and monthly teleconference calls with the entire study team
	• We held separate monthly interventionist supervision telephone calls for only the interventionists and our team clinical supervisors (CC; GE). The decision to restrict these calls to only the interventionists was at the suggestion of a team member; this decision promoted confidentiality of the participants and also promoted further autonomy and sense of connection among the team interventionists
	• Georgetown University Medical Center sent team emails with project updates and other items, such as webinars and articles, at least once per month to the entire study team
	• Polls and team surveys were conducted as an additional means of collecting team member ideas and opinions about the implementation and progress of the project
	• Annual meetings featured diverse discussion methods. Both large group discussions and small break-out sessions were organized and implemented
	Process elements of communication
	• Communication was conducted in an accepting, considerate environment to accommodate and value different personalities and interpersonal styles, creating balanced but diverse discussions
	• Each person was asked for input during monthly teleconferences and annual meetings; each CBO site was asked for group input
	• Each site shared ideas, successes, and difficulties during recruitment
	• Team members were offered support and reassurance throughout the process

(continued)

Table 16.1 (continued)

PCOR element	Research Democracy Approaches in the Nueva Vida Intervention
Establishment of shared goals; [12]	• Voting to identify intervention topics • All team members shared a passion for improving outcomes among the target population of Latina breast cancer survivors and their caregivers
	• During proposal planning and writing, team members identified initial shared goals for improving quality of life among Latina breast cancer survivors and their caregivers
	• During intervention adaptation and planning, team members voted on which intervention topics were most relevant to the "core" five session content areas out of eight total sessions
	• During implementation, team members identified and acted upon shared goals for recruitment; intervention implementation; and quality of communication among team members and with participants, including dissemination of results. These goals were determined through discussions that engaged all team members
	• At the first intervention session with each new group, participants (Latina breast cancer survivors and their caregivers) voted on topics for 3 sessions (out of a possible 6 elective session topics). This ensured that interventions received by the participants were appropriate to their interests and needs. For example, some groups consisted of caregivers who were adult children of the survivors, while other groups consisted of spouses or partners of the survivors
Establishment of mutual trust [12]	• Site principal investigators emphasized mutual trust and were receptive and responsive to difficulties encountered by team members without causing fear of penalty or embarrassment, thus promoting a culture of transparency with meeting expectations
Promotion of team pride [9]	• A team logo and motto were developed as a team and used in team materials across sites
	• Each phone, email, or meeting communication began with sharing team or individual members' study-related accomplishments
	• A private Facebook page allowed sharing of articles and photos documenting team successes
Fostering creativity and innovation [9]	• Created a basic study structure that could easily be adapted based on team member feedback and community interactions • Team members suggested that the research be prioritized over peripheral tasks or that requests be made in smaller, more manageable steps
	• Created a press kit based on one site's previous experience
	• Gifts sent to participants were chosen as a team
	• Changed newsletter format and delivery
	• Created an introductory video used for participant recruitment
	• Sites hosted events to accomplish a number of goals to:
	(a) Educate the desired target population about the importance of clinical research
	(b) Share the outcomes of the research as a way to disseminate results and show the research team's appreciation for participant involvement

(continued)

Table 16.1 (continued)

PCOR element	Research Democracy Approaches in the Nueva Vida Intervention
	(c) Encourage participants and team members to feel proud of how their engagement made success possible
	(d) Provide participants an opportunity to share what important things they learned in the process and what ideas they had for future research
	• Creative thinking helped clarify consultant roles and responsibilities. For example, one consultant with expertise in clinical aspects of supporting caregivers was invited to facilitate a discussion about caregiver needs in a conference call and to provide an update to the team during one of our annual team meetings
	• At a recruiter's suggestion, we created a 'recruitment flipbook' that consisted of photos only (no text) to convey steps of study involvement for community members with low literacy
	• Created a media engagement plan provided by a site PI who was a former news reporter
Seeking partnership synergy [13, 14]	• Two sites in New York hosted an event emphasizing the importance of Latino participation in cancer research. Two other sites adopted that idea and hosted an event in the DC metropolitan area
	• One CBO site principal investigator shared that work on the PCORI Nueva Vida Intervention generated greater internal team cohesiveness. Other team members (a CBO site principal investigator; advisory board member) identified and followed through on opportunities to submit an abstract as first author and co-present an invited presentation
	• One site had its entire team complete HIPAA and Human Subjects Research training
Promotion and practice of cultural humility [13]	• Some research team members acknowledged lack of familiarity with cultural norms
	• Some community partners acknowledged lack of familiarity with research
	• The minimum inclusion age was changed from 21 (often the norm in research studies) to 18 when we realized that young caregivers are common among the patient population
	• Stopped using the word "study" when publicizing and recruiting, because community partners informed us that the word "study" elicited images of blood being drawn
Connecting your team to resources [9]	• Provided human subjects training to community partners using CERTification, a training approved by our IRB that is designed for community-based partners; adapted training into Spanish
	• Included professional development opportunities in team emails
	• Leveraged existing meeting schedules to maximize learning opportunities and make attendance more convenient. For example, one annual meeting was scheduled around the National Latino Cancer Summit and another was scheduled around a survivorship conference in DC
	• Minimized administrative burdens such as secure file sharing across sites. Ultimately we simplified data requests and input from site team members and increased data input among the Georgetown PI's study team to lessen CBO team member burden

Table 16.2 Team member satisfaction and experiences survey results

Item text	
Please circle a response to indicate if the following changes have occurred since joining the team:	***% of team members who reported "increased"***
My willingness to express my point of view has increased	45
Trust between the group members has increased	81
Please circle a response below to indicate your level of satisfaction with the following:	***% of team members who reported "satisfied" or "extremely satisfied"***
The impact of study involvement on my agency	100
The amount of influence I have over team decisions	95
Based on your experience with the Nueva Vida Intervention study, please circle a response to indicate how likely are you to:	***% of team members who reported "likely" or "extremely likely"***
Collaborate in other research	100
Seek out new research collaborations	100

Table 16.3 Barriers identified during work on the Nueva Vida Intervention study

Category	Barrier
Communication	"Organizational barriers/limitations to understanding/complying with research practices and communicating to potential participants"
	"Labor intensive, [lack of] clarity in startup conversations, time [zone] difference[s]"
	"Staff mobility and communication issues"
Recruitment	"Recruitment and retention barriers were expected"
	"[Difficulty with] Caregiver recruitment"
Other	"Some language barriers but resolved"
	"Progression of disease as a hindrance to participation"
	"[Difficulty understanding and accepting] Randomization"

Table 16.4 Benefits identified during work on the Nueva Vida Intervention study

Category	Benefits
Collaboration	"Collaboration"
	"Collaboration with other subcontractors"
	"Wonderful collaboration, organizational structure and team spirit"
	"Collaboration with other organizations and working with Kristi [Graves] and her team"
Learning about the research process	"Internal abilities to collect and disseminate lessons learned throughout the research process
	"[Ability to] Participate in research study"
	"Great model for staff to learn how such a project works"
Other	"Could not be happier!"
	"I feel my work with A[frican] A[merican] community and other advocacy work contributes"
	"Closer connection with all sites"
	"Learning about caregiving"

Results

Table 16.1 illustrates how we applied elements of PCOR using research democracy approaches during the randomized controlled trial to evaluate the Nueva Vida Intervention. We identified these elements based on evidence from studies of employee engagement, team engagement, and community-based participatory research [13, 14].

During the study period at one of the annual in-person team meetings, we administered a survey to assess team member satisfaction and experiences (see Table 16.2 for a summary of survey results). Team member feedback on this survey helped set the agenda and procedures for upcoming team calls. We specifically asked for barriers and benefits to individual team member's success and involvement with the study. By eliciting input during open communication on team calls and also through a survey, we obtained feedback about team procedures so that adjustments could be made, as needed. We presented results to team members to promote transparency and open communication. Team members identified barriers (Table 16.3) and benefits (Table 16.4) during the Nueva Vida Intervention Study.

Sites also reported enhanced team engagement within their own organizations. One site principal investigator reported that participation in the project contributed to restructured roles, unified people as a team pursuing a common goal, and fostered creativity and collaboration. The methods used to promote team engagement thus appeared to be advantageous not only for the larger research team but also for the individual community-based organizations. A critical component to whether partners on a research team can thrive involves recognition of their time and expertise through appropriate compensation for time and inclusion in the dissemination of results.

Discussion

Research democracy, a process by which all members of a research team (patients, CBOs, scientific investigators, and other stakeholders) are engaged, valued, respected, and heard through both direct voting and open communication, resulted in a successful PCOR project, the Nueva Vida Intervention study. The management strategies employed kept the study running efficiently and effectively and established mutual trust. Setting clear expectations provided opportunities to foster such trust, and listening to team member concerns promoted transparency and sharing of information in a safe environment. Transparency and effective communication alerts a site to events occurring at other sites which may disrupt study flow such as staff turnover, staff illness, site moves, or other obligations. Team cohesion, developed using the elements of team engagement, generated enthusiasm for the research project among the team members. The diversity of the team was an asset, contributing to the goals of team members individually and the research project as a whole.

For example, flexibility during implementation of the study and dissemination of information to the community was particularly important, because the CBOs were more familiar with the community and culture than the researchers. Elements of team engagement that value each person may be more likely to promote community members' participation in future research. These preliminary results suggest that active application of research democracy elements may promote team engagement and satisfaction as well as awareness of project barriers and benefits, which may, in turn, strengthen and promote PCOR. Future research can systematically explore approaches for how to best assess team engagement to strengthen and promote PCOR.

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Part VIII
Engaging Latinos in Cancer Research

Chapter 17
Es Tiempo: Engaging Latinas in Cervical Cancer Research

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Overview of Community-Driven Research

Community health science is an approach that takes science to the community and ensures that the community participates in the scientific process in order to improve quality of life [1]. It is the development of a two-way street between communities and academia that helps solve some of the most challenging scientific health problems at the community level. Academic–community partnerships provide one mechanism to facilitate engagement of communities in research. The goal is to improve access to services, research participation, access to technology, and information/knowledge transfer or faster dissemination of information. As the Latino community ages, grows, and spreads throughout the United States, bridging the gap between science and practice becomes more urgent, especially among older segments of the Latino population whose cancer risk profile may be increasing. This is needed especially in cancer prevention and control, if Latinos are to benefit from new and emerging technological advances and engage in precision medicine more fully.

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In the United States, Latino communities are changing demographically and culturally. Latinos are not a monolithic unit, but are instead a very heterogeneous group with differences in acculturation, immigration, documentation status, country of origin, and racial/ethnic make-up. In spite of this heterogeneity, their connection with each other is central to the Latino community. The values that Latinos share are central to the essence and culture of being Latino. Most share in the Spanish language, except Brazilians who speak Portuguese and some indigenous communities from Central and South America who predominantly speak an indigenous language, even if they have learned Spanish. Common to the culture is an emphasis on *personalismo*, *familismo*, *simpatia*, collectivism, harmony, and cooperation in the group [2, 3]. These characteristics have often been found to be protective and have served as deterrents to unhealthy life styles, such as alcohol, drug, and tobacco use in some segments of the Latino community. Although other groups may share in similar values, solutions found for other cultural/ethnic and racial groups may not necessarily apply to Latinos and to Latinas in particular. For example, the Latino Epidemiologic Paradox shows that in spite of living in poverty and having low educational attainment, some segments of the Latino population have very positive health outcomes on specific indicators and have shown important gains in life expectancy.

Unfortunately, Latino populations are not always well informed of recent advances in research, nor do they benefit equally from scientific discoveries as other populations. On average, research can take 17 years to go from bench to bedside [4], which is why community-based models are needed; these models engage participants in research, not just as subjects but also as planners, implementers, and disseminators of information, so information can be transferred more quickly. Community-based participatory models can decrease this time gap by utilizing patient-centered approaches and by including patient advocates, citizen scientists, and community health workers, who are trusted by their respective communities to research and deliver life-saving information and accelerate knowledge transfer. These programs work best through the establishment of equal power-sharing partnerships, which effectively accelerate health improvements that more quickly achieve health equity [5]. The World Health Organization (WHO) defines equity as "the absence of avoidable or remediable differences among groups of people, whether groups are defined socially, economically, demographically, or geographically" [6]. In our research, we strive to achieve health equity in cancer-related diseases and to adequately reduce risk factors via participation in research and more timely dissemination of information to the Latino community.

Israel et al. [7] described key principles for community engagement which we utilize in our research with Latinos. These include (1) engaging community partners from the beginning stages; (2) working on the principle of shared equity and decision-making; (3) engaging in mutual learning in all stages of research; (4) negotiating a common vision, goals, values, priorities; (5) compensating community partners; (6) hiring staff from the local community; (7) training community health workers/*promotoras de salud*; (8) allowing community partners to influence program direction; (9) sharing equal power among partners; (10) planning jointly with

partners; and (11) working with partners on dissemination of information. These are principles that form part of community-based participatory research (CBPR). Even though it is not always possible to implement all CBPR principles in cancer research, some cancer research can still be community driven and abide by many of the principles described above.

Our over 25 years of experience show that to actively engage Latinas in cervical cancer and other cancer-related research, it is critical to build strong relationships in the Latino community over time. We build community trust by establishing several partnerships that are still in effect years later. Further, we engage Latino communities and Latinas, in particular, directly and indirectly in the research. Latinos are engaged as participants and as community scientists. Once the research is finalized, we give information back to these communities. Further, we follow up in terms of policy or services that are needed to further community goals, and we work with volunteer organizations, such as the American Lung Association and the American Cancer Society in policy and advocacy.

One important mechanism we have utilized is the establishment of community advisory boards/committees (CABs/CACs) [8]. Through our CABs we have engaged key community members in guiding the research from its initial stages through to its dissemination [9]. This implies that the CABs are truly heard and that academic researchers recognize the importance of their contributions from conceptualization to decisions on analysis and information dissemination. We have also engaged patient advocates, community scientists, citizen scientists, and/or community health workers (CHWs) and *promotores de salud* as vehicles for listening to community voices. These key community representatives do not necessarily have a formal science or research background, but they contribute time, effort, and resources toward scientific research. Citizen scientists work often with professional scientists or alone [10]. Citizen scientists and patient advocates are helping to bridge gaps in research, as everyday people contribute to the scientific enterprise. In these days of Big Data, they can contribute to data collection by accumulating photographs and videos of their environment and by providing context for interpretation of data from these large datasets. Ability to help culturally interpret findings is critical.

Current Work

Although much has been accomplished in reducing morbidity and mortality from cancer, cervical cancer remains a serious health threat for Latinas in Los Angeles. In LA County, the incidence of cervical cancer is as high as 8.0 per 100,000 among Latinas, compared to 6.3 per 100,000 among Asian/Pacific Islander women, 10.5 per 100,000 among African American women, and 7.3 per 100,000 among non-Hispanic White women [11]. These statistics are particularly worrisome, especially for Los Angeles, a county heavily populated by Latinos. Women present them-

selves to local clinics with advanced stage of disease and limited survival and treatment options.

Past Interventions

A multidisciplinary team at the University of Southern California (USC) conducted 12 focus groups [12], which resulted in the development of two research/intervention programs: *Tamale Lesson* (Murphy/Baezconde-Garbanati, NCI-R01CA144052), Es Tiempo (California Community Foundation, the Norris Comprehensive Cancer Center, P30 CA01408939S4), and the SC Clinical Translation Science Institute (CTSI-UL1TROOO130).

Tamale Lesson: Transforming Cancer Information Through Narrative

For *Tamale Lesson*, we developed two 11-min English films with the goal of reducing the burden of cervical cancer. *Tamale Lesson* was also translated and adapted into Spanish. *Tamale Lesson* was produced using a culturally tailored narrative format which aimed to provide information on the human papillomavirus (HPV), the virus that causes cervical cancer; cervical cancer prevention via vaccination; and cervical cancer detection via Pap test screening and new genetic tests. The second film, *It's Time*, was developed as a non-fictional, non-narrative alternative to *Tamale Lesson* and also included similar information. Details of development are presented elsewhere [13]. Short 3-min clips of these videos are available on YouTube, as well as longer versions on DVD. A sample of 900 European American, African American, and Mexican American women living in Los Angeles were recruited through random digit dialing (RDD) and were randomly assigned to receive either the narrative or the non-narrative film in the mail. All women were surveyed to assess their level of cervical cancer-related knowledge, attitudes, and behavior before receiving the film, 2 weeks and 6 months after viewing the film. Latinas participated in many aspects of the research. They were active participants in the focus groups, and also participated in focus groups that viewed and edited the films to make them more culturally specific. Through funding from the SC CTSI, *promotoras de salud* were included. They participated in the research via the formation of a community advisory board that produced the Spanish language version of *Tamale Lesson*. Findings from the study revealed that the narrative and non-narrative films were successful interventions in both the short-term at posttest and long-term at 6-month follow-up [14]. The narrative film was more effective in increasing cervical cancer-related knowledge and attitudes at posttest than the non-narrative. Moreover, the narrative film reduced cervical cancer screening disparities for Mexican American women from pretest to the 6-month follow-up. Fifty percent of non-Hispanic whites, 32% of Mexican Americans, and 36% of African Americans did not need a Pap test at baseline. Within 6 months after viewing the *Tamale Lesson*, the disparity disappeared,

and 78% of non-Hispanic whites, 83% of Mexican Americans, and 77% of African Americans had a Pap test or made an appointment for cancer screening [14]. The program has been disseminated not only throughout California but also across several countries in the Caribbean and Latin America, including Colombia, Mexico, Panama, Costa Rica, and Argentina through *Buena Salud* America of the National Alliance for Hispanic Health and the Healthy Americas Institute. In Panama, the Ministry of Health is distributing *Tamale Lesson* throughout 900 jurisdictions, including rural indigenous areas.

Es Tiempo: The Jacaranda Initiative

Our multidisciplinary team at USC developed *Es Tiempo*—a stunningly beautiful and innovative campaign to prevent cervical cancer among Latinas. It was built on the 12 Latina focus groups [13] and environmental scans conducted by students in the Designmatters Program at the ArtCenter College of Design. *Es Tiempo* uses the annual blooming of the purple jacaranda tree in Los Angeles to remind us all that we can prevent cervical cancer and to remind women to vaccinate their sons and daughters from HPV. *Es Tiempo's* design elements were created by students from the ArtCenter College of Design, Designmatters Program and developed and tested by investigators from the Norris Comprehensive Cancer Center, Institute for Health Promotion and Disease Prevention Research, Department of Preventive Medicine, Keck School of Medicine of USC, and the Annenberg School for Communication and Journalism. The program was pilot tested and launched with cooperation from community clinics, Clínicas Monseñor Oscar Romero (Pico Union and Boyle Heights). We obtained support from the Office of Women's Health (OWH) at the L. A. County Department of Public Health.

The bilingual *Es Tiempo* campaign has three components: (1) an outdoor media educational campaign; (2) a clinic intervention in partnership with Clínicas Monseñor Oscar A. Romero in Boyle Heights and Pico Union; and (3) a community component, where *promotoras de salud* deliver community educational workshops and collect intercept surveys to measure knowledge increases at the community level. Latinas are and have been engaged in this project from its creation all the way through to its implementation and dissemination in the community. Outdoor media materials include billboards, bus benches, and light post banners with the OWH cervical cancer helpline number. When Latinas call the helpline, trained callers make appointments and referrals for free or low-cost cervical cancer screening and HPV vaccinations for qualifying women. Intervention clinics mail postcards to women who have not had a Pap test in the last 3 years (based on current guidelines), and clinic banners remind women to schedule their cervical cancer screening or vaccinate their sons and daughters. OWH and the clinics report the number of women who call or make appointments pre- and post-intervention. In addition, *promotoras de salud* conduct community workshops which have a pre- and post-survey of knowledge on cervical cancer and the HPV vaccine. At the end of the workshop, participants are provided with referrals, places where they can receive low or no

cost screening and HPV vaccinations. Also, women are encouraged to follow-up if they have abnormal Pap test results. Lastly, intercept community surveys are conducted to assess the campaign and understanding of the material; knowledge-related questions pertaining to cervical cancer, the HPV vaccine, and Pap test; format in which they have received health information; and how they would like to receive health information in the future.

Clínicas Monseñor Oscar Romero (community partner in *Es Tiempo*) reported that 1428 women were eligible for Pap tests in the community intervention clinic and 745 women were eligible from a control clinic located in another area of the city. Our findings show that there was a statistically significant difference in percent of women who became compliant during the intervention period. The percentage of women in the Boyle Heights intervention clinic was higher than the Pico Union no intervention (46% vs. 33%, $p < 0.01$). Also, there was a statistically significant difference in percent of women who received a Pap test based on the type of intervention they received. Women in the Boyle Heights clinic who received a postcard at home with the same imagery as the outdoor media had higher rates of Pap testing than women in Pico Union who received only the postcard (65% vs. 34%, $p < 0.001$). Our findings demonstrate the effectiveness of a multicomponent intervention to promote screening for cervical cancer that incorporates Latinas in various aspects of the program.

Identified Gaps

There continues to be a need for the inclusion of Latinas in cancer prevention and control research. Latina involvement in our research helped us develop interventions that include social and cultural assets, which are essential elements that can make a difference in the elimination of health disparities in cervical cancer screening and in HPV prevention and control. For example, our research shows that Latinas respond well to narrative or storytelling in an educational campaign such as *Tamale Lesson*. Feeling transported into a storyline, being able to identify with the characters, and being emotionally impacted by the narrative [14] will go a long way to help eliminate cancer disparities. There is also a need to target a more diverse population (e.g., region and age), because cultural elements that resonate best with one Latino community may not resonate best for others, such as El Paso, Chicago, Watsonville, or Miami.

Future Research

Greater engagement of Latinas in cervical cancer research may provide opportunities for eliminating this cancer health disparity. Working in partnership with Latino-driven clinics, community-based organizations, and volunteer agencies, our

researchers can commit to the translation of research into policies and public health initiatives that have the potential for making a difference at the community level. In order to engage Latinas in cervical cancer research, we can work with the community and not only engage in research but also in its translation and dissemination, so it can reach our various communities more quickly. *Es Tiempo* and *Tamale Lesson* demonstrate ways in which we can provide a research environment that is more conducive to participation and engagement. Our campaigns and intervention programs model cultural strategies that can be used not just for cervical cancer but also for other diseases. Community-level interventions that are conceptualized, developed, and implemented using community-based participatory principles and that engage Latinas from the beginning of the research through the dissemination of data, have the potential of increasing Latina research engagement, helping to reduce cancer disparities and save lives.

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Chapter 18
Reaching Latinos Through Social Media and SMS for Smoking Cessation

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Background

Smoking is the leading cause of premature, preventable death in the country, accounting for about 480,000 deaths per year, including 41,000 from secondhand smoke. This means that one in five deaths per year are due to cigarette smoking. Tobacco's impact on cancer and heart/lung disease is well known [1, 2]. Of all smoking-related premature deaths, about 36% are due to cancer, 39% due to heart disease, and 24% due to lung disease. In general, mortality among smokers is three times higher than that among nonsmokers. On average, smokers die 10 years earlier than nonsmokers and cost billions of dollars to the nation, including $170 billion in direct medical care; more than $156 billion in lost productivity due to tobacco-related diseases and disability, of which $5.6 billion are due to secondhand smoke exposure [2–4].

In Texas, smoking kills more than 25,000 people per year and 3000 of those are in South Texas [5]. Almost 90% of adult smokers start smoking by age 18, and almost all (99%) of daily tobacco users try their first cigarette by age 26 [2]. Smoking prevalence is highest (23.5%) among US young adults aged 18–29 and even higher among those with less than a high school education (28.7%) and those living at or below the poverty level (25.5%) [1, 2, 6–8]. About 24% of Latinos aged 18–39 in

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the program areas are current smokers [6]. Among young adult Latinos aged 18–29 in the study areas, smoking rates are similar to those in this age group nationally and the state overall [7]. Smoking rates are low among older Latinos in Texas, and notably higher among young adult Latino men than women.

For young adults, particularly among lower-income Latinos, mobile and social media are increasingly viable communication choices [9–12]. Nine out of ten Latino adults own a smartphone [9] and have a Facebook account, making Facebook the most frequently used social media platform in this group [10, 11]. Latino young adults are heavy users of mobile-only texting, apps, and Internet, and trends in use of mobile-only social media are rapidly rising among lower-income Latinos [11]. Smartphone social media interventions are an innovative, evidence-based, recommended approach for promoting healthy behavior changes among young people [13–18].

Telephone counseling is a well-studied service with strong evidence of effectiveness [19], particularly among younger smokers—among whom rates of cessation are more than doubled by telephone counseling [20–23]. However, telephone counseling services reach only 1–2% of smokers annually and only 0.9% of Latinos [24, 25]. Online and mobile applications have also been validated by research indicating similar levels of effect on cessation rates at much lower unit costs [13, 14, 26–28]. Smartphones have the potential to provide personalized smoking cessation support. Research has shown that support delivered via mobile phone text messaging doubled rates of biochemically validated smoking cessation rates at 6 months over controls (10.7% vs. 4.9%) [13]. More recent studies, including a Cochrane Review [26], concluded unambiguously that texting interventions can significantly increase odds of successful smoking cessation, with a pooled RR of 1.7, with some studies performing even better [26]. Motivational messages and behavior-change methods in phone or face-to-face smoking cessation support can be modified for delivery via text messaging combined with social media with content tailored to the quitter's gender, ethnicity, and age [13, 27, 28]. Thus, support can be delivered where the person is located without them having to attend services, providing anonymity people like, and it can be interactive, allowing participants to get extra help if needed [13, 27, 28]. Text messaging can also include embedded links to videos and other content to offer peer modeling for cessation behaviors [29]. Its usefulness can be further increased by adding connections to social media and obtaining user profiles to personalize messages to gender and marital and parental status [30]. Young smokers, and particularly lower-income Spanish-speaking young adults for whom mobile devices are a primary point of Internet access, can be effectively served by text messaging cessation program methodology [13, 14, 27–29, 31].

We present results from Quitxt, a text-messaging tobacco cessation program promoted via social media to reach young adult Latinos aged 18–29 in South Texas, a marginalized population with low access to cessation services.

Methods

The Quitxt geographic area is South Texas, a 53,000-square-mile area that borders Mexico and contains 4.9 million people. This region includes the Rio Grande Valley, one of the most medically underserved and impoverished areas in the nation, characterized by gaps in public health services, poor access to health care, significant environmental health concerns, and elevated chronic disease rates. About 72% of young adults in this region are Latino [32]. Of this region's 38 counties, 25 are rural and 21 are Health Professional Shortage Areas. The region's population is more than 30% uninsured, younger and less educated than the state average, and experiences high poverty rates (23.6%). About 70% of residents in this region speak Spanish at home [32, 33].

Program Development

Formative research took place during the first 6 months of the program, including review of existing evidence-based short message service (SMS) cessation services (i.e., smokefree.gov) and focus groups with young adults (English and Spanish) from San Antonio and the South Texas border area, to ensure that the program message library was culturally and linguistically appropriate.

Pretesting

With input from focus groups, we developed preliminary content and protocols for our intervention and constructed beta versions of all key promotional messages and protocol elements for pretesting. To identify any potential technical issue prior to program launch, we conducted beta testing of the program with young adult smokers who enrolled in the program via Facebook, received texts, and responded to social media and video links embedded in texts.

Process

To enroll in the program participants must be 18 years of age or older, current smokers, willing to set a quit date within 14 days, and provide baseline data. The program responds to text codes with a sequence of interactive messages beginning with collection of baseline data that includes basic demographics (i.e., age, ethnicity, gender),

number of cigarettes smoked per day, e-cigarette use, and binge drinking behavior. Participants are then prompted to choose either "quit tomorrow" or set a "quit date" within 2 weeks. Based on the selection, a specific message sequence follows. The program provides motivational messages, tips to manage cravings and difficult situations, and support 24/7. After their quit date, enrollees are also encouraged to text "help" if they are having difficulty avoiding cigarettes; when they text "help," the system texts to ask if the help needed is due to "stress" or "mood," and depending on their text reply, they are then sent either a prompt and link to breathing exercises (for stress) or a message with links to diverting, humorous videos (for mood). When enrollees fail to reply to texted questions at any point in the protocol, the system is designed to repeat the question twice before moving forward with the messaging sequence whether replies are received or not. Texts also include links to mobile webpages with short videos, music, and other fun and helpful content. These pages (Fig. 18.1) correspond to primary elements of the text messaging component: (1) reasons and motivation for quitting; (2) obtaining social support; (3) nicotine replacement therapy; (4) increasing physical activity; (5) breathing exercises for managing stress; (6) things to do instead of smoking; (7) avoiding relapse by talking yourself out of smoking; (8) predicting, planning, and practicing for difficult situations; and (9) avoiding binge drinking (Fig. 18.1). The messaging system was built and operated by the Software Communication and Navigation Systems Laboratory at the University of Texas at San Antonio.

Fig. 18.1 Screenshots of webpages. (Reproduced with permission of Quitxt/Institute for Health Promotion Research, UT Health San Antonio; © 2018 Quitxt/Institute for Health Promotion Research, UT Health San Antonio. All rights reserved)

Program Promotion

Program enrollment is promoted using mainly social media (i.e., Facebook, Instagram, Twitter), in addition to local mass media publicity and outreach at colleges, universities, trade schools, and other venues attended by young adults. The program uses social media ads with different themes (i.e., disgust, confidence in quitting) and styles (cowboy, metro, punk, graphic novel). Participants are prompted to click on the ad to visit the program homepage for more information or to text a code corresponding to the channel of recruitment (Fig. 18.2).

Results and Discussion

This was not an experimental trial, and no data were collected to control for use of pharmacological or other behavioral interventions, but we did collect data on enrollment, continuation of service utilization, and self-reported cessation status.

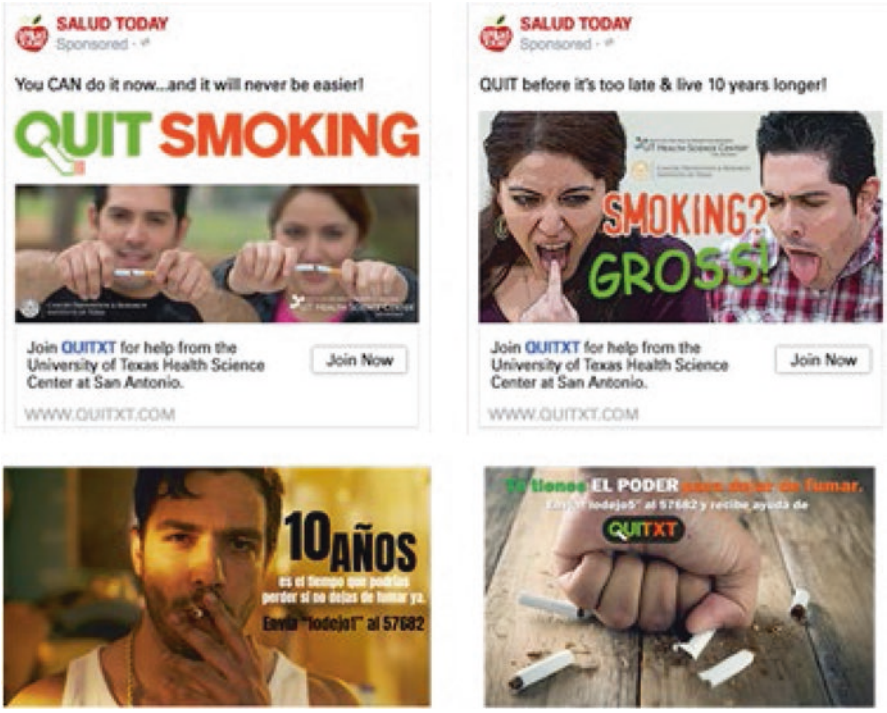

Fig. 18.2 Sample of social media ads. (Reproduced with permission of Quitxt/Institute for Health Promotion Research, UT Health San Antonio; © 2018 Quitxt/Institute for Health Pro-motion Research, UT Health San Antonio. All rights reserved)

Cessation success was assessed with a question texted from the service 222 days (7 months) following the enrollees' selected quit dates that measured 24-h point prevalence abstinence (no smoking in the past day). This measure of cessation yields estimated cessation rates that are highly correlated with abstinence assessed for longer intervals, and the question can be answered more accurately than questions about smoking in the past week or month [34]. If this were a clinical trial, more extensive measures of cessation success would be warranted, but guidelines for research on cessation do not call for biochemical validation of self-reported abstinence in texted or other low-response demand measurement contexts [35].

A total of 798 enrollees are included in the present group assessment. Participants were recruited from October 2015 to January 2016, with 70% (555) texting in response to Facebook advertising, 14% (111) responding to publicity, 9% (70) responding to outreach, and 8% (62) responding to Twitter or Pandora Internet Radio. Facebook advertising with a theme of confidence and the metro/urban style was the most productive recruitment source and yielded enrollees at a cost of approximately $120 each.

Chi-square tests and multivariate analyses were used to determine the statistical significance of differences between program user groups. The mean age of Quitxt participants was 29.3, and 55% were below the age of 30 (Table 18.1). More men (57%) than women (43%) enrolled in the program, and 36% identified themselves as Hispanic or Latino. The mean number of cigarettes smoked per day was 11.5.

Table 18.1 Quitxt participant characteristics and cessation rates

Characteristic	Frequency (%)	Cessation (%)	OR
Age			
≤29	398 (55.1)	23.9	Ref
≥30	324 (44.9)	23.5	0.90
Gender			
Male	400 (56.5)	23.7	Ref
Female	308 (43.5)	24.7	1.05
Ethnicity			
Hispanic/Latino	246 (35.5)	25.2	1.18
Non-Hispanic/Latino	446 (64.5)	24.4	Ref
Cigarettes smoked per day			
<10 cigs/day	308 (46.4)	26.3	Ref
≥10 cigs/day	356 (53.6)	25.3	0.97
Use of e-Cigs (ever)			
Yes	302 (49.6)	19.9	**0.34**∗
No	307 (50.4)	36.2	Ref
Binge drinking			
Yes	385 (64.1)	23.4	**0.37**∗
No	216 (35.9)	37.5	Ref

∗$p < 0.001$

Approximately half (302) of the 609 enrollees who replied to the question about e-cigarette use reported that they were using e-cigarettes to help reduce their cigarette smoking. Among the 601 enrollees who texted a reply to the question about alcohol use, 64% (385) reported binge drinking (4 or more drinks on a single occasion in the past month among women, 5 or more among men).

Regarding cessation rates, 21.4% of participants (171/798) reported 24-h point prevalence abstinence from smoking 7 months after their selected quit date. There were no significant differences in cessation rates between males and females, younger and older enrollees, or Latino enrollees and others. Participants who reported use of e-cigarettes were less likely to report smoking cessation at 7 months than those who did not report e-cigarette use: 20% (60/302) versus 36% (111/307; chi-square test, $p < 0.001$). Those who reported binge drinking were less likely to report smoking cessation at 7 months than those who did not report binge drinking: 23% (90/385) versus 37% (81/216; chi-square test, $p < 0.001$).

Smoking cessation rates reported here are higher than the rates reported in previous studies of mobile cessation services [26], but are consistent with research on telephone counseling for young adults [20]. Measurement of point prevalence of 24-h abstinence yields cessation rate estimates that are slightly higher than longer-reported intervals of abstinence [34]. In addition, enrollees in this service were mostly light to moderate smokers (mean consumption 11.5 cigarettes per day at baseline), which may have contributed to the relatively high cessation rates achieved.

Conclusion

Texting and mobile media services for smoking cessation can be effectively delivered to young adults in South Texas. Support can be delivered 24/7 wherever the person is located, providing the anonymity people like, and it can be interactive, allowing participants to obtain help when it is most needed. This is a highly scalable service, which makes mobile personalized smoking cessation advice/support an affordable approach to reach disadvantaged population groups, produce a public health impact, reduce health service costs, and reduce smoking-related health disparities.

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Chapter 19
The Need for a Holistic Approach to Prevent Reproductive Cancers Among US Latinas: The Potential Impact of Normalizing Sexuality and Improving Communication

Julia Lechuga and Katherine Melo

Introduction

US Latina women are disproportionately affected by cervical cancer incidence compared to non-Latina white women. The cervical cancer incidence rate among US Latinas is estimated at 9.9/100,000 compared to the 7.7/100,000 estimated rate of non-Latina white women [1]. Compared to non-Latina white women, Latinas are less likely to screen for cervical cancer, more likely to get a cervical cancer diagnosis later in the course of the disease, and less likely to receive follow-up treatment services after a positive diagnosis, leading to increased risk of mortality [2].

Research suggests that a myriad of factors, operating at multiple levels of influence, negatively influence cervical cancer screening and receipt of follow-up treatment in a timely fashion. Factors at the individual level include low knowledge about the causes of cervical cancer and forms of prevention, screening, and treatment [3] and demographic factors such as low acculturation, foreign birth, and low income and educational attainment [4, 5]. Other factors operating at the individual level include adherence to Latino cultural beliefs and norms such as dignity, respect, fatalism, and traditional gender norms [6]. At the structural level, factors such as lack of access to health care services and logistical barriers to accessing services such as lack of transportation and childcare have been shown to affect screening and receipt of follow-up treatment [7, 8].

To promote cervical cancer screening and treatment, a literature review was conducted on interventions; several gaps were identified, including few interventions uniquely targeting Latinas and a dearth of interventions informed by theories explicating the manner in which culture may affect screening and treatment, such as the PEN-3

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model of cultural influence [9]. Specifically, most cervical cancer screening promotion interventions have been informed by health–behavior change theories prominent in psychology, such as the Health Belief Model, Theory of Reasoned Action, Transtheoretical Model, Social Learning Theory, Social Cognitive Theory, and Social Influence Theory. The literature review clearly identified a need for interventions that simultaneously target factors operating at multiple levels of influence and for a broadening of focus beyond cancer screening as end outcomes to include improvements in sexual and reproductive health, broadly speaking [9]. Using a theoretical lens accounting for the complex interplay of factors affecting human behavior, a closer look at research findings and intervention efforts undertaken in other domains of Latino sexual and reproductive health may promote the development of interventions targeting multiple levels of influence, including structural-level factors beyond individual-level precursors of behavior change.

A closer look at disparities in sexual and reproductive health among Latinos indicates that Latinos experience negative health outcomes in multiple domains of sexual and reproductive health, not only cervical cancer. For example, Latinas are less likely to screen for breast cancer and are at increased risk of mortality compared to non-Latina white women [10]. Furthermore, the rate of sexually transmitted infections (STIs) including HIV and unintended teen pregnancies among Latinos is double the rate of non-Latino whites [1, 2, 11]. These statistics underscore the need to develop and test interventions aimed at targeting root causes of disparities in sexual and reproductive health.

We argue that there is the need to conduct research informed by theories which conceptualize the individual as nested in complex systems, to further understand the manner in which contextual and individual-level factors interact and influence adoption of sexual and reproductive health preventative behaviors across domains. Culture is a powerful system that influences human behavior. According to the socioecological model by Bronfenbrenner [12], culture is a macrosystem in which individuals are nested; it can be conceptualized as institutional and familial socialization practices that transmit values, norms, and behavioral expectations through generations. Past research has examined the effect of culture on various domains of sexual and reproductive health among Latinos. However, when considering how culture may influence various systems in which the individual is embedded and how it may ultimately lead to individual differences in sexual and reproductive health decision-making, there is a need to operationalize it and its effects in a more complex way. Here we present findings from two separate studies that highlight the influence of two important cultural factors operating at the macro and micro levels of influence: embarrassment and shame ascribed to sexuality (macro level) and communication about sexuality among members of a social network (micro level).

Study 1

The purpose of the first study was to understand the influence of communication about sexuality in adoption of the HPV vaccine—a three-dose vaccine recommended for children and pre-adolescents between the ages of 11 and 12. Catch-up vaccination is recommended for adolescents who were not vaccinated at the recommended

age. Our study sample consisted of 65 mother–daughter dyads who self-identified as Latino. We purposefully sampled 50% of daughters who had received at least one dose of the HPV vaccine and employed a mixed methods qualitative dominant sequential design.

Materials, Procedure, and Approach to Analysis

Participants were recruited from a variety of venues including churches, schools, and supermarkets. Mothers and daughters were interviewed separately. Mother was asked to sign an informed consent form for her and daughter, and daughter was assented separately. Participants answered open-ended questions as part of the qualitative portion of the study followed by a brief demographic survey, which also assessed whether mother had engaged in the discussions about sexuality with daughter and the specific sexuality-related topics discussed. We content analyzed open-ended responses, computed chi-square tests of association, and performed a logistic regression analysis. We computed a chi-square test to assess the association between having engaged in discussions about sexuality with daughter and vaccination uptake. We computed a stepwise blocked logistic regression to understand which sexuality-related topics were significantly associated with vaccination uptake. In the first block of the regression equation, we entered the daughters' age. In the second block we entered specific sexuality-related topics using the stepwise procedure. Our goal was to assess which of these variables would emerge as significantly associated with vaccination uptake.

Results

A larger proportion of mothers who had vaccinated their daughters (64%) reported to have engaged in discussions about sexuality with daughter compared to mothers who had not vaccinated (36%) ($\chi 2 = 5.38$, $p = 0.02$). Content analysis of the responses suggested that the content of sexuality-related discussions differed between those who had and had not vaccinated. Specifically, the content of discussions between mothers and their daughters who had been vaccinated seemed to encompass a variety of topics related to sexual health including anatomy, puberty, appropriate timing of initiation of sexual relations, and the importance of engaging in behaviors to protect oneself against STIs. In contrast, the majority of mothers of daughters who had not been vaccinated conveyed feeling uncomfortable and embarrassed about speaking with daughter about sexual health, and the content of their communication was value-based including admonishing daughter about the inappropriateness of initiating sexual relations before marriage. Table 19.1 presents the results of the last step of the logistic regression analysis. Daughters' age emerged as a significant predictor of uptake; the older the daughter the more likely she is to be vaccinated. Furthermore, engaging in discussions about birth control emerged as significantly associated with uptake, predicting 40% of the variance in vaccination uptake.

Table 19.1 Factors associated with vaccination uptake

Variable	*B*	SE	OR	95% CI	Wald statistic	*p*
Daughter's age	0.50	0.21	1.65	1.09, 2.50	5.68	0.01
Talk birth control	1.71	0.77	5.56	1.21, 25.50	4.87	0.02

Note: Data is for mothers ($N = 65$). Talk birth control = extent to which mothers reported having discussed birth control methods with daughters. Talking about birth control with daughters alone predicted 40% of the variance in vaccination uptake

Study 2

The purpose of the second study was to understand the sociocultural factors associated with attitudes toward cancer screening in a sample of US Latinas. A cross-sectional survey was administered to a sample of 85 US Latinas as part of a larger study designed to test the effect of a community-based, participatory, sexual-health intervention delivered by community health workers.

Materials, Procedure, and Approach to Analysis

Community health workers (CHWs) recruited participants in locations where Latinos congregate regularly (e.g., supermarkets and churches). To be eligible to participate, participants had to be 18 years old and self-identify as Latina. Participants who volunteered to participate were asked to answer a survey asking demographic questions including age, household income, and whether they had ever had a Pap smear test and/or mammogram if eligible. The survey also included questions assessing negative attitudes toward cancer screening and sociocultural constructs such as shame and embarrassment ascribed to sexuality. To understand whether sociocultural factors such as shame and embarrassment ascribed to sexuality would emerge as significant predictors of attitudes toward cancer screening, we computed a hierarchical multivariate linear regression analysis. In the first block of the equation we entered demographic variables including age, income, and whether the participant had ever had a Pap smear test and/or mammogram using the enter procedure. In the second block of the regression equation, we entered sociocultural variables using the stepwise procedure.

Results

Table 19.2 presents the results of the last step of the regression model. The sociocultural variable shame and embarrassment ascribed to sexuality was significantly associated with negative attitudes toward cancer screening above and beyond demographic variables typically associated with access to health care and predicted an additional 30% of variability in negative attitudes toward cancer screening.

Table 19.2 Factors associated with negative attitudes toward cancer screening

Variable	*B*	SE	*β*	95% CI	*T*
Age	−0.03	0.02	−0.35	−0.07, 0.01	−1.53
Household income	0.00	0.00	−0.08	−0.01, 0.00	−0.48
Ever had a pap test	0.38	0.45	0.16	−0.56, 1.33	0.83
Ever had a mammogram	0.81	0.46	0.35	−0.12, 1.74	1.77
Shame and discomfort with sexuality	0.54	0.18	0.52	0.16, 0.92	2.92

Note: Data is for Latina women ($N = 85$). The addition of shame and discomfort with sexuality predicted an additional 30% of the variance in negative attitudes toward cancer screening

Discussion

Operating at multiple levels of influence, culture is a key factor to be considered in order to move the field forward and reduce Latino health disparities in sexual and reproductive health broadly speaking. Our argument is put forth in light of several factors. First, the majority of the prominent behavior change theories which have dominated health promotion and intervention research rest on the assumption that the most powerful determinants of behavior are personally derived attitudes and cognitions about the health behavior in question, such as perceived benefits and consequences of the behavior [13]. This assumption is questionable as research with individuals who conceptualize the self as an extension of the in-group (i.e., Latinos) compared with individuals who conceptualize the self as separate from others (i.e., non-Latino whites) [14] suggests that the function of behavior is to fulfill social obligations [15]; and self-efficacy is more the product of support from important members of the social network than volitional control [16]. Second, sexual and reproductive health behaviors around the world are heavily influenced by societal level norms and expectations; consequently, developing interventions that target multiple levels of influence with culture considered as a central piece could yield interventions that target root causes of disparities and yield sustainable behavior change.

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Chapter 20
Critical Steps for Engaging Hispanics in Cancer Research: Building Capacity to Enhance Participation in Biospecimen Donation with Hispanic Communities

Elisa Marie Rodriguez and Deborah O. Erwin

Introduction

The disproportionately lower number of certain subpopulations participating in clinical and prevention research has a significant impact on the representativeness of scientific outcomes and results in social and clinical injustices [1]. A sequential set of community-based studies were conducted to engage diverse medically underserved populations in biospecimen donation for cancer genomic research [2, 3]. This chapter is organized around three critical steps of community engagement that are relevant to participatory research as applied to novel and formative efforts focused on biospecimen science that were used in the Hoy y Mañana (translated to Today and Tomorrow) study. Specifically, these studies developed and tested community-based interventions to identify influential factors regarding participation in biospecimen donation to a biorepository at a cancer center in upstate New York for future cancer research from a Northeast Hispanic, predominantly Puerto Rican population [4].

Three Critical Steps for Engaging Hispanics in Cancer Research

Community engagement is an essential component to reaching and including diverse and\or hard-to-reach populations in biomedical research with a focus on reducing health disparities and improving individual health. There are three overarching steps that can be applied when working at the community level that facilitate

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engaged approaches to research and enhance the relevance of research as an opportunity to build capacity and increase health equity. The following steps are not exclusive to biospecimen research studies but can be applied to a variety of public health issues and research topics targeting efforts at a community level.

Step 1: Know the Community

The first step is to know the community. Knowing the community requires an in-depth understanding of community members and stakeholders, barriers and assets, population demographics, and community context. The Community Development Model for Public Health Applications is a comprehensive model that integrates the factors essential to knowing a community as the primary unit of analysis and can be used as a framework to guide community-engaged research efforts [5]. Additionally, Community-Based Participatory Research (CBPR) principles and methods also serve as a foundation for collaborative approaches to research that enhance and support community engagement research activities across a variety of topics and disciplines.

Involving the community at the earliest stages of the research process can better ensure acceptability and relevance to the population of interest. The Hoy y Mañana (HyM) study focused on the opportunity to build capacity with preexisting community partners around the topic of biospecimen donation for future cancer research [3]. Capacity building is a key component of the CBPR principles that values skill building and co-learning [6]. Community partners played an integral role in linking the pilot research project to the community and vice versa. Transparent and consistent communication was an important factor throughout the process and contributed to an effective partnership process in engaging the community and assessing feasibility to conduct community-based cancer research involving the collection of biospecimens.

Formative research including structured in-person interviews and focus groups were completed with Hispanic community leaders, staff from the biorepository at the cancer center, and Hispanic participants from the community. Table 20.1 provides examples of the qualitative methods employed in the HyM study to illustrate the process used to gain the community perspective regarding biospecimen donation for cancer research and how the data informed each step of the research. The key informant interviews with Hispanic community leaders were part of the first level of community data collection. These individuals are best described as community leaders (e.g., pastors, civic leaders, and clinicians who practice in the community). They are trusted individuals who often assume an informal gatekeeper role in the community because of their established relationships with members of the community at large. Knowledge of the community facilitates an understanding of who these respected and trusted leaders are and the potential impact they can have in linking the community to collaborative research opportunities. Rodriguez et al. describe the methods and community-engaged research process in detail as well as

Table 20.1 Summary of formative research methods used in the Hoy y Mañana study

Objective	*n*	Method	Findings (examples)
Gain perspective of Hispanic community leaders	6	Structured in-person key informant interviews	Lack of awareness
			How are specimens used?
			Never asked to donate
			Integration/application:
			These findings informed focus group topics with broader community
Gain perspective of biorepository staff at the cancer center	5	Structured in-person interviews	Identified staffing needs to ensure community competence
			Integration/application:
			Informed protocol for collecting samples in the community to maintain scientific rigor while enhancing community access to participation in biospecimen donation
Identify barriers and assets in recruiting diverse populations to biospecimen donation (e.g., Hispanic community)	24	Focus groups ($n = 4$) with participants from the community	Lack of awareness
			Interest in research opportunities
			Need for translated materials and consent process
			Integration/application:
			Disseminated results to community advisors and informed the design of a community-based pilot

the resultant findings from a predominantly Puerto Rican population with regard to their self-reported awareness and interest in biospecimen donation for cancer research [3].

Step 2: Know the Goal of Engagement Activities

Community-engaged research efforts often require understanding and commitment to an iterative process; however, the goal of engagement activities should be transparent and mutually agreed upon prior to research implementation to ensure acceptance and commitment to the process. In the HyM study, the objective of this first step was to better understand the community's awareness, knowledge, attitudes, and interest in biospecimen donation for cancer research. The results from the formative research were shared with stakeholders including the Community Advisory Board (CAB) members during a partner education component of the study to finalize concepts to be covered in the biospecimen science education program. Dissemination activities require thoughtful planning, because there may be different audiences (e.g., CAB and community members) and time points within the research process that require their own feedback loops for sharing information as it is developed and analyzed. Likewise, how information is developed and analyzed requires

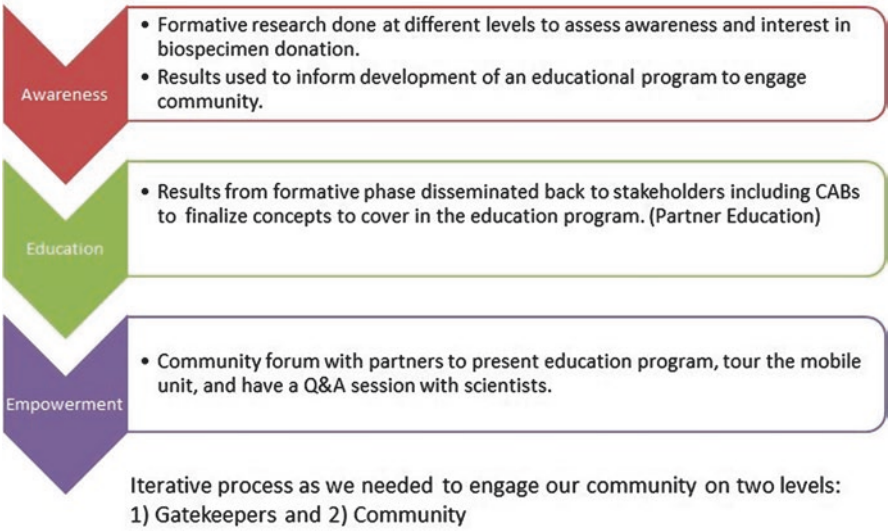

Fig. 20.1 Study schematic describing examples during each phase of the research process: (1) Formative phase: assess awareness; (2) development phase: create a culturally appropriate biospecimen science education program to deliver in the community; (3) implementation: test the education program and feasibility of mobile lab unit to facilitate community participation in biospecimen donation for cancer research

consideration of the goal and transparency in why and how specific partners are included throughout the research process.

The HyM study involved multiple phases that fed into each other and led to the testing of a mobile lab unit that could be used to collect and process biospecimen donations from willing community members at onsite events in the community. Each phase of the research included specific activities and processes that were meant to assess, deliver, or support the intended research goals of the study (Fig. 20.1).

Step 3: Design Activities Using Best Practice Strategies

As with any type of research, there is an emphasis on scientific rigor and the process applied to draw conclusions from study findings. Community-based research will often vary with respect to the level of community partner involvement, and this is unique to each collaboration; however, in studies that apply CBPR methodology, there are accepted and best practice strategies that can be used to ensure scientific rigor while addressing the issues most relevant to the community [6]. Best practice strategies should be applied at all phases of the research process and considered as an opportunity to further integrate community partners as citizen scientists who are the rightful experts with respect to the communities they live in.

Table 20.2 Application of best practices in the Hoy y Mañana (HyM) study

HyM study component	Best practice strategies applied
Study design	Community-Based Participatory Research (CBPR) Approach
Implementation	Informed by CBPR principles
Assessment/collect data	Mixed methods
Culture and literacy	All program materials were translated to Spanish to meet community language needs and preferences
	An Audience Response System was used to engage the community audience in the educational presentation and facilitate an interactive survey process
Evaluation and refinement	Revisions were made after multiple pilot programs
	Spanish translation and verification process
	Process measures were collected on efficacy of the community pilot including implementation of tools and the mobile unit
Public dissemination	Hispanic newspapers and radio

The HyM study applied best practice strategies throughout each component of the research process from study design to public dissemination (Table 20.2). The CBPR principles were followed from the onset of the grant writing process and applied to all steps of the educational tool development, implementation, and dissemination processes [7]. Ultimately the application of a CBPR approach served to broker communication among scientists and community stakeholders and members throughout the biospecimen science co-learning process. An important implication included a detailed understanding of methods for introducing biospecimen science to diverse communities such as the Hispanic community engaged in the HyM study.

Discussion and Lessons Learned

Hispanics represent a significant proportion of the diverse minority populations that make up the United States and are underrepresented in biomedical research studies and even more so in biospecimen banks [8, 9]. A growing number of cancer research studies include the collection of biospecimens as part of the research participation process. It is important that this rapidly evolving field of cancer research as it relates to precision medicine and/or immunotherapy not contribute to further gaps and disparities across the cancer care and research spectrum. The HyM study sought to engage and partner with an underserved Hispanic community to (1) understand their awareness and interest in biospecimen science (2) develop a community-based education program to increase awareness and facilitate informed decision-making with regard to biospecimen donation and (3) test the feasibility of community-engaged culturally appropriate approaches in recruiting diverse and underserved

community participants to biospecimen donation for cancer research using a mobile lab unit for onsite collection and processing of biospecimen donations.

Most Hispanic groups do not have a historical context of mistrust with regard to the medical community. Other studies including Hispanics have also found that lack of awareness regarding biospecimen science and/or not having been asked to participate in cancer research are the primary reasons cited by this population regarding their lack of participation in biospecimen donation [2, 4, 9]. Cancer research opportunities inclusive of Hispanics are critical to understand the molecular differences in cancer cells compared to populations that have been better studied and represented in research [10]. Community-engaged studies have shown that several Hispanic groups indicate a willingness to donate biospecimens for cancer research and also support the use of trained non-medical staff to obtain consent for the biospecimen request [2, 11]. Engaging Hispanic communities in a culturally appropriate manner at the very beginning is necessary and essential to the collection of biospecimens for cancer research. This research requires a commitment to collaboration across disciplines and values community engagement as part of the research process.

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Part IX
Charting the Future of Cancer Health Disparities Research in Latinos

Chapter 21
Emerging Policies in US Health Care

Amelie G. Ramirez and Edward J. Trapido

Many of the issues discussed at the conference, such as testing, clinical product rules, drug approvals, and funding for research, clearly touch the arena of public policy. At the close of the conference, Dr. Ruben Mesa, Director of the Mays Cancer Center at UT Health San Antonio, chaired a panel discussion on emerging policies in US health care. The diverse, expert panel offered different perspectives on emerging health policy. The panel included:

- Congressman Joaquin Castro, Representative from the 20th Congressional District in Bexar County, Texas
- Dr. Esteban López, Chief Medical Officer, Clinical Strategy and Innovation at Blue Cross and Blue Shield of Texas
- Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences at the National Cancer Institute
- Dr. Elena Rios, President and CEO of the National Hispanic Medical Association

Congressman Joaquin Castro, Representative from the 20th Congressional District in Bexar County, Texas

Congressman Castro began the session by stating that cancer and heart disease are the two diseases that claim the most lives of Latino Americans. In Texas, that problem is especially pernicious. Congressman Castro pointed out that he is very much

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involved in public policy that supports the research that many of the researchers at the conference are doing—research that will help save the lives, not only of many Latinos, but of all Americans. His main message to researchers was to advocate for their own work and educate policy makers in Congress of its value in helping people and saving lives. In doing so, he suggested that researchers should be persistent because lawmakers are juggling many issues in addition to healthcare and may need reminding to refocus their attention. He reminded the audience that there was an infusion of new money earmarked for cancer research, with Vice President Biden's MoonShot Initiative funded through the 21st Century Cures Act, but warned that National Cancer Institute would still need to cut their operating budget and deal with increasing requests for research funding. Congressman Castro has been speaking out about the need to increase funding for cancer research and not back away from that commitment.

Ruben Mesa, Director, Mays Cancer Center at UT Health San Antonio asked, "*What opportunities are there for being the voice in getting important policies implemented related to issues regarding cancer in Latinos?*"

Congressman Castro responded that there is an incredible opportunity for researchers and community leaders and many members of Congress and state legislatures to make an impact in funding and policies passed by legislative bodies. For example, the Tri-Caucus, which comprises the Congressional Asian Pacific American Caucus (CAPAC), the Congressional Black Caucus (CBC), and the Congressional Hispanic Caucus (CHC), led legislation efforts in previous years that would improve cancer funding and cancer research among minority groups. But that legislation did not move in Congress the way it was expected. Therefore, there is a great need for advocates to come to Washington and make the case that this is important work.

We must also protect the Affordable Care Act because one part of it, the individual mandate, has been recently removed. Latinos were the biggest beneficiaries of the Affordable Care Act; more Latinos than any other group were able to receive insurance coverage because of that act, so researchers and community members must make sure that it is not eroded any more. One other important issue that must be addressed is the environmental quality of many Latino communities. This is deeply challenging in places like Texas. For example, the environmental agency that regulates companies in Texas is the Texas Commission on Environmental Quality (TCEQ). It is charged with enforcing air, water, and waste management violations. Over a multi-year period, the state agency found only a fraction of the air and water violations from different polluters. As a consequence, there are huge Latino communities that are exposed to damaging environmental factors because of weak enforcement in certain states like Texas. This is important when one considers the health effects of the environment on cancer and other illnesses. Thus, everyone must be mindful, not only of Congress and the federal government, but also of state and local jurisdictions.

Dr. Esteban López, Chief Medical Officer, Clinical Strategy and Innovation at Blue Cross and Blue Shield of Texas

Dr. Lopez spoke about Understanding Drivers and Barriers for Latinos in Cancer Care; he began by addressing the difference between "Equal and Equitable." While physicians may try to treat patients in an equal manner and offer equal care, equal care is not necessarily equitable, because patients face different challenges to receive the care that they need. Blue Cross wants to not only give patients access to care but also address social indicators of health that prevent patients from receiving their highest potential level of care.

Addressing cancer disparities among Latinos first requires knowledge about what health challenges Latinos face. In addition to using published research, Blue Cross is using online research to see how Latinos are communicating online. Blue Cross partnered with a vendor who mines and structures qualitative data; examines who is talking, where users are talking and what they are talking about in reference to cancer; and determines underlying drivers and barriers. Blue Cross wants to know what the barriers and attitudes are, so they can understand in real time what their Latino members are experiencing. Using breast cancer as an example, he described the following strategies for offering culturally relevant care:

- *There is a crucial need for early detection*. Breast cancer is the most common cancer in Hispanic women. As a population, Hispanic women are reactive to care; they seek medical care when they are sick but do not necessarily go to a physician to seek preventative care. To encourage proactive screening, there is a need to go where they are, such as their places of business, with mobile mammography; and we must find other methods to ensure screening as we continue to educate the Latino population.
- *Respect cultural differences*. Latinos online show less knowledge about breast cancer and express the competing priorities of job and family in relation to getting mammograms. In terms of Latino care, we must include the whole concept of family and community. We have a call to action to design dedicated strategies, interventions, and activations that tackle the specific unmet needs and cultural nuances of Hispanic breast cancer patients and their caregivers.
- *Target both patients and caregivers, including male caregivers*. Latinos tend to be collectivistic, so the caregivers are influential in the lives of patients with cancer. The goal is to create a two-pronged approach that involves and educates the caregiver as well as the patient.
- *Target primary care physicians*. Primary care physicians (PCPs) can be the number one driver or barrier for proper cancer care and adherence to treatment. Latinos tend to be deferential to their physician and may not question a treatment that will be given. Because a small percentage of physicians are Latinos, we must empower non-Latino physician partners with cultural competence to enhance their relationship with breast cancer patients and their caregivers.

- *Foster advocacy within the community*. Data from social media and chat rooms show that while there are many conversations happening online, there is a lack of advocacy for Latino cancer survivors. There is a need to involve Latino cancer survivors in advocacy, sharing the issues they faced. The powerful voice of survivors can be leveraged to motivate women to seek breast cancer screening.
- *Leverage online channels*. Many Latinos actively use social media and smart phones, and they go to online communities for information about cancer care. So, health care systems must give out information where Latinos are going first. We must also look beyond Facebook and Twitter to online chat communities and message boards. Because the Internet is a powerful channel for Hispanics to find information and support, there is a call to action to think holistically and include online as another channel along the path to treatment.
- *Protect patients through local policy.* Physicians, health care systems and insurance companies must step up to advocate for the communities they serve. For example, Blue Cross and Blue Shield of Texas helped to raise the minimum age to buy tobacco to 21 in Bexar County and San Antonio. While the Latino health care population is younger and often has good health habits, once Latinos are treated for a chronic condition, unfortunately they often experience higher incidence of complication and death. And so, advocacy is important.

Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences at the National Cancer Institute

The field of health disparities research is evolving. Ten years ago, much of the disparity research was pigeon-holed into work on documenting gaps in access to care. It was important to document, understand, and explain health disparities, but the next generation of health disparity researchers is now focusing on disparities across the board, regardless of which community is being studied. That is, the science has moved from documenting what is wrong to raising aspirations and goals to what is possible. What is really compelling and exciting about this meeting is how much solution-focused research is now being done including interventions that are working, risk reductions that are happening, solutions around the uninsured and distance to care, use of technology, culturally appropriate care, building bridges between specialty and oncology care and primary care, and the expansion of navigation.

At NCI we need feedback, criticism, and honest talk. We need to know about many of the great innovations that occur at the local level in your communities, so that we can scale them up at a national level. So, in terms of raising our aspirations, one of the ways we do that is through the tremendous research infrastructure that the NCI supports along with NIH. This depends upon an adequate budget, and so at NCI, we feel fortunate because we have been told that the very last bipartisan area of agreement on the Hill is NIH. One of the ways we try to raise the bar across the whole span of basic, clinical, and population research in cancer is recognizing that

all domains of this research need to be revolutionized to better inform Latino health. At this meeting, we heard about basic science and the acquisition of biospecimens, genomics, molecular epidemiology, and the need for the representation of biological specimens from all communities—without which you can make erroneous inferences and conclusions.

Clinical research still has a long way to go in terms of underrepresentation of Latinos in cancer clinical trials. One of the barriers to Latino accrual is the use of comorbidities, such as hypertension and obesity, as exclusion criteria for enrollment in clinical trials. So, one question we are asking in our clinical research community and the NCI is: Are all these exclusion criteria really necessary in terms of eligibility to clinical trial enrollment? Some of these exclusion criteria are not even necessarily evidence-based. Researchers are being very cautious, trying to understand and reduce toxicity and side effects. But if you are excluding a very large proportion of our population for not a very thorough and sound evidence-based reason, we need to revisit it.

NCI has a large research infrastructure; we are proud of the 69 NCI-designated cancer centers around the country, but they do not reach all parts of the country yet. As a federal agency that funds grants, NCI has been raising the criteria, expectations, and standards to fund these cancer centers over the past several years. For example, community outreach engagement in our cancer centers is a requirement that has been enhanced in our funding guidelines. That has had a great spillover effect; many cancer centers now have associate directors of community outreach engagement. NCI will continue this strategy by adjusting criteria every year. More recently, NCI asked cancer centers to clearly define their population catchment area. Have some ownership, have some engagement, and describe who you think you are serving in your community. It is no longer acceptable for cancer centers to say, "these are the people in trials, because these are the people who can afford to travel, who can come to our center and stay here in a hotel for a week." So NCI has raised the bar in expectations and provided the additional money to do that. It is one thing to change the rules, but we want to avoid unfunded mandates as well.

Another important role that NCI plays is through its cancer registry systems, which have been discussed throughout the conference. The way NCI tries to validate its cancer statistics is by branching cancer registry data and linking it to census data. The census is where people self-report their race and ethnicity, so it is viewed as the gold standard. Data linkage is really of key importance, and without a good census, we cannot track progress in cancer at a national level. The census is not only the key denominator to cancer but also for other diseases that reach across the country. So we are proud of our cancer registry system, our surveillance system in the United States. This is our national report card. We are going to be finishing our next annual report on the nature of cancer shortly, focusing on prostate cancer. This is a data quality issue, so if you want to support cancer research, support a good census. And that means not including elements that deter people from participating.

Finally, there is the issue of cultural competence of non-Latino physicians in Latino communities. One of the most common complaints we still receive from cancer patients is poor communication. "I don't understand my treatment." "I don't

understand the diagnosis." "I don't understand the prospects for recurrence." "What's going to happen to me next?" "What are my side effects?" In response to this, NCI has been trying to contribute to a solution in a small way by translating the patient-reported outcome system we use for clinical trials into 14 different languages. So the measures we use in our research have to be available in Spanish language and must be carefully done and carefully validated.

Dr. Elena Rios, President and CEO of the National Hispanic Medical Association

Dr. Rios spoke about cancer and Hispanic Advocacy. There are two important trends from current health policy issues that impact all of us. The first is that the size of the Latino population is growing; in 2015, 1 in 5 people in the United States were Hispanic, and by 2045, the ratio is projected to be 1 in 4 [1]. This growing demographic has the potential to use the power of the vote to shape public policy. The second trend is that the uninsured rate for Hispanics declined significantly after the Affordable Care Act (ACA)—the most transformative law in healthcare policy since Medicare for the elderly and Medicaid for the poor. The ACA gave Hispanic communities access to doctors, clinics, and hospitals with less financial burden, because insurance pays not only for medical and hospital care, but also medications. However, even though Hispanics have gained the most in terms of having more insurance, they still face many disparities. Thus, health care policy, for Hispanics, is important.

Congressional Legislation in the 115th Congress (January 3, 2017 to January 3, 2019)

The National Hispanic Medical Association is interested in advocacy; it is co-chair for the National Hispanic Leadership Agenda that includes the top 40 Hispanic organizations in the country, and it works with other coalitions for minority health. Some of the most important issues that need advocacy include:

Health Insurance Reform The Affordable Care Act (ACA) is the law of the land. Even though the individual mandate has been taken away, there are still essential benefits, consumer protections, and state marketplaces where competition drives the prices down. An important advocate, the Congressional Tri-Caucus, has influenced health care policy by promoting the need to address disparities in health care among minorities; they have introduced legislation every year for the last decade and have supported major parts of the ACA.

Research The 21st Century Cures Act provides funding to the FDA and NIH for expediting the development and delivery of new medical advances to patients who have hard to treat diseases such as cancer and Alzheimer's. The NIH earmarked funding from this bill for a program known as All of Us, which includes three initiatives—Beau Biden Cancer Moonshot Initiative, Brain Initiative, and Precision Medicine Initiative. The intent is to involve a diverse cohort of one million volunteers to provide personal health data and biological specimens for research. The NHMA is a national partner with the All of Us Research program and is interested in finding ways to involve the next generation of doctors in sharing the idea that more patients should become involved in clinical trials. Finally, there is the second study period of the Study of Latinos—a large NIH community-based, longitudinal, cohort study of Hispanics/Latinos in the United States.

CDC Cancer Prevention Programs Advocacy groups and coalitions, such as One Voice Against Cancer (OVAC), actively lobby Congress to appropriate funds to the Centers for Disease Control to conduct or support cancer research. The CDC Division of Cancer Prevention and Control has many cancer prevention programs that offer grant money including National Comprehensive Cancer Control Program, National Program of Cancer Registries, National Breast and Cervical Cancer Early Detection Program, Colorectal Cancer Control Program, National Skin cancer Prevention Education Program, Prostate Cancer awareness Campaign, Ovarian Cancer Control Initiative, Gynecologic Cancer and education and Awareness (Johanna's Law), and Cancer Survivorship Resource Center.

Health Workforce Programs: HRSA and Department of Education Health workforce programs of the Health Resources and Services Administration (HRSA) and Department of Education include funding for diversity recruitment and training, faculty development, and scholarships. On the House side, the Health and Education Workforce agreed with NHMA Summit recommendations for President Obama's STEM initiative, a major goal of which is to increase the diversity of underrepresented groups within science, technology, and mathematics. Also, it is time for reauthorization of the Higher Education Act (HEA). The NHMA has worked for years with Congressional offices to reauthorize HEA, which is a federal aid program administered by the Department of Education that supports students seeking postsecondary education. The hope is that there will be more opportunities for students in high school and college to become students for medical, nursing and dental schools, or to become STEM researchers of the future. Congressmen Raul Ruiz (D-CA) and Ruben Hinojosa (D-TX) have introduced bills to give more flexibility to Hispanic-serving institutions so that they may use their HEA grant funds for mentoring and advising students to enroll in medical and graduate programs that prepare students for health care occupations. As a result, more Hispanic students may enter the pipeline for health care professions, because their eyes will be open to the opportunity.

Minority Health: HEAA 2018 in Progress A large coalition has formed around Minority Health that is broader in scope than ethnic minorities; it also includes the disabled, women's health, and the LGBT communities. They are all working on a bill with the Tri-Caucus, which is called the Health Equity and Education Act (HEAA). This comprehensive bill aims to improve the quality of health care and eliminate disparities. It will address culturally and linguistically appropriate and value-based health care, as well as promote research and data collection on health needs and outcomes in diverse communities.

Health Policy Trends

There is polarization in Congress with more people at the extremes, so we must find a way to bridge the gap in order to make progress in addressing health care issues and disparities. For example, Democrats are promoting Medicare for All, a universal health insurance that is paid for with taxes; Republicans are proposing block grants, a set amount of money given to states to administer Medicaid that would not be responsive to changes in demand. However, there is bipartisan support for some insurance reforms such as reinsurance programs and subsidies including cost-saving reductions (CSRs) that enable insurance companies to help the poor, lower income and middle class in the United States. A new low premium/high deductible insurance product, the copper plan, is being proposed to offer more affordable insurance. There is also bipartisan support for Medicare Advantage, which is now 30% of the Medicare population. It was designed originally to offer a comprehensive insurance product with medication coverage before Part D was available.

Another health policy trend at both the federal and state level is the recognition that where people are located and the conditions in which they live influences their health risks and outcomes. Thus, there is a focus on social determinants of health such as poverty and income, housing, food security, transportation, financial literacy, education, employment, behavioral health, homelessness, and being in or having been in prison. In Massachusetts, which has been the leader in health reform and health insurance, measures of the social determinants of health are now being incorporated into research, state programs, Medicaid, Medicare, and the marketplace.

Health Care Trends: Medicaid

Medicaid is now the largest insurance with a new focus on flexibility at a state level. There is a push from the Trump administration to allow states to impose work requirements on Medicaid recipients. Ostensibly, the intent is to make recipients lead healthier, more productive lives. This is not the first time that work require-

ments have been part of policy. At the end of the Clinton administration, work requirements were imposed during welfare reform as an incentive to find jobs. One caveat is that there is no money allocated for child care or transportation.

States are experimenting with other ways to improve health and contain costs. For example, some states want to require Medicaid recipients to pay premiums and contribute to health savings accounts. If recipients are too poor to make these payments or do not understand the logistics, they risk losing coverage. To lower drug costs, some states are trying to negotiate value-based purchasing agreements with drug manufacturers. Some states are requesting waivers to allow providers to require participation in wellness programs, and some are allowing Medicaid recipients to use telehealth and telemedicine services so that they can receive medical care at home, giving access to health care for people who lack transportation or who are isolated in rural areas. There is also a move to improve outreach and to measure social determinants of health to inform health management policy and better serve the needs of low-income Americans.

Care Management Trends

When we started managed care in this country in the 1970s, it consisted of just administration of benefits and financing. Then we moved into an era of provider care management, where the emphasis was on the supply side to keep costs down and included measures such as utilization review, risk contracting, diagnostic-related groupings (DRG), and pay for performance (P4P). Now providers are using mainly consumer care management, which emphasizes the demand side, viewing patients as consumers who have choices. It focuses on how to change consumer behavior, for example, to visit the doctor and practice healthy behavior to prevent disease. The strategies for consumer care management are based on factors such as consumer centric behavior, work–life balance, population management, and outcome data. Community care management is a future model of care management that is gaining interest, primarily from Medicaid. This model moves the focus beyond the individual consumer to the community; the intent is to provide accountable, coordinated, whole-person care that will involve not only hospitals and clinics but also home care and caregivers. There will be a shift from hospital-based care to residence-centered care with decreased hospital stays and readmissions. Community budgets will be established for the target population with shared risk strategies between providers and the community, and there will be a shift from volume to value of care received.

Federal Strategic Plans

Some of the federal strategic plans are trendsetters for policies and are thus important to understand; a few of the more influential ones are mentioned here. The strategic plan from the US Department of Health and Human Services (HHS) focuses on high-risk populations now. In the new plan, the words diversity and disparities have been minimized; Latinos are still considered high risk, but are just not named. Another point of note is that every section of the new HHS strategic plan mentions giving more funding to religious and faith-based organizations, so researchers seeking funding might consider partnering with these groups.

The HHS Office of Minority Health (OMH) has a National Plan to Eliminate Disparities and has continued to support the National Partnership for Action (NPA). The OMH also has a history of support for the National Standards for Culturally and Linguistically Appropriate Services (CLAS) in Health and Health Care to be adopted by hospitals and leaders of our institutions and communities. Since 2003, the Agency for Healthcare Research and Quality (AHRQ) has put out an annual National Healthcare Quality and Disparities Report. This assessment of the US healthcare system points out the strengths, weaknesses, and disparities that exist in both quality and access to care. In 1999, the Institute of Medicine (IOM) was asked by Congress to examine health care disparities in the United States. In 2002, the IOM published Unequal Treatment, an influential report that was the first to document widespread health inequities in the United States and to map out general strategies for how to address them, including increasing awareness among the public, policy-makers, and health care industry and promoting evidence-based medicine to insure consistent, equitable care.

Finally, two other reports that have had important impacts on policy are Healthy People and the Report of the Lung Cancer Progress Review Group. Healthy People is a federal strategic plan that focuses on disease prevention; it is updated every 10 years and is administered by the Office of Disease Prevention and Health Promotion (ODPHP) at HHS. Healthy People 2020 aims to:

1. Identify nationwide health improvement priorities
2. Increase public awareness and understanding of the determinants of health, disease, and disability and the opportunities for progress
3. Provide measurable objectives and goals that are applicable at the national, state, and local levels
4. Engage multiple sectors to take actions to strengthen policies and improve practices that are driven by the best available evidence and knowledge
5. Identify critical research, evaluation, and data collection needs. (https://www.healthypeople.gov/2020/About-Healthy-People)

Published by NCI in 2001, the Report of the Lung Cancer Progress Review Group presented a vision for cancer research that is more multidisciplinary. Its “highest priority” was to foster the creation of integrated, multidisciplinary, multi-institutional

research consortia organized around the problem of lung cancer rather than around specific research disciplines.

Future: Cancer and Hispanics

Looking to the future for cancer and Hispanics, the National Hispanic Medical Association sees the need to educate policymakers. Each year NHMA has a national conference in Washington DC which includes a Lobby Day and a session for doctors, medical students, and others to stress the importance of not only cancer but also chronic disease in general in our communities and the need for more doctors. There are many issues discussed, but it is always about access for Hispanic communities, cultural competence, research, and whatever else we can do to help. We also work with coalitions such as the Tri-Caucus, Healthy Equity and Education Workgroup, Medicaid coalitions, Better Medicare Alliance, PhRMA Advisory Council, Public Health Institute new community-based coalition, National Hispanic Health Agenda, Children's Health Group, Immigrant Children Committee (AAP), and Health Professionals/Nursing Education Coalitions (AAMC). Finally, the NHMA supports Political Action Committees such as Hispanic Congressmen (GoBold), Poder PAC—Latina Congresswomen, and the Victory Fund started by Eva Longoria. It is not necessary to have much money to help political action committees, because Congressmen have their own mechanisms for generating funds which can be directed toward future Congressmen that will champion for cancer research. One recommendation for the future is to start a PAC that is just about healthy living in general, not just for Hispanics, but for everyone.

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Chapter 22
A Way Forward: The Future of Cancer Health Disparities Research in Latinos

Amelie G. Ramirez and Edward J. Trapido

The vision for *Advancing the Science of Cancer in Latinos* was to bring together researchers, scientists, physicians, health care professionals, patient advocates, and students from across the nation and beyond, engaging them in open dialogue to summarize research advancements to date, identify gaps, and develop actionable goals to translate basic research into clinical best practices, effective community interventions, and professional training programs to eliminate cancer disparities in Latinos.

This conference not only brought together a diverse group of researchers, but it also built upon the pioneering work of *Redes En Acción: The National Latino Cancer Research Network* (*Redes*). The Institute for Health Promotion Research established the long-standing network in early 2000 under the National Cancer Institute's (NCI) Center to Reduce Cancer Health Disparities (formerly the Special Populations Networks program). Nineteen years later, *Redes* maintains collaboration with six regional sites (San Antonio, San Francisco, San Diego, Houston, Miami, and New York) with a combined network of more than 2000 community leaders, researchers, government health agencies, and public advocates, from across the nation dedicated to fighting cancer among Latinos through research, training, and awareness.

Early on, *the Redes* network identified cancer issues of greatest relevance to Latinos. These identified issues laid the foundation for a national Latino cancer agenda, providing a useful tool for individuals and organizations engaged in cancer prevention and control efforts among Latino populations [1–4]. The *Advancing the Science of Cancer in Latinos* conference provided a pulse check to see what has

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been accomplished, what has been learned, what is still unknown, and what is next. Toward that end, most of the conference presenters made recommendations for a way forward; some of the suggestions are specific to their field of study and others are intended to be applied more broadly. The following are some key recommendations abstracted from their conference presentations.

Genetics, Environment, Lifestyle, and Cancer

- **Cancer prevention strategies are needed now to address changing demographics in the United States.** The US Latino population is growing and is projected to double in the next 40 years. Because US Latinos are a young demographic whose cancer burden will rise as they age, there is an urgent need for prevention strategies now, such as promoting cancer screening and altering modifiable risk factors (Chap. 2; Pinheiro, Callahan, and Kobetz; Chap. 21; Rios).
- **Disaggregate Latino cancer data into subgroups.** The US Latino population is a heterogeneous mix of subgroups that may differ in country of origin, acculturation, nativity, socioeconomic status, and US region in which they reside; these factors can influence cancer risk and outcome. Most US cancer data reports on Latinos as an aggregate group, obscuring the differences that exist among subgroups (Chap. 2: Pinheiro, Callahan, and Kobetz).
- **Improve data collection on Latino national origin so that cancer registries can account for Latino heterogeneity in their analyses.** State death certificates can supplement surveillance data (incidence and survival) in order to find Latino-specific group and place of birth—key pieces of information needed to analyze Latino heterogeneity (Chap. 2: Pinheiro, Callahan, and Kobetz; Chap. 5: Stern).

Cancer Risk, Prevention, and Screening

- **Consider heterogeneity among Latinas when estimating breast cancer risk and mortality rates.** There is evidence that both the risk of developing breast cancer and mortality rate varies among and within Latino subgroups based upon country of origin, nativity, and genetic ancestry (Chap. 4: Fejerman, Serrano-Gómez, and Tamayo).
- **Support international collaborations to access population data and biorepositories in Latin America**. Acquisition of these data will enrich the study of the molecular diversity of cancer in Latinos, helping researchers to better understand cancer risk and outcomes related to biological, environmental, cultural, and access-related factors in individuals of Latin American origin (Chap. 4: Fejerman, Serrano-Gómez, and Tamayo).
- **Conduct more epidemiological studies on prostate cancer using adequate risk factor data that includes Latinos**. Prostate cancer (PCa) is the top cancer

that affects Latino men, yet few Latinos have been included in epidemiological studies in the United States. Also needed are analyses of genetic ancestry and PCa risk among Latinos, which may inform some of the cancer incidence findings; and patterns of tumor localization must still be characterized to improve PCa detection among Latinos. Finally, patterns of care and adherence to active surveillance must be studied to design culturally-sensitive interventions (Chap. 5: Stern).

- **Consider ethnic and cultural background in the design of research and interventions to improve diet among Latino groups.** Most Latino groups fall short of American Cancer Society recommendations for the ideal preventative diet. Incorporate cultural dietary patterns and emphasize traditional healthy foods when designing nutritional interventions and research; this will help to reduce bias and establish reasonable portion sizes. Conduct longitudinal studies of diet and cancer outcomes among understudied Latino populations to reduce current cancer risk and prevent widening risk with the adoption of a Western diet (Chap. 6: Tucker).

The Biology of Cancer Health Disparities

- **Find biomarkers associated with gastric pre-malignant lesions in Latinos**. Gastric cancer disproportionately affects Latinos, and because early stage disease produces no symptoms, this cancer is often diagnosed as stage IV disease with low survival. It would be of great benefit to find biomarkers of treatable, pre-malignant stages and to devise strategies for the prediction of disease aggressiveness and outcome (Chap. 7: Garai, Li, and Zabaleta).
- **Conduct comprehensive tumor genomic studies of gastric cancer in Latinos**. Research suggests that the molecular profiles of gastric cancer in Latinos are unique. Thus, there is a need to characterize genetic and genomic patterns of gastric cancer in patients of Latino ancestry and to conduct preclinical and translation studies in driver genes and molecular subtypes that are more prevalent in Latinos (Chap. 8: Carvajal-Carmona).
- **Elucidate biological factors that promote outcome disparities among Latinas with breast cancer.** Breast cancer in Latinas develops at a younger age, and there is evidence that this early onset disparity may result from genetic, environmental, and biological factors such as altered estrogen metabolism resulting from childhood obesity (Chap. 9: Colon-Otero).
- **Investigate the role of ethnicity in breast cancer susceptibility**. Differences in gene expression profiles of breast cancer may be a consequence of ancestry and thus may be useful for studying breast cancer susceptibility in Latinos. Researchers must properly classify genetic ancestry in admixed Latino populations not only to understand the role of genetics in disease susceptibility, but also to provide Latinos the benefits of recent treatment advances (Chap. 10: Serrano-Gomez and Zabaleta).

Advances in Cancer Therapy and Clinical Trials

- **Structure diverse ethnic patient participation in biomarker trials.** This will provide the most comprehensive ability to apply data to the general population. One important issue is determining the sufficient number of diverse patients to adequately do the analysis (Chap. 11: Perez).
- **Include biomarker-negative patients in clinical trials.** Limiting a study to marker-positive patients may characterize a drug/diagnostic poorly. Sometimes researchers incorrectly assume that a biomarker is required for a response and may thus deny effective therapy to marker-negative patients (Chap. 11: Perez).
- **Improve Latino recruitment into cancer clinical trials.** Latinos are underrepresented in cancer research, data registries, and genomic databases; this disparity can be addressed by improving Latino accrual into clinical trials. Suggestions are to educate physicians to promote enrollment, build awareness among Latinos about the role of clinical trials in improving cancer care, enhance care navigation for treatment planning; and develop language- and culture-appropriate educational materials (Chap. 12: Mesa and Ramirez).
- **Use comorbidities as exclusion criteria only for sound evidence-based reasons.** One of the barriers to Latino accrual in clinical trials is the use of comorbidities such as hypertension and obesity. Carefully determine if these exclusion criteria are necessary and evidence-based (Chap. 21: Croyle).
- **Attract more Latinos into the pipeline for higher education in the health professions and medical school.** Provide opportunities for Latinos to become health professionals or STEM researchers of the future. Try to attract more Latinos into the pipeline for higher education and medical school (Chap. 12: Mesa and Ramirez; Chap. 21: Rios).

Cancer in the Era of Precision Medicine

- **Include more Latinos in precision medicine research.** Genomic and transcriptomic studies are based primarily on tumors from Americans of northern European ancestry. Without adequate representation of patient diversity, precision medicine based on these studies may actually worsen health disparities (Chap. 13: Zabaleta et al.).
- **Consider ethnicity and genetic ancestry when making cancer treatment choices based on gene expression profiles**. For example, luminal breast cancers in Latinos may have distinctive biology due to non-genetic and/or ancestry-linked factors (Chap. 13: Zabaleta et al.).
- **Ensure that Latinos have access to tumor molecular analysis for targeted cancer therapy.** Targeted therapy is recommended as standard of care for colorectal and thyroid cancers. Compared to non-Latino whites, Latinos have

higher incidence rates of these two cancers, so it is crucial that they have access to tumor molecular analysis (Chap. 14: Rodriguez-Rodriguez).

Cancer Outcomes and Survivorship in Latinos

- **Provide access to cancer survivorship care that is linguistically and culturally appropriate for Spanish-speaking Latinos.** Engage Latino communities in design and implementation of behavioral interventions that can be delivered in community settings and are linked to cancer care systems. Investigators can integrate evidence-based programs with community knowledge and best practices to test and disseminate co-developed programs to meet the needs of vulnerable cancer survivors (Chap. 15: Nápoles).
- **Engage multiple stakeholders in patient-centered outcomes research on intervention design.** Research democracy, where all stakeholders—including patients and their caregivers—have a voice and a vote in research decisions, can improve patient-centered outcomes research (PCOR) by promoting team engagement, satisfaction, and awareness of project barriers and benefits (Chap. 16: Kuo et al.).

Engaging Latinos in Cancer Research

- **Engage Latinos in cancer prevention and control research.** Community-level interventions that use community-based participatory research principles and that engage Latinos from the beginning of the research through the dissemination of data have the potential to reduce cancer disparities and save lives. Latina involvement can help researchers develop interventions that include social and cultural assets—essential elements that can help to eliminate disparities in cancer screening, prevention, and control (Chap. 17: Baezconde-Garbanati et al.).
- **Deliver personalized interventions through texting and mobile media services.** This scalable service makes mobile, personalized advice/support affordable; it can reach disadvantaged populations, produce a public health impact, reduce health service costs, and reduce health disparities in Latinos. Effectively used for smoking cessation, text messaging is interactive and can be delivered anonymously wherever the person is located (Chap. 18: Chalela et al.).
- **Design cervical cancer interventions that target cultural factors which may operate at various levels of influence.** Also, broaden the focus of interventions beyond cancer screening to improved sexual and reproductive health. Such interventions can target root causes of disparities and yield sustainable behavior change (Chap. 19: Lechuga and Melo).
- **Use a community-based approach to increase participation of Latinos in biobanking and biospecimen research.** Latinos are underrepresented in

biomedical research and biospecimen banks. One solution is to partner with Latino communities in a culturally appropriate manner; deliver community-based education programs to increase awareness and informed decision-making about biospecimen donation; and use mobile lab units to collect and process biospecimen donations onsite (Chap. 20: Rodriguez and Erwin).

Emerging Policies in US Health Care

- **Researchers who study cancer in Latinos must advocate to Congress for their own work and educate policy makers of its value in helping people and saving lives.** Researchers should be persistent in this effort, because lawmakers deal with many issues in addition to health care and may need reminding to refocus their attention (Chap. 21: Castro, Rios).
- **Protect the Affordable Care Act.** More Latinos than any other group were able to receive insurance coverage because of that act, so researchers and community members must make sure that it is not completely eroded (Chap. 21: Castro and Rios).
- **Address the health effects of environmental quality on cancer and other illnesses.** Some Latino communities are exposed to damaging environmental factors because of weak enforcement in certain states. Be mindful not only of Congress and the federal government but also of state and local jurisdictions (Chap. 21: Castro).
- **Empower non-Latino physician partners with cultural competence to enhance their relationship with Latino patients and their caregivers.** Only a small percentage of physicians are Latino, and the primary care physician can be the number one driver or barrier for proper cancer care and adherence to treatment (Chap. 21: López and Croyle).
- **Foster survivor advocacy within the community.** Involve Latino cancer survivors in advocacy, because the powerful voice of survivors can be leveraged to motivate Latinos to seek cancer screening (Chap. 21: López).
- **Leverage online channels.** The Internet is a powerful channel for Latinos to find information and additional support along the path to treatment (Chap. 21: López).
- **Protect patients through local policy.** Physicians, health care systems, and insurance companies must advocate for the communities they serve. Latinos treated for chronic conditions often experience higher incidence of complication and death than their non-Latino counterparts, so advocacy is important (Chap. 21: López).

Charting the Future of Cancer Health Disparities Research in Latinos

The purpose of this conference was to move beyond documented health disparities in Latinos to set a new agenda for future initiatives that specifically address cancer health disparities and improve outcomes in Latino communities. At the close of the conference, Drs. Trapido (LSU Stanley Scott Cancer Center), Cruz-Correa (University of Puerto Rico Comprehensive Cancer Center), and Stern (University of Southern California) moderated a session entitled *Charting the Future of Cancer Health Disparities Research in Latinos*. The group determined research priority areas based upon the papers presented at the meeting. Attendees were asked to respond to a live poll and select up to three areas they considered top priorities for cancer research in Latinos.

The top five priority areas for cancer research in Latinos for Parts II, III, and IV were ranked from one to five as follows:

1. Larger cohort studies on genetics vs. environment in Latinos to understand health differences.
2. Translate effective lifestyle programs to fit the community context and population.
3. Multinational studies comparing native born in countries of origin vs. United States.
4. Investigate ancestry and infectious agents which cause cancer.
5. Develop and implement interventions for sexual health (i.e., assessment of outcomes, longitudinal designs, standardization).

The top five priority areas for cancer research in Latinos for Parts V, VI, and VII were:

1. Reduce barriers of enrollment for Latinos in clinical trials and include patient reported outcomes and ethnic diversity.
2. Link databases to catalyze biomarker precision medicine and precision oncology.
3. Examine the relationship of genes/pathways to determine metaplasia that might progress to cancer, as well as SNPs in key genes among Latinos.
4. Mitigate the impact of trial globalization on the relevance of medical products/drugs to the Latino community.
5. Evaluate pathways in carcinogenesis in HCC to explore therapies.

The top five priority areas for cancer research in Latinos for Parts VIII and IX were:

1. Conduct long-term follow up in intervention studies.
2. Include more family system-based approaches.
3. Improve integration across disciplines.

4. Get Latinas and other minorities to participate in cancer research and pay it forward.
5. Measure depression better in Latinos.

This publication describes the beginning of much needed research tailored to improve understanding of key contributors to cancer in the Latino population. Recommendations from the conference participants give us a direction for future research that will advance the science of cancer in Latinos and eventually lead to lives saved. And until we reach populations with needed screening, treatment, and improved quality of life for cancer survivors, we will not see a decline in cancer deaths. Reducing the cancer burden in Latino communities takes all of us working together throughout the continuum of cancer.

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Appendix A: Advances in Biology and Treatment of Cancer

Does Metformin Modify Racial/Ethnic Disparity in Hepatocellular Carcinoma?

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Background: Racial/ethnic disparity in hepatocellular carcinoma (HCC) is well-established. However, the extent to which the disparity in HCC is attributed to factors that are independent of the disparity associated with chronic liver diseases (CLD) and type 2 diabetes (T2D) is not clear. This study assessed (1) the race/ethnic disparity in HCC incidence among men with T2D but without CLD and (2) whether the race/ethnic disparity HCC was modified by the use of T2D medication: metformin.

Methods: The study cohort was derived from the electronic medical records in the nationwide Veterans Administration Health Care System. Inclusion criteria: 40–89 years old, male veterans with T2D; without prior diagnosis of cancer, cardiovascular diseases, CLD, or renal diseases; without prescription for insulin or thiazolidinedione. Logistic regression model was used to compare the HCC incidence between race/ethnicity groups under no use of metformin adjusting for covariates and propensity scores for race/ethnicity. The generalizability weighting technique was incorporated in the logistic regression model to assess the heterogeneity in the odds ratio (OR) of HCC associated with metformin use among race/ethnicity groups. Covariates adjusted for in the analyses included study duration, social economic status, use of statins and beta-blockers, age, LDL, HbA1c, BMI, (alcohol related) mental health disorders, abnormal liver functions, obstruction of the gallbladder, cholecystectomy, tobacco-related complications, blood transfusion, and residency location.

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Results: The study cohort consisted of 84,433 men with T2D but without prior CLD; mean follow-up 6.10 ± 2.87 years; 67,065 (79.47%) non-Hispanic white (NHW), 13,125 (15.5%) African American (AA), 4243 (5.03%) Hispanics; mean age 67.8 ± 9.8 years, mean HbA1c 6.57 ± 0.98%, 121 (0.14%) HCC cases, 31,036 (36.76%) metformin users, 65,612 (77.71%) statins users, and 46,961 (55.62%) beta-blocker users. The IOM concordant disparity measures showed that NHW and Hispanic had a similar HCC risk (OR = 0.95 (0.40–2.24)); AA had a 40% lower HCC incidence compared to NHW (OR = 0.60 (0.40–0.92)). Metformin use was associated with an overall 50% reduced HCC risk (OR = 0.49 (0.36–0.66)). Metformin's HCC prevention effect was superior among Hispanics compared to non-Hispanics: OR associated with metformin use was 0.57 (0.40–0.81) for NHW; OR = 0.35 (0.25–0.47) for AA; OR = 0.31 (0.22–0.43) for Hispanics. There was no significant synergistic HCC prevention effect associated with the combination use of metformin and statin ($p = 0.76$). For NHW, metformin's HCC prevention effect did not differ by the average daily dose; for AA, higher average daily dose of metformin was associated with a less HCC prevention effect (ORs associated with ≥1000 mg/day (vs. <1000 mg/day) were 3.48 ($p = 0.001$), 2.68 ($p = 0.02$), and 2.76 ($p = 0.02$) under ≥90, ≥120, and ≥180 days of prescription, respectively); for Hispanics, higher average daily dose of metformin was associated with a greater HCC prevention effect (ORs associated with ≥1000 mg/day (vs. <1000 mg/day) were 0.11 ($p = 0.004$), 0.07 ($p = 0.002$), and 0.07 ($p = 0.002$) under ≥90, ≥120, and ≥180 days of prescription, respectively). Significant covariates for NHW were statin use (OR = 0.44), age (OR = 1.02), comorbidity (OR = 1.35), BMI (OR = 0.98), LDL (OR = 1.01), and poverty (OR = 1.06); significant covariates for AA were comorbidity (OR = 1.56), abnormal liver functions (OR = 5.22), and residing in south Texas (OR = 42.54); significant covariates for Hispanics included statin use (OR = 0.19), beta-blocker use (OR = 0.16), age (OR = 1.13), comorbidity (OR = 1.60), and binge drinking (OR = 7.01).

Conclusion: In men with T2D but without CLD, AA had a lower HCC incidence compared to NHW or Hispanics; HCC incidence was similar between NHW and Hispanics. The similar HCC incidence between Hispanic and NHW observed in this cohort suggested that the ethnic disparity in HCC could be mediated by CLD, T2D, or other unmeasured factors. The superior HCC prevention effect of metformin use among Hispanics could be attributed to the pharmacogenomic heterogeneity. The differential HCC prevention effects by metformin, statins, and beta-blockers among race/ethnic groups shed some light on the potential interventions to reduce race/ethnic disparity in HCC.

Oxidized Low-Density Lipoprotein Is a Potentially Potent Mediator of Proteasome Inhibitor Resistance in Obese Multiple Myeloma Patients

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Background: Multiple myeloma (MM) is a malignancy of plasma cells that accumulate in the bone marrow. While treatment advances, particularly proteasome inhibitors (PIs) and immunomodulatory drugs have improved survival, MM is incurable. Latinos have the worst overall survival compared with other racial-ethnic groups. Obesity is an established risk factor for MM mortality, and because it is rampant among Latinos, it may play a role in contributing to this survival disparity. Oxidized low-density lipoprotein (OxLDL), a key atherogenic factor that is elevated in obesity, has emerged as a risk factor for the development and progression of some solid cancers, and it has been shown to stimulate pro-oncogenic signaling; its role in MM is unexplored. We evaluated the influence of OxLDL on MM cell killing by chemotherapeutics used to treat MM. OxLDL, at concentrations within the range reported for patients with metabolic syndrome, suppressed MM cell killing by the therapeutic PIs bortezomib and ixazomib. Native LDL (nLDL) did not affect the anti-MM effects of these PIs, which suggests that the oxidative modification of lipids or apolipoprotein in OxLDL are the mediators of cytoprotection. OxLDL did not affect MM cell killing by other agents with distinct targets such as the immunomodulatory drug lenalidomide and doxorubicin. OxLDL appeared to restore proteasome activity as evidenced by its suppression of bortezomib-induced accumulation of ubiquitinated proteins and pro-apoptotic unfolded protein response signaling. The cytoprotective effects of OxLDL were suppressed when lipid hydroperoxides (LOOHs) associated with the lipoprotein were specifically reduced by pretreatment with the glutathione-dependent selenoperoxidase mimetic Ebselen. Finally, immunohistochemical analysis of bone marrow biopsy samples from newly diagnosed MM patients demonstrated the presence of OxLDL in macrophages/histiocytes scattered among MM cells. Our findings suggest that OxLDL may be a potent mediator of chemoresistance to therapeutic PIs in obese MM patients. OxLDL appears to counteract the anti-MM effects of PIs through LOOH-mediated restoration of proteasome activity. Our findings raise the potential benefit of LDL cholesterol-lowering therapy, or pharmacological targeting of intracellular pathways used by OxLDL, to increase the efficacy of therapeutic PIs and improve the survival of obese MM patients.

Mechanisms of Radioprotection in Intestinal Stem Cells

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Introduction: Pancreatic cancer is one of the leading causes of cancer mortality in developed countries and one of the most lethal malignant neoplasms across the world with an overall 5-year survival rate of 6%. The reasons being because there are no current screening recommendations, it is diagnosed at later stages, and it presents a challenge for treatment. For radiation treatment, this challenge arises because of the anatomical position of the pancreas in relation to the small intestine. Unfortunately, radiation therapy to the pancreas can lead to toxicity of the duodenum with lethal consequences. Studies demonstrate HIF2 is radioprotective when expressed in all GI epithelial cells. But further studies are needed to demonstrate that HIF2 might have key mediators in this protective mechanism. Interestingly, it has been shown that Wnt ligand was required for crypt regeneration after injury in mice. This work attempts to study the mechanisms of regeneration of intestinal stem cells post radiation through Wnt regulated pathways.

Methods: Intestinal stem cells are harvested from mice and pass through a series of washes using PBS with EDTA, HBSS with EDTA, and Wash Media. A mixture of Matrigel and crypt stem cells is produced for plating in 12-well plates. Conditioned medium is prepared from L-WRN cells and added to each well. The conditioned medium is changed every 2 days. To study the mechanisms of radioprotection of intestinal stem cells, crypt organoids were infected with Cre adenovirus to delete Wnt gene and irradiation was performed using 6 Gy. Then, recombinant Wnt was added to the conditioned medium, and differences in dose concentration were compared (rWnt: 10,600 and 1200 ng/mL).

Results: Wnt provides protection after radiation treatment to stem cells, and it is concentration dependent. Twenty-four hours after radiation, there was no growth in the 6Gy + adCre+ organoids and an increase in growth in correlation to rWnt concentration.

Conclusions: This preliminary data support our hypothesis that Wnt proteins are required for intestinal epithelium regeneration and repair after radiation. Additionally, it demonstrates that this growth is concentration dependent. These results provide information for intestinal epithelium regeneration pathways and could potentially lead to future treatments for intestinal protection against radiation to the pancreas.

Future Work
- Optimization of experiments for accurate quantification of cell survival
- Study the role of Wnt receptors in the protective mechanism
- Perform RNA profile studies and promoter analysis for key Wnt targets

Genetic Markers for Treatment-Related Pancreatitis in an Exclusive Cohort of Hispanic Children with ALL

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Background: Treatment-related pancreatitis (TRP) is a rare but serious complication impacting up to 18% of children with acute lymphoblastic leukemia (ALL). Those affected risk severe organ toxicity and treatment delays impacting outcomes. TRP is associated with asparaginase, a backbone therapeutic agent in childhood ALL. Native American ancestry, older age, high-risk leukemia, and increased asparaginase are linked to pancreatitis risk. However, dedicated gene studies evaluating pancreatitis in childhood ALL include few Hispanics. Thus, there remains a gap in understanding the genetic basis for pancreatitis risk among Hispanic children with ALL.

Methods: We reviewed children with ALL treated over a 20-year period in South Texas (1994–2013) and identified 14, all Hispanic, who developed pancreatitis related to asparaginase therapy. Forty-six Hispanic controls, children treated on the same regimens without pancreatitis, were selected for comparison. Total DNA isolated from whole blood was utilized for targeted DNA sequencing on 23 selected genes including those known to be involved in pancreatitis in other populations and those involved in asparagine metabolism.

Results: Non-synonymous polymorphisms and frameshift deletions were identified in 15 genes with most TRP cases demonstrating variants in ABAT, ASNS, and CFTR. Notably, leukemic children with pancreatitis harbored increased CFTR variants (71.4%) over controls (39.1%). Among these, V470M (rs213950) was most frequent (OR 4.27, $p = 0.029$).

Conclusion: This is the first study of genetic factors in treatment-related pancreatitis for Hispanic children with ALL. Identifying correlative variants in ethnically vulnerable populations may provide an innovative screening method to identify those at greatest risk for pancreatitis.

Bladder Cancer Cell-Intrinsic PD-L1 Signaling and Its Influence on the Bladder Microenvironment

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Background/Introduction: Nearly 80,000 new cases of bladder cancer (BC) are diagnosed in the US annually. A primarily carcinogen-driven cancer, certain occupational and environmental exposures are known significantly affect BC incidence. BC also has the highest lifetime treatment costs per patient of all cancers, owing in part to its high recurrence rate. BC particularly affects Latinos because of the high prevalence of Latino workers in construction, agricultural, and cleaning/maintenance positions, putting them at risk for persistent BC carcinogen exposure, along with the potentially lower income (and thus diminished healthcare access) that can be associated with these positions.

The carcinogen-induced progression that results in BC formation increases the tumor mutational burden, which can increase the likelihood of response to immune-based therapies. The newest immunotherapies in the treatment of BC target the programmed death-1 receptor (PD-1) and one of its ligands programmed death ligand-1 (PD-L1), and specifically anti-PD-L1 (αPD-1) and αPD-L1 antibodies have shown durable responses, yet only 10–30% of patients respond. Optimal predictors of response are yet to be elucidated, with expression of target molecules (e.g., PD-L1) serving only as incomplete markers of treatment response.

Previous immunotherapy studies have focused on the extrinsic effects of tumor PD-L1 and T-lymphocyte PD-1 interaction. Seminal work from our group has recently reported tumor cell-intrinsic PD-L1 effects on cancer immunopathology and immunotherapy in multiple cancer types. As we have previously shown the importance of the tumor microenvironment in cancer immunotherapy outcomes, we tested the hypothesis that BC cell-intrinsic PD-L1 and PD-1 signals drive bladder microenvironment-specific immunity and influence BC immunotherapy responsiveness.

Methods: We used transplantable MB49 BC cells that we engineered to be PD-L1 null and a carcinogen (BBN)-induced BC model to study BC tumor cell PD-L1. We used fluorescence-activated cell sorting, Western blots, PCR, Luminex protein detection, and histopathology to assess environmental factors and effects of tumor PD-L1. MB49 tumors were engineered to express luciferase to measure tumor growth in vivo. Human BC tissues were also studied.

Results: Our preliminary results suggest that the unique bladder immune microenvironment influences immunotherapy treatment outcome in BC through the effects of T cells, natural killer cells, and interferon-γ among other factors. BC-intrinsic PD-L1 signals affected mTOR, autophagy, and chemokines distinctly from other cancers. Ongoing work is assessing effects on treatments.

Conclusion/Significance/Impact: Data from this work can be used to improve BC immunotherapy. We hope to use our data as the launching point from which to pursue clinical testing with Latino BC patients in San Antonio and South Texas, filling a major unmet medical need to include Latinos in the rapidly advancing world of cancer immunotherapy.

Ancestry-Associated Molecular Portraits of Luminal Breast Cancer in Hispanic/Latinas May Have Prognostic and Therapeutic Implications

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Hispanic/Latino (H/L) populations are a genetically admixed and heterogeneous group, with variable fractions of European and Indigenous American and African ancestries. Although breast cancer incidence tends to be highest among non-Hispanic whites (NHW) and African Americans, some studies suggest that breast cancer-specific 5-year survival rate in US H/L is lower than in NHW after adjustment for socioeconomic status and education. This may be due to numerous factors, including access to optimal care and the effect of comorbidities such as obesity and diabetes. Additionally, there remain significant knowledge gaps on the biology of breast cancer in minorities including H/L. The molecular profiles of breast cancer have been extensively examined in NHWs but equivalent knowledge is lacking in Hispanic/Latinas. Importantly, we know little about the validity of gene expression-based

molecular tests used to classify breast cancers and predict outcomes in genetically admixed H/L patients. We have previously reported that the most prevalent breast cancer-intrinsic subtype in Colombian H/L women was luminal B as defined by surrogate St. Gallen criteria. Luminal B tumors tend to have poorer prognosis and develop endocrine resistance more frequently than their luminal A counterparts. More recently, we explored ancestry-associated differences in molecular profiles of luminal B tumors among highly admixed Colombian H/L women. Using whole transcriptome analysis and a set of ancestry-informative markers selected to be most informative in H/L patients, we identified genes potentially modulated by genetic ancestry: ERBB2, GRB7, GSDMB, MIEN1 and ONECUT2. ERBB2, GRB7, and MIEN1 are contiguously located in a region of chromosome 17q that is frequently amplified in HER2-enriched breast cancers. Expression of ERBB2 (Her2/Neu) is associated with endocrine resistance in luminal cancers. We also observed statistically a significant association of ERBB2 expression with Indigenous American ancestry ($p < 0.001$, $B = 3.82$). Our results suggest that genetic ancestry in Hispanic/Latina women may modify ERBB2 gene expression in luminal breast cancers. These results suggest that ERBB2, a gene responsible for endocrine resistance in a significant fraction of luminal breast cancers, may be more likely to be highly expressed in women with higher Indigenous American ancestry. As ERBB2 is a therapeutically important gene, which encodes the target of trastuzumab and other Her2-targeted agents, these findings may have important therapeutic implications in Hispanic patients with luminal breast cancers. Additionally, we observed considerable discordance between immunohistochemistry and PAM50-assigned intrinsic subtypes in our patient population. Only 50% of the patients identified as luminal B by immunohistochemistry were accurately classified as luminal B by PAM50. Yet, their clinicopathological features and outcomes were consistent with luminal B classification in other ethnic groups. Thus, our data suggest that commonly used breast cancer molecular tests should be validated in diverse populations including sufficient numbers of Hispanic/Latina patients. Given the considerable genetic heterogeneity of Hispanic/Latinos, more studies are necessary to confirm these findings in patients from the USA and other Central and Southern American countries.

Latinas and Breast Cancer: Discovery of Mutations in Non-BRCA1/2 High- and Moderate-Penetrance Breast Cancer Susceptibility Genes

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Background: Breast cancer (BC) is the leading cause of cancer deaths among Hispanic women, who represent the largest and fastest-growing minority population in the USA, yet genetic susceptibility to BC has been largely understudied. BRCA1 and BRCA2 (BRCA) mutations explain approximately 25% of familial BC, and the proportion associated with other BC susceptibility genes is unknown. We determined the rate of mutations in 12 additional BC susceptibility genes among Hispanic women who tested negative for BRCA mutations.

Methods: BRCA-mutation-negative Hispanic women with familial BC (diagnosis of BC under age 50 years, bilateral BC, or both breast and ovarian cancers, and/or with at least two first- or second-degree relatives diagnosed with BC under age 70 years) were selected from participants in a large registry and whole exome sequencing was performed. We analyzed data for 12 known and suspected high- and moderate-penetrance BC susceptibility genes (ATM, BRIP1, CDH1, CHEK2, NBN, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, and TP53).

Results: We identified 51 (4.8%) pathogenic or likely pathogenic variants (PV) in 48 of 1058 (4.6%) participants, including 21 frame shift leading to truncation, 19 missense, 5 nonsense, and 7 splice site variants. The distribution genes with PVs were PALB2 ($N = 18$), CHEK2 (20), ATM (6), and BRIP1(2), TP53 (2), and CDH1, NF1, PTEN, and STK11 (all $N = 1$). No PVs were observed in NBN, RAD51C, or RAD51D. Nine participants carried the same PALB2 PV ($n = 8$; 1.1%) and 14 carried the same CHEK2 PV.

Conclusions: Of the 1058 BRCA-negative high-risk Hispanic women, 4.6% carried a PV in a BC susceptibility gene. Recurrent PVs in PALB2 and CHEK2 were the most frequent findings, representing 45% (23/51) of all PVs; the recurrent mutations likely are due to founder events. PVs in ATM were seen less frequently than in non-Hispanic white populations.

The Role of *Six Transmembrane Epithelial Antigen of the Prostate 2* in Hepatocellular Carcinoma

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Introduction: Hepatocellular carcinoma (HCC) is the most common type of liver cancer in adults and the third most common cause of cancer death worldwide. Its incidence and mortality rates are two times higher in Latinos than those in the US general population with the highest incidence rate among Latinos in the South Texas region. The molecular etiology associated with the increased incidence of HCC in this population is largely unknown. We performed whole genome RNA sequencing in paired HCC tumor and adjacent nontumor tissue total RNA from nine South Texas Latino patients. Analysis of differentially expressed genes revealed significant alterations in pathways associated with oxidative stress; most importantly, we found that the expression of STEAP2 (Six Transmembrane Epithelial Antigen of the Prostate 2) is increased fivefold in HCC tumor tissue compared to adjacent-normal tissue. In comparison to a non-Latino population, this finding was unique to South Texas Latinos. STEAP2 is a metalloreductase of iron and copper; reduced iron and copper ions can mediate the production of hydroxyl radicals resulting in increased oxidative stress, which can cause DNA damage and lipid peroxidation. We aim to prove that STEAP2 through the regulation of iron and copper homeostasis, and an increase in oxidative stress, will lead to malignant progression of HCC, including obese hosts.

Materials and Methods: Hispanic paired HCC and adjacent normal tissues were collected for RNA sequencing, metal ion measurement, and oxidative stress markers. STEAP2 RNA and protein expression levels in Hispanic and Caucasian samples were evaluated by RT-PCR, Western blot, and immunohistochemistry. HCC cell lines (SNU398 and HUH7) with knockdown (KD) and overexpression (OE) of STEAP2 were created to examine the proliferation, migration, anchorage independent growth, and oxidative stress in vitro.

Results: Analysis of RNA sequencing data demonstrated the overexpression of STEAP2 in HCC tumors in Hispanic patients, which were validated by RT-PCR and Western blot data. Lipid peroxidation product, 4-hydroxynonenal, and copper levels were higher in HCC tumor vs. adjacent tissue. KD of STEAP2 in the HCC cell lines decreased proliferation, migration, and anchorage-independent growth, while OE of STEAP2 increase migration and anchorage-independent growth but not proliferation in 2D culture.

Conclusions: STEAP2 is specifically overexpressed in HCC tumors in Hispanics in comparison to HCC tumors in non-Hispanic whites and appears to play a malignant-promoting role in HCC cells. Further studies on the role of STEAP2 as a novel tumor promoter in HCC and the mechanisms by which it promotes carcinogenesis are underway. The proposed studies will likely yield mechanistic insights into the molecular mechanisms that drive HCC development and progression in South Texas Hispanics and potential therapeutic targets.

Aberrant Epigenomic and Functional Regulation of Endometrial Cancer Intercellular Communication in Young, Obese Latino Patients

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The incidence of obesity-related endometrial cancer is increasing in our catchment area, Bexar County, and vicinity in South Texas. Strikingly, we observed a sharp rise of this disease in Hispanic Latinos between 2005 and 2014, bringing the number of diagnosed endometrial cancer cases higher than whites, in contrast to the previous 10 years. In addition, the death rate in our catchment area was higher than the national mortality rate. Further highlighting this disparity is that based on the Texas Cancer Registry, Cancer epidemiology and Surveillance Branch, the age at diagnosis of Hispanics (mean age ~50 years) in our catchment area is much lower than non-Hispanic whites (mean age ~60 years). In this study we examine the epigenetics, molecular etiology, and functional biology underlying this unique endometrial cancer in young obese Hispanic patients.

Emerging evidence suggest that adiposity-associated endometrial tumorigenesis may be driven in part by adipose stromal cells (ASCs), which are resident precursor cells to adipocytes in fat tissue. ASCs may exert their oncogenic effects, which are associated with inflammation, on endometrial tissue through paracrine actions, as some evidence suggest ASCs are trafficked to tissue sites via chemokine actions. To simulate ASC paracrine actions on endometrial epithelial cells (EECs), we preformed co-culture studies exposing EECs to ASCs over a 3-week period. Expression profiling revealed extensive transcriptome changes in EECs exposed to ASCs compared to control EECS (no ASCs). Bioinformatics analysis revealed a significant repression of gap junction (GJ) genes and related genes involved in the regulation of gap junctions. Gap junctions are intercellular channels that allow for electrochemical communication by transfer of small molecules and ions between cells. Deregulation of gap junctions has been shown to be involved in oncogenesis. Our studies show that gap junction activity in endometrial cancer cells is stunted, which can be restored by epigenetic modification, namely treatment with DNA demethylation agents. This treatment also led to restoration of gap junction plaques on the cell surface of endometrial cancer cells, which was predominantly intracellular without treatment. As DNA methylation is a marker of gene silencing, which affects tumor suppressor genes during tumorigenesis, we examined DNA methylation

patterns in Latino Hispanic endometrial cancer patients in Bexar County (average age 42 years) compared to a Midwestern cohort of predominantly white patients (average age 60 years). The data reveal distinct and significant elevation of DNA methylation in the main gap junction gene GJA1 and a gene coding for a regulator kinase (PRKCA) in the young Hispanic cohort.

Additionally, when accounting for comorbidity, both GJA1 and PRKCA exhibited higher methylation levels in obese compared to nonobese patients in the Hispanic cohort. This distinction was not evident in the Midwestern cohort. Our data suggest that deregulation of GJA1 gap junction cellular communication by epigenetic means is a marker for obesity-associated endometrial cancer in young Latino patients in South Texas. Further studies are needed to assess if this is applicable to other Latino populations in the USA.

Novel Use of Estrogen Receptor-β Agonists in the Treatment of Endometrial Cancer Cell Lines

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Introduction: Endometrial cancer (EC) is the most common gynecologic malignancy in the country, with increasing incidence in premenopausal obese patients. In breast cancer, it has been previously reported that ER-β agonists exert antitumor activity. ER-β agonists are also being studied for the treatment of vasomotor symptoms, ovarian cancer, and brain cancer. However, the role of ER-β in the endometrium and in EC is only theorized. Therefore, we evaluated the effectiveness of the ER-β agonists: S-Equol, LY500307 (LY), and Liquiritigenin (LIQ) on two commercially available human endometrial cancer cell lines. We developed two unique models in which we sought to emulate the premenopausal and postmenopausal endometrial environments. Using media with fetal bovine serum (FBS) known to contain estradiol, we emulated the premenopausal environment, and for the postmenopausal environment, we used media with charcoal-stripped serum (CSS) devoid of estradiol.

Methods

Endometrial cancer cell lines: Premenopausal: Ishikawa (ECACC 99040201). Postmenopausal: RL952 (ATCC® CRL1671™).

Cell culture: Cells were maintained in phenol red-free minimum essential media α (MEM α) supplemented with 1% penicillin/streptomycin and either 10% FBS or 10% CSS. Cells using CSS media were incubated 48 h prior to treatment.

Cell proliferation and vitality assay: Cells were grown in 96-well plates at a density of 5×10^3 cells/well. Cells were treated with various concentrations of S-Equol, LIQ, and LY. Cell viability was detected by MTT assay at 48 and 96 h after treatment. Proliferation rate was obtained by measuring the changes in absorbance at 595 nm. Optical density was measured by a 96-well microplate reader.

Statistical analysis: Graphpad Prism version 5 (SPSS, Inc., Chicago, IL, USA) was used. Paired *t*-test was used for normally distributed data. Differences were considered statistically significant at $p < 0.05$.

Results: Premenopausal cell line Ishikawa expressed ER-α and ER-β protein. Under premenopausal (estrogen rich) conditions, both cell lines exhibited antiproliferative response to all three ER-β agonists. In postmenopausal (estrogen devoid) conditions, the premenopausal cell line Ishikawa displayed antiproliferative activity with S-Equol and LY while postmenopausal cell line RL952 exhibited no antiproliferative response to any ER-β agonists. LIQ exerted no significant effect on either cell line in the postmenopausal model.

Conclusion: This is the first study to suggest a differential effect of ER-β agonists based on menopausal status. We hypothesize that ER-β has a greater effect in an estrogen rich (premenopausal environment). Results using a postmenopausal environment showed greater variability to ER-β agonists, particularly in the postmenopausal cell line. Studies in our lab showed high level of expression of ER-β in premenopausal EC cancers. ER-β agonists appear to exert stronger antiproliferative effects under premenopausal conditions, our data suggests that ER-β signaling may be less effective in the hypoestrogenic postmenopausal environment.

Intratumoral Environment of Premenopausal Endometrial Cancers in South Texas Hispanic Patients

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Introduction: There is a high incidence of endometrial cancer (EC) in young Hispanic women residing in South Texas. EC is a devastating disease in young women who desire childbearing ability. Medical management with progestin therapy is rarely effective treatment. Recent evidence has shown that cancers have a unique intratumoral environment which allows them to make their own growth factors. In this study we sought to characterize the intratumoral environment of EC in a cohort of premenopausal patients.

Methods: The study included 114 surgical specimens from women aged 25–50 years; of which 74 had a diagnosis of EC and 40 had benign pathology (controls). Clinical data were abstracted from the EMR. Immunohistochemistry was used to evaluate the expression of estrogen receptors α and β, progesterone receptors A and B, progesterone receptor B alone, aromatase, TNF-α, IL-6, IGF-1, IGFR-1, and IGFBP-1. Scores were assigned for proportion (0–5) and intensity of staining (0–3), then a total score was determined (0, 2–8). Statistical analysis was carried out using Kendall rank correlation coefficient and Kruskal–Wallis test as appropriate. $P < 0.05$ was considered significant.

Results: All patients were of Hispanic ethnicity. Average age was 42 years with a mean BMI of 40 kg/m^2. The majority of cancers were type 1. ERα and β had high levels of expression in cancers, 68.5% and 60.5%, respectively. TNF-α had increased expression in the cancers as compared to controls, $P = 0.001$. Furthermore, TNF-α expression was positively correlated with the expression of aromatase and ERβ, $P = 0.002$ and 0.05, respectively. IL-6 expression was also positively correlated with the expression of ERβ, $P < 0.001$.

Conclusion: EC in this young, obese cohort had high levels of expression of hormone receptors, aromatase, and the inflammatory cytokines TNF-α and IL-6. Overexpression of intratumoral TNF-α may be a driver of carcinogenesis through the induction of aromatase and subsequent increase in local estrogen production. Expression of both TNF-α and IL-6 correlated with increased expression of ERβ. Increased levels of ERβ have been associated with good prognosis in EC, suggesting a possible antiproliferative effect. The role of ERβ agonists in the treatment of premenopausal EC is an area of active research.

Effect of Estrogen Receptor-β Agonist in the Treatment of Endometrial Cancer

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Introduction: The correlation between obesity and type 1 endometrial cancer (EC) is of particular importance in the Latino community given the high obesity rates, particularly in premenopausal patients. This has led to an increase in the incidence of EC. The role of ER-β in the endometrium and in EC is currently unclear and only theorized. Following our previous research, we decided to evaluate the effectiveness of the ER-β agonist: LY500307 (LY) and the aromatase inhibitor letrozole (LET) independently and in combination with human endometrial cancer tissue. We used media supplemented with fetal bovine serum (FBS) known to contain estradiol or with charcoal-stripped serum (CSS) known to be devoid of estradiol.

Methods

Human endometrial cancer: EC was obtained from the UTHSA Ob-Gyn department tumor bank following guidelines established by the UTHSA and the University Hospital System IRB.

Tissue media: Phenol red-free RPMI media were prepared, one with 10% FBS and the other with 10% CSS. Each was supplemented with 1% anti-anti (antibiotic antimycotic), 1% sodium pyruvate, 1% sodium bicarbonate, and 0.1% insulin. In addition, CSS containing media was supplemented with androstenedione 100 nM before treatment.

Tissue maintenance and processing: Once obtained, the fresh EC was divided into eight triplicates and plated in two different 24-well plates on gelatin sponges and incubated in prepared FBS media for 24 h. After 24 h, plate 1 was kept with FBS and treated with LY 5 μM, LET 1 μM, and combination, then incubated for 72 h. Plate 2 was then changed to CSS containing media and incubated for 48 h prior to treatment. Post incubation, androstenedione was added to plate 2 and then treated with LY 5 μM, LET 1 μM, and combination, then incubated for 72 h. Post treatment, both sets were evaluated using immunohistochemistry and examining the expression of ER-α, ER-β, PR, aromatase, and Ki-67.

Scoring: Scoring was based on percent total stain. Classified as weak (<30%), moderate (30–60%), and strong (>60%).

Results: Tissue supplemented with FBS and CSS both had increased ER-β expression when treated with LY. We observed a decreased expression of ER-α in the FBS and CSS group of 40% and 50%, respectively, when treated with the same compound and compared to controls. Ki-67 expression was stronger in the group supplemented with CSS when compared to FBS and controls.

Conclusion: Preliminary results suggest that ER-β activation might have an effect on downregulation of ER-α on endometrial cancer, as evidenced by the decreased expression of ER-α in both groups (FBS and CSS). Ki-67 expression was increased in tissue with CSS + androstenedione suggesting that precursors to estradiol will have a greater effect on proliferation versus estradiol supplementation. This may indicate that paracrine stimulation of endometrial cells rather than endocrine stimulation could lead to proliferation.

Appendix B: Cancer Epidemiology and Prevention

The Incidence of Endometrial Cancer in Bexar County Hispanics Is Increasing at an Alarming Rate

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Introduction: South Texas has a large Hispanic "minority" population which raises the concern for poorer health outcomes. We sought to determine the demographic and geographic factors underlying the racial disparity in the incidence of endometrial cancer (EC) in South Texas.

Methods: We queried the Texas Cancer Registry (TCR) which is a state-wide population-based tumor registry. We searched the TCR for all cases of uterine cancer from 1995 to 2010 and abstracted data on cancer incidence, race, age at diagnosis, county of diagnosis, and year of diagnosis. We accessed the Texas Behavioral Risk Factor Surveillance System (BRFSS) which provides data on obesity, diabetes, physical activity, sleep, drinking and driving, tobacco, and alcohol use, and other health-related issues by year and county of origin.

Results: Data from 2008 to 2012 indicates that the incidence of uterine cancer in Hispanic females increased by 2.3%, second only to liver and bile duct cancer. From 1995 to 2010 the incidence of EC in Bexar for Caucasians decreased from 22.7 to 21.1 per 100,000. During the same time period, the incidence of EC in Hispanics increased from 18.7 to 25.4 per 100,000. Data from the BRFSS looking at risk factors for EC found a marked disparity between Caucasians and Hispanics in multiple areas including increased incidence of obesity and diabetes, as well as lower education levels and socioeconomic status (SES).

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Conclusion: Hispanics in Bexar County currently have an incidence of EC which exceeds that of Caucasians and is rapidly increasing. We have identified an unequal distribution of modifiable risk factors for EC in Hispanics including obesity, diabetes, low education level, and low SES. This marked racial disparity warrants dedicated social and political efforts as many of these risk factors are modifiable.

Implementing Hepatitis C Screening and Treatment of Minority, Uninsured Baby Boomers: Best Practices in HCC Prevention Through the Chronic Care Model

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Background: Hepatitis C virus (HCV) is the leading cause of hepatocellular carcinoma (HCC), the most common type of primary liver cancer. Mortality from liver cancer along the Texas–Mexico border is among the highest in the USA. HCC can be prevented with direct-acting antiviral therapy, emphasizing the need for early detection and treatment of HCV. The US Preventive Services Task Force endorsed one-time screening in patients born in 1945–1965 (baby boomers, BBs). However, screening rates have risen only slightly in the 5 years since guidelines were published. Furthermore, most BBs diagnosed with chronic HCV fail to complete the care continuum to cure. Novel integrative models of care are needed to diagnose and treat HCV in order to prevent HCC, especially for uninsured populations that lack access to care.

Methods: Through an 1115 Medicaid Waiver, the chronic care model (CCM) for HCV screening and care was implemented in two Rio Grande Valley federally qualified health centers in FQHC1 and FQHC2 serving Hispanic, uninsured patients. The CCM included (1) electronic medical record redesign to support screening; (2) registry to monitor chronic HCV patients; (3) quality reports; (4) team-based care by a physician champion, licensed vocational nurse, and social services; and (5) personalized patient education with navigation. A specialist provided distance support for onsite management of chronic HCV. For the uninsured, all tests were funded, and free therapy provided through pharmaceutical assistance programs. Data are presented from October 2014 to June 2017.

Results: FQHC1 screened 3001 (71.2%) of 4189 eligible BBs while FQHC2 screened 5051 (34.0%) of 14,866. FQHC1 identified 49 BBs with chronic HCV and 61 in FQHC2; at both sites >93% received education. In FQHC1 28 (77.6%) of

chronically infected BBs received FIB-4 staging, 35 (71.4%) had specialist review, 22 (44.9%) were treated, and 19 (38.8%) cured at 12 weeks posttreatment. In FQHC2, these figures are 32 (52.5%), 36 (59.0%), 13 (21.3%), and 12 (19.7%). Notably, all patients who initiated treatment successfully completed it and were confirmed cured at 12 weeks posttreatment.

Implications: Both FQHCs outperformed national rates of HCV screening and care. Facilitators to higher performance in FQHC1 than FQHC2 include greater staff continuity, higher-quality EMR, centralization of services, and increased social services support. These data suggest that the CCM offers a valuable infrastructure for implementing HCV preventive care; however, coverage for tests and treatment is needed for the uninsured. Lessons from this program should be evaluated in other settings serving vulnerable populations with higher HCV prevalence.

Hepatocellular Carcinoma Prevention in the High-Risk Region of South Texas Through Baby Boomer Screening for Hepatitis C and Linkage to Care

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Introduction: Texas has the highest age-adjusted incidence of hepatocellular carcinoma (HCC) in the USA. One-time screening of baby boomers (BBs, born in 1945–1965) has been endorsed by the US Preventive Services Task Force to prevent HCC and liver disease. Over half of incident HCC cases in Texas are in South Texas (S TX) where most residents are Hispanic and many uninsured. Because treatment of hepatitis C infection (HCV) reduces the risk of HCC, S TX is a priority location for novel approaches to implement HCV screening and linkage to care.

Methods: From June 1, 2016 to August 31, 2017, a program for HCV screening and treatment was operationalized in 19 primary care practices within four S TX clinic systems. The program includes electronic medical record (EMR) modification; clinician/staff training; patient education; coverage of testing for uninsured; anti-HCV antibody testing with reflex HCV RNA testing; case management; and telehealth specialty support for onsite direct-acting antiviral (DAA) therapy. We compare results of anti-HCV screening and RNA testing for chronic HCV across the four systems.

Results: The clinic system with the highest rate of screening had 275 eligible BBs and tested 209 (76%) while the clinic with the lowest had 2336 eligible BBs and tested 374 (16%). Anti-HCV+ rates for screened BBs ranged from 5% to 15%. Overall for all sites, 78% of anti-HCV+ BBs had follow-up RNA testing. Among all 1462 anti-HCV tested BBs, 121 (6%) were RNA+ (chronic HCV), varying from 2% to 10% by system. Characteristics of BBs with chronic HCV included: mean age 57 years, 80 (66%) men, 71 (59%) Hispanic, and 68 (56%) uninsured. Primary care clinicians received telementoring by a specialist to deliver DAA therapy onsite. As of August 31, 2017, 12 BBs completed DAA therapy, 14 were on treatment, 13 had had a telehealth review, and 29 were having data collected for review.

Conclusion: In four S TX clinic systems serving low income patients, 16–72% of eligible HCV BBs were screened for HCV, all exceeding the reported national rate (13%). The yield of screening was high, with 6% of all screened patients diagnosed with chronic HCV. Of all 121 BBs diagnosed with HCV, 21% have been or are being treated and 35% in the process of gaining access to treatment.

Using a Culturally Tailored Narrative to Increase Cervical Cancer Detection Among Spanish-Speaking Mexican American Women

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Background: Hispanic women are more likely to develop and die from cervical cancer than non-Hispanic whites. Factors contributing to disparities in morbidity and mortality from cervical cancer between Hispanic and non-Hispanic white women include low levels of knowledge, limited access to healthcare services, and barriers that lead to failure to adhere to screening guidelines or inappropriate follow-up. Culturally targeted interventions are needed that promote the benefits of early vaccination against the human papillomavirus (HPV) and of the utilization of the Pap test, among women over 26 years of age, who no longer qualify for HPV vaccination.

Methods: A randomized controlled telephone trial that surveyed the effectiveness of two films on cervical cancer-related knowledge, attitudes, and behaviors of Mexican origin women in Los Angeles County was conducted by a team of multidisciplinary investigators. A sample of 300 women aged 25–45 years who spoke Spanish were recruited using random digit dialing (RDD) procedures. Participants were randomly assigned to view either a narrative (Tamale Lesson) or a non-narrative 11 min film

(It's Time) that contained information about cervical cancer prevention via the HPV vaccine and early detection via regular screenings. Data was collected by phone at baseline, 2 weeks after, and 6 months after viewing either film. Descriptive statistics were performed to analyze and summarize demographic and health information. Analysis of covariance will be conducted to examine if there was a main effect on cervical cancer-related knowledge, attitudes toward Pap tests and HPV vaccine, and behavioral intentions of getting a Pap test based on film condition (narrative vs non-narrative), after adjusting for specific variables. We hypothesize that women who view the narrative film will have increased knowledge, more positive attitudes, and increased behavioral intention to get a Pap test than the identical information presented in a nonnarrative film.

Results: A total of 140 women completed the three surveys. At baseline, 74% of the women were foreign born, 30.1% had some college education, 30.5% had a high-school education, and 39.3% had completed less than high school education. 62.1% of the women were married, and 42.1% of the women were employed either full- or part-time. Over 66% of the women found the narrative film to be either excellent or very good; 49.6% of the women stated they learned something about Pap tests; 45.9% of the women stated they learned something about the HPV vaccine; 51.5% stated they learned something about cervical cancer in general.

Conclusion: Findings support the use of a culturally tailored narrative/storytelling to inform and engage high-risk women in cancer screening. This contributes substantially to a better understanding of how to both facilitate and maintain behavior change. A narrative format is a useful tool for eliminating cervical cancer health disparities, and a preferred tool over fact based, non-narrative, especially among less acculturated Spanish-speaking women. These findings have implications for health education delivery methods, helping to save lives.

"Nuestra Pareja" [Our Partner]: Together Against Cervical Cancer: Interim Results

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Introduction: Cervical cancer incidence and mortality are higher for Hispanic women in Texas compared to non-Hispanic whites (13.9 vs. 8.2 per 100,000). The majority of deaths are preventable through early detection and screening. Cervical cancer screening is recommended every 3 years for women 21–65 years old and HPV co-testing starting at age 30 years every 5 years. However, Hispanic women in Texas are under screened. Reported barriers to cervical cancer screening among Hispanic women include cultural beliefs, socioeconomic status, education level, limited English proficiency and health literacy. We seek to investigate the links between health literacy, socio-demographic variables, access and utilization of care, culture, and language related to cervical cancer screening practices among Hispanic women.

Methods: A mixed-method community-based study using focus group interviews and survey data with Hispanic males and females is being conducted. Using the Paasche-Orlow and Wolf (2007) model linking health literacy to health outcomes, we aim to identify individual level factors that influence cervical cancer screening behaviors. Focus group discussions were led by bilingual/bicultural researchers, audio-recorded, and transcribed verbatim. Survey data includes cervical cancer knowledge, attitudes, beliefs, self-efficacy, health literacy, and acculturation.

Results: Eleven focus groups and 100 surveys (n = 74 females and n = 26 males) have been collected thus far with Hispanic males and females in South Texas. The majority were Mexican-American (50%) and Mexican (35%), and the mean age was 51 years (SD 13). The majority (93%) of females reported having a Pap smear; however, 50% of these same women had not had a Pap smear in 3 years or more, potentially exceeding the recommended interval. In addition, participants did not know if they had HPV co-testing (45%). A majority of participants (55%) reported primarily receiving medical information from the doctor's office. Focus group narratives were analyzed using thematic content analysis. The preliminary theme from female focus group interviews is "include males" in cervical cancer prevention education. The overreaching theme from male focus group is a "clash of cultures" or navigating between scientific knowledge and expected Hispanic cultural norms.

Conclusion: These results suggest the need for concerted efforts to improve consistent, regular recommended cervical cancer screening and the importance of provider recommendation for cervical cancer screening. Community-based, culturally competent cervical cancer screening intervention strategies including male partners are needed to decrease Hispanic cervical cancer health disparities in Texas.

An Evidenced-Based Services Program to Increase HPV Vaccination Rates

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Introduction: Cervical cancer is the most common HPV-associated cancer among Hispanic women. In the Hidalgo County, women experience higher incidence and mortality from cervical cancer compared to the state and nation. Prevention of cervical cancer is possible using the HPV vaccine, which the Advisory Committee on Immunization Practices recommends for males and females aged 11–26 years. Despite this recommendation, uptake of the HPV vaccine remains low for Hispanic adolescents and young adults in Texas. The Entre Familia (EF) program integrates a community education component (public education and health professional training/education) and clinic component (provider-directed intervention and healthcare system-based intervention) to increase HPV vaccine initiation and completion rates in Hidalgo County.

Methods: Community health workers (CHWs) at community and clinic sites recruit parents of Hispanic adolescents (aged 11–17 years) and young adults (aged 18–26 years) who have not initiated or completed the vaccine series. As part of the community component of EF, CHWs engage in county-wide outreach activities, delivering group health education sessions using a flipchart and one-on-one sessions with an educational brochure. This component also provides education and training for community-based healthcare providers. The clinical component of EF will educate and train healthcare providers to implement evidence-based strategies to increase vaccination rates and to make strong recommendations for the HPV vaccine to their patients. CHWs will implement healthcare system-based interventions (e.g., clinic-based patient education and patient reminders) selected by the lead clinical provider at each site to increase vaccination rates.

Results: The EF program is currently underway. We expect EF to increase HPV immunization rates (initiation and completion) through the implementation of clinic and community components in Hidalgo County. From March 2017 to May 2017, we (1) reached 1157 adult residents of Hidalgo County through outreach, (2) educated 349 adult residents of Hidalgo County using EF's evidence-based education sessions and brochures, (3) educated 109 healthcare professionals, (4) served 46 vaccine-eligible clinical patients through the clinic CHWs. We also plan to (5) educate 60 healthcare providers on evidence-based HPV vaccination practices, (6) increase over baseline the proportion of healthcare providers that routinely offer the HPV vaccine, and (7) meet or exceed Texas' vaccine initiation (39%/16%) and completion (20%/8%) rates for adolescents and young adults using clinic electronic medical records.

Conclusion: By increasing vaccine initiation and completion among adolescents and young adults, EF has the potential to reduce cervical cancer incidence and mortality among Hispanic women in Hidalgo County.

Increasing Providers' Recommendation for HPV Vaccination Using Academic Detailing in South Texas

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Introduction: Cervical cancer is the most common human papillomavirus (HPV) associated cancer among Hispanic women. Prevention of cervical cancer is possible through the HPV vaccine; however, HPV vaccination rates for Hispanic adolescents in Texas remain low. Studies show that a strong provider recommendation is a factor influencing HPV vaccination. Academic detailing (AD), which uses brief, facilitator-led face-to-face evidence-based education sessions with providers, is one method for increasing provider recommendation for the HPV vaccine. Our two projects are using a provider-directed intervention (PDI) using AD sessions, which we designed to give providers key evidence-based messages to use with patients. The purpose of the PDI is to improve vaccination initiation and completion rates for adolescents aged 11–18 years in five rural counties in south Texas.

Methods: Research staff collected baseline data including clinical reports on HPV vaccination, initiation, and completion rates; clinical staff surveys on knowledge and attitudes regarding the vaccine; and provider interviews about HPV vaccination. Additionally, the study team developed an AD booklet with supplemental materials using the Centers for Disease Control and Prevention's "You are the Key to HPV Cancer Prevention" curriculum, the Immunization Schedule for Preteens and Teens, and The Community Guide. Clinical facilitators will deliver 4 monthly AD sessions to providers followed by two sessions to develop a strategic plan. Each session will last 30–60 min and give providers Continuing Medical Education credits for their participation. The AD sessions cover the following themes: (1) understanding the burden of HPV infection and disease; (2) evidence-based strategies to HPV disease prevention; (3) talking about HPV vaccine to patients; and (4) strategies to improve HPV vaccine coverage.

Results: Eleven clinics in five Texas counties are participating in the PDI. Two clinical facilitators are collecting baseline data and implementing the PDI in two distinct territories. Reports summarizing baseline data have been shared with the lead provider at four participating clinics, while baseline data is being finalized for four other sites.

Conclusion: We expect that AD will empower providers to make a strong recommendation for the HPV vaccine and increase HPV vaccine initiation and completion rates in these rural clinic settings. Thus far, providers have been receptive to and interested in our findings, specifically showing interest in decreasing missed opportunities for vaccination, increasing the number of patients offered the vaccine, and developing strategies to remind patients to complete the vaccine series.

Human Papillomavirus (HPV) Vaccination Rates Among Childhood Cancer Survivors in South Texas

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Background: Initiatives targeting the uptake of human papillomavirus (HPV) vaccination have improved rates nationally; however, HPV-related diseases remain a significant health concern. Childhood cancer survivors (CCS) are uniquely vulnerable to HPV-related second malignancies. Female CCS are 40% more likely and male CCS are 150% more likely to develop an HPV-related malignancy compared to their age-matched peers without a history of cancer. This increased risk is even more pronounced among CCS who received allogeneic stem cell transplantation, which is a common therapy for a subset of childhood cancer patients. Despite higher risks, a recent survey found that CCS have very low rates of HPV vaccination. Little is known about HPV vaccination rates among Hispanic CCS.

Objectives: Study aims included evaluation of (1) HPV vaccination rates among pediatric cancer survivors in South Texas and (2) HPV vaccination rates by demographic and clinical factors in this population.

Methods: Medical records of childhood cancer survivors treated at the South Texas Children's Cancer and Blood Disorders Center in San Antonio, Texas, were retrospectively reviewed to identify all patients potentially eligible to receive the HPV vaccine (age 11–26 years during 2006–2016). Review of vaccine records through Texas ImmTrac vaccine registry and electronic clinical records verified HPV vaccination status. Demographic and clinical variables collected included DOB, gender, race/ethnicity, cancer diagnosis, and cancer treatment.

Results: Of 210 records reviewed, 156 survivors were deemed vaccine-eligible. Of these, 21 (13.5%) received at least one vaccine, and only nine (5.9%) completed the three-dose series. Among females, 19% (16/84) initiated and 10.7% (9/84)

completing the vaccine series. Among males, only 6.9% (5/72) initiated the series and no males completed all three doses (0/72). Approximately 76% (119/156) of the sample was Hispanic/Latino. Among them, 14% (17/119) patients initiated the vaccine series and only 5.9% (7/119) completed. Furthermore, patients who received high-risk therapies (radiation, SCT) did not have increased uptake of the HPV vaccine compared to patients receiving only chemotherapy.

Conclusions: HPV vaccination rates among childhood cancer survivors in South Texas are lower than in the general population, both regionally and nationally. Given the increased susceptibility to secondary HPV-related malignancies, this study demonstrates a clear need for enhanced efforts to increase HPV vaccination rates in this at-risk population.

Barriers and Facilitators to HPV Vaccination Series Completion Among Adolescent Hispanics in Tampa and Ponce

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Background: The Advisory Committee on Immunization Practices (ACIP) recommends routine human papillomavirus (HPV) vaccination for adolescents aged 11–12 years. HPV vaccination is a series of two or three doses depending on the adolescents' age. While vaccine initiation in Hispanics is higher compared to non-Hispanics both in the United States and Puerto Rico (PR), series completion remains an important concern. While many studies have explored series initiation, few studies have specifically examined barriers to series completion in minority populations, including Hispanics. To fill this knowledge gap, we conducted a qualitative study to explore barriers and facilitators to series completion among caregivers of Hispanic adolescents in Florida and PR.

Methods: Hispanic caregivers of adolescent boys and girls between the ages of 11 and 17 years who received at least one dose of the HPV vaccine were recruited through community-based approaches at both sites, as well as local clinics in Tampa and the Puerto Rico Immunization Registry (PRIR). Eligible participants were consented and participated in either a telephone or in-person interview focused on understanding caregiver knowledge about HPV, exploring perceptions of HPV vaccination, and the barriers and facilitators of series completion. Quantitative data were analyzed using frequency distributions and qualitative data using deductive content analysis and coded using relevant constructs from the socio-ecological model.

Results: Of 57 caregivers assessed for eligibility, 26 (46%) were consented, and 21 (37%) completed the interview. All caregivers who were interviewed were female whose children had health insurance; one-third were between the ages of 30–40 years and most preferred communicating with their adolescents' healthcare provider (HCP) in Spanish (~67%). Based on preliminary analysis of interviews, the most common intrapersonal-level (patient-related) barrier consisted of a lack of time to return for subsequent doses, while interpersonal-level (physician-related) barriers were lack of a strong recommendation, reminders for follow-ups, and confusion about how many doses were required and why. Organizational-level (system-related) barriers included patients having to go elsewhere for subsequent doses and clinics not having the vaccine in stock. Key facilitators of vaccination were awareness of HPV prevalence and the vaccine efficacy, trusting the educational information provided and having a personal experience with cancer.

Conclusions: Multiple factors contribute to low series completion rates among Hispanic adolescents. Results suggest that physicians and vaccination staff should emphasize the importance of series completion to patients and caregivers. This could in turn influence caregivers to prioritize returning for follow-up doses by sending reminders and reduce any potential confusion about how many doses are needed and why. Additionally, clinics should ensure that they have enough vaccine supply to meet the needs of age-eligible patients.

Correlates of Accurate Parental Reporting of Hispanic Daughters' HPV Vaccination Status

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Background: HPV vaccination is recommended for adolescents and young adults aged 11–26 years. Studies of adolescent HPV vaccination often rely on parental reporting of their children's vaccination status when medical record review is not feasible. We evaluated the accuracy of parental reporting of daughters' HPV vaccination status among Hispanic parents who reported their daughters had not received any vaccine doses. We then examined parental correlates of correct classification of vaccination status.

Methods: To assess eligibility for an HPV educational intervention, interviewers asked parents of Hispanic girls, aged 11–17 years, about their daughters' HPV vaccination history. We reviewed medical records to validate parental reports. We calculated the proportion of parents who accurately reported their daughters' vaccination status and used hierarchical logistic regression modeling to determine socio-demographic characteristics associated with accurate vaccination reporting (AVR).

Results: We verified HPV vaccination status of 1109 daughters of participants. Overall, 70% of parents accurately reported their daughters' vaccination statuses at baseline, and 30% inaccurately reported their daughters' vaccination statutes. Most daughters (56%) were between 13 and 17 years of age. Mean parental age was 38.79 years and most parents (72%) had less than a 12th grade education. Most participants (56%) lived in households earning more than $15,000 per year. Multivariable regression analysis revealed parents with younger daughters and households with higher income were significantly associated with accurate reporting of a daughter's HPV status. Parents with daughters aged 11–12 years had higher odds of accurately reporting (OR = 1.68; 95% CI 1.19–2.38) that their daughters were unvaccinated at baseline compared to parents with daughters aged 13–17 years. Parents with a household income greater than $15,000 per year had higher odds of accurately reporting (OR = 1.44; 95% CI 1.02–2.04) that their daughters were unvaccinated compared to parents with household incomes less than $15,000 per year.

Conclusion: The results highlight the still prevalent problem of inaccuracies between actual HPV vaccination and self-report of vaccine receipt. Parental recall must be examined in studies that determine baseline vaccination rates to enable comparisons across groups. These findings have implications for future routine monitoring of vaccination coverage and may be particularly important for healthcare providers who need to ascertain the vaccination status of young adults.

Association Between Family History of Cancer and HPV Vaccination in Puerto Rico

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Background: Groundbreaking milestones in regard to vaccine development are overshadowed by the low HPV vaccination rates nationwide. Data from the 2016 National Immunization Survey Teen for youth aged 13–17 years indicates that only 43.0% of females and 31.5% of males received all recommended doses. While the rates for Puerto Rico (PR) were similar to the rates observed at a national level,

both are still lower than the Healthy People 2020 goal of reaching an 80% uptake. Compared to other cancers, less is known about the role of family history of cancer as an influence on HPV vaccination. This study aimed to determine the association between family history of cancer among parents/guardians and vaccinating their children against HPV.

Methods: An educational activity entitled "¡Habla de VPH!" for parents/guardians of newly admitted students from the University of Puerto Rico, Rio Piedras Campus (UPR-RP) held in the summer of 2014. This activity was a collaboration with the UPRRP Medical Services Department, the Puerto Rico Comprehensive Cancer Control Program, and the Puerto Rico Community Cancer Control Outreach Program (CCCOP) with the objective of disseminating general information to parents/guardians regarding HPV and HPV vaccination, as well as provide information of the vaccination clinics available in PR. For this study, eligible participants included parents/guardians and those who answered a survey that collected demographic information, HPV vaccination status of their children, HPV knowledge and family history of cancer. A multivariate logistic regression model was used to estimate the prevalence odds ratio (POR) with their 95% confidence intervals (CI) for the association of family history of cancer among parents/guardians and vaccinating their children against HPV.

Results: Four hundred thirty-eight parents/guardians completed the survey. The mean age was 46.02 ± 2.26 years and the majority were females (84.5%). Age, sex, annual family income, and health insurance were significantly associated with having their child vaccinated against HPV ($p < 0.05$). Multivariate logistic regression models showed that females (POR = 1.90, 95% CI: 0.99–3.64, $p = 0.052$) and parents/guardians with the government health insurance (POR = 2.84, 95% CI: 1.41–5.72, $p = 0.003$) were more likely to vaccinate their children against HPV. Although family history of cancer was not significantly associated with HPV vaccination, parents/guardians with family history of cancer were 11% (POR = 1.11, 95% CI: 0.70–1.78, $p = 0.648$) more likely to vaccinate their children against HPV than parent/guardians without family history of cancer.

Conclusions: To our knowledge, this is the first study in PR to assess the association between family history of cancer and HPV vaccination. Gender and insurance are important predictors to consider when developing future HPV vaccination campaigns. Although we did not observe a statistically significant association between HPV vaccination and parent's family history of cancer, future studies should consider if a specific cancer history (HPV-related cancers, genetic or behavioral related) or their own personal experience with HPV infection might drive the association with HPV vaccination of their children.

Factors Affecting Behavioral Intentions to Obtain Screening for CRC in Hispanics of Mexican Descent

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Background/Purpose: Colorectal cancer (CRC) is the second most commonly diagnosed cancer and the third leading cause of cancer-related deaths among Hispanic men and women in the USA. While Hispanics in the USA show favorable outcomes for CRC compared to all other racial ethnic groups, Hispanics residing along the US–Mexico border exhibit disparities in both CRC incidence and mortality. Several risk factors may account for these late CRC stage diagnoses and mortality rates. The purpose of this study was to examine general (e.g., confidence to obtain screening) and cultural beliefs (e.g., fatalism) that may increase or reduce behavioral intentions to participate in CRC screening among Hispanics of Mexican descent.

Methods: Study participants included 153 Hispanic adults, who had never been screened/diagnosed for CRC, were at least 50 years old, and lived in the US–Mexico border region (e.g., Dona Ana, NM and El Paso, TX counties). Women composed 73% of the sample. Factors assessed in this study included (1) perceived benefits of screening, (2) self-efficacy to obtain screening, (3) subjective (injunctive) norms for screening, (4) fear of screening, (5) cancer fatalism, (6) acculturation, (7) machismo, and (8) behavioral intentions to get screened. All measures were assessed via a self-report survey in the participants' preferred language. Pearson correlations were calculated.

Results/Findings: Perceived benefits of screening, self-efficacy to obtain screening, and subjective (injunctive) norms for screening were all positively related (all r's > 0.38, $p < 0.05$), and acculturation and machismo were negatively related (both r's > 0.17, $p < 0.05$) to behavioral intentions to screen for CRC. Interestingly, cancer fatalism and fear demonstrated no significant relation to behavioral intentions.

Discussion: Hispanics of Mexican descent would benefit from interventions that target those belief systems that promote CRC screening. It is important to address culturally related beliefs acting as barriers to cancer screening and prevention.

Implementation of Screen to Save: NCI Colorectal Cancer Outreach and Screening Initiative in South Texas

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Background: Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer and the second leading cause of cancer-related death in men and women combined in the USA. If detected early, CRC is preventable and curable; however, low-income and minority groups carry the majority of the disease burden and have poorer survival once diagnosed compared to upper- and middle-income non-Hispanic whites. Minority groups in the USA also receive fewer colorectal cancer screening tests and are less likely to be up-to-date with screening than the population as a whole. In most states, less than 20% of minorities have been screened within the past year. In 2016, only 60% of Texans were up-to-date with screening. In Bexar County, San Antonio, the screening rate is even higher at 66%. However, several census tracts within Bexar County have CRC screenings rates below 50%. The purpose of this study was to increase CRC knowledge, attitudes, positive behavior change, intent for screening, and screening in South Texas through the implementation of Screen to Save: NCI Colorectal Cancer Outreach and Screening Initiative.

Methods: From March to December 2017, we partnered with CommuniCare Health Centers to recruit 139 patients and provide culturally tailored, evidence-based CRC education to increase knowledge, awareness, and CRC screening. CRC education was provided via Flip Chart, and pre/post surveys were administered to assess changes in CRC knowledge and intention to screen. A total of three surveys were offered in both English and Spanish, based on participants' preference. The pre-knowledge survey consisted of demographic information (education, ethnicity, and insurance status), screening history, family health history, and a total of 14 pre-knowledge test questions. The post-survey consisted of the same 14 knowledge questions as well as a section on intentions where patients were given five intention statements (such as "As a result of this initiative, I am more likely to talk to my doctor about screening") and asked to rank on a scale of strongly agree to strongly disagree. A 3-month follow-up survey was conducted as a short phone interview and collected information on whether the individual completed screening, any barriers/challenges that prevented them from getting screened, and positive behavior change which evaluated whether the individual followed through with the intentions stated in their post-knowledge survey. All patients received CRC screening via FIT kit from CommuniCare Health Centers. All returned FIT kits were analyzed by CommuniCare in their lab. Patients who tested positive were linked to follow-up care.

Results: Of the 139 patients enrolled in the study, majority were female (74.1%), Hispanic (97.8%), and between the ages of 50 and 59 years. Eighty-two percent of

patients had an education level of high school or lower, and half (49.6%) of patients were uninsured. Over half of patients (57.6%) had never been screened for CRC in their life. Increase in CRC knowledge was observed for all 14 questions of the pre- and post-knowledge tests. Interestingly, only 8.3% of patients knew the risk factors for CRC. Majority of patients also did not know the age at which a colonoscopy and a stool test should be performed. At baseline, patients showed strong intention for positive behavior change and screening, with nearly all patients strongly agreeing or agreeing with all five intention statements. At 3-month follow-up, strong positive behavior change was observed with majority of patients (73.4%) talking to their doctor about CRC screening and half of patients (51.1%) completing CRC screening as a result of the initiative. About half (48.2%) of patients talked to friends or family about CRC screening.

Conclusion: Overall, Screen to Save was effective in improving CRC screening knowledge and intentions among CommuniCare patients using Flip Chart as an educational tool. At 3-month follow-up, strong positive behavior change was observed. However, patient-reported barriers and challenges show that stigma surrounding CRC still remains.

Implementation of a National Colorectal Cancer (CRC) Initiative Among Hispanics Across NCI-Designated Cancer Centers

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Introduction: Increasing CRC screening rates is one of the ten recommendations of the Blue Ribbon Panel for the Cancer MoonshotSM. To address these recommendations, the National Cancer Institute's (NCI) Center to Reduce Cancer Health Disparities (CRCHD) launched the national CRC Outreach and Screening Initiative, Screen to Save (S2S). S2S aims to increase CRC screening rates among men and women 50 years and older from racially and ethnically diverse communities and in rural areas across the USA. Among Hispanics in particular, CRC is the second most commonly diagnosed cancer and third leading cause of cancer death.

Methods: NCI-funded National Outreach Network (NON) and Partnerships to Advance Cancer Health Equity (PACHE) community health educators (CHEs) collaborated with community stakeholders to recruit participants and provide culturally tailored, evidence-based CRC education at various community, clinical and academic settings to increase knowledge, awareness, and CRC screening in their respective catchment areas. CHEs provided CRC education through an inflatable colon, an NCI PowerPoint presentation, and/or NCI flipcharts. CHEs administered NCI developed pre/post-surveys to participants during their S2S activities to assess any changes in CRC knowledge and intention to screen. This abstract focuses on Hispanic/Latino S2S participants 50 years and older. Statistical tests will be conducted to evaluate the influence of S2S on participants' CRC knowledge and screening intention scores.

Results: The S2S intervention was delivered to 3881 individuals, of which 1544 self-reported as Hispanics/Latinos. Though data analysis is ongoing, we hypothesize that CRC knowledge and screening intention will increase significantly after implementation of S2S. We also predict that there will be no significant difference regionally but that differences may be seen by method and setting of intervention delivery.

Impact: The preliminary analysis will show the overall efficacy of S2S in increasing CRC screening knowledge and intentions among Hispanic/Latino participants 50 years and older through the use of culturally tailored, evidence-based methods. Differences seen by implementation type and setting may suggest that some methods or settings are more effective than others at improving CRC screening knowledge and intentions.

Based on those findings CHEs will be able to target Hispanics/Latinos 50 years and over more effectively and perhaps improve lagging screening rates by using the most effective evidence-based implementation method.

Racial Disparities in Comorbidities, Income Levels, and Surgical Procedures Observed in Hispanic Patients with Pancreatic Cancer Compared to Non-Hispanic Patients: Results from the National Inpatient Sample Database

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Background: Higher incidence and lower survival rates have been linked to racial/ethnic and socioeconomic (SES) disparities in patients with pancreatic cancer. However, systematic evaluation of the interaction between race/ethnicity, SES, comorbidities, and type of surgical procedures to predict outcomes associated with pancreatic cancer are missing. Hence, we conducted this study to investigate these risk factors and outcomes of discharges associated with pancreatic cancer, with a specific focus on Hispanic population.

Methods: We surveyed Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) database for year 2014 to identify patients with pancreatic cancer (ICD9: 230.9, 157.1–157.4, 157.8, 157.9). To identify racial disparities, we examined age, median household income at zipcode level, various comorbidities (e.g., alcohol abuse, diabetes, obesity, liver disease, hypertension, and chronic pulmonary disease), types of surgical treatments (surgical vs. nonsurgical options; Whipple vs. others) as a treatment choice, and death during hospitalization.

Results: From approximately seven million records, we identified 18,069 pancreatic cancer-related discharges. Majority of patients were non-Hispanic whites (NHW) (73%) followed by black (14%), Hispanic (8%), and others (5%) with a median age of 68 years (range: 0–90 years). Compared to NHW, Hispanics had a significantly higher prevalence of diabetes (40% vs. 30%, $p < 0.001$) and liver disease (8% vs. 5%, $p < 0.001$), whereas no significant differences were observed for obesity, hypertension, congestive heart failure, or alcohol abuse. Majority of Hispanic patients (39%) with pancreatic cancer belonged to lowest income quartile ($1–$39,999 per year) compared to NHW (20%), *P*-value <0.001. The only two factors associated with the difference in receiving Whipple procedure were having underlying liver disease and the income level, stratified by race/ethnicity. We did not identify any factors associated with differences in mortality rates during hospitalization.

Conclusions: We identified significant racial disparities such as higher prevalence of comorbidities, lower income levels, and different types of surgical procedures in Hispanic versus NHW patients hospitalized for pancreatic cancer. Future studies quantifying the impact of stage of illness at presentation, multiple comorbidities including smoking, rural/urban care setting, SES, insurance coverage on treatment choices, and outcomes associated with pancreatic cancer in different racial/ethnic groups are needed.

Characterization of Localized Osteosarcoma of the Extremity in Children, Adolescents, and Young Adults from South Texas: Increasing Insights into Hispanic Populations

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Background: There is a need for describing and characterizing cancer treatments and outcomes in Latino populations. Osteosarcoma is the most common bone malignancy in children, adolescents, and young adults. Most study cohorts have 10–15% Hispanic patients that encompass many different Hispanic backgrounds. The University of Texas Health Science Center at San Antonio (UTHSCSA) Sarcoma Team serves a Latino population that is predominantly Mexican American, thus providing a unique opportunity for the evaluation of this population. This study expands on previous data collected from January 2000 to December 2010 from the same institution, providing increased insights into outcomes of Mexican American children, adolescents, and young adults with osteosarcoma.

Methods: A retrospective analysis of demographics, tumor characteristics, response to treatment, and survival outcome of all localized osteosarcoma of the extremity patients below 30 years of age diagnosed and treated by the UTHSCSA Sarcoma Team between January 2000 and June 2017 was performed.

Results: In our original cohort from January 2000 to December 2010, we observed a significantly decreased 5-year event-free survival (EFS) in patients diagnosed before age 12 years (preadolescent) relative to patients diagnosed between ages 12 and 29 years (11% vs. 57%, $P < 0.001$). Patients had a 5-year overall survival (OS) and event-free survival of 65% and 48%, respectively. In our expanded cohort from January 2000 to June 2017, we evaluated 66 patients with a median age of 14 years (range, 2–28 years) with localized high-grade osteosarcoma of the extremity. The expanded cohort was 68% Mexican American, with a median follow-up of 59 months (range, 5–192 months). The analysis of our expanded cohort is ongoing, and we postulate that the findings will hold true, as we increase the cohort size and length of follow-up.

Conclusions: Analysis of our previous cohort, predominantly of Mexican American ethnicity, showed that preadolescent patients had an increased rate of relapse when compared with previous large studies. We also showed a trend toward decreased EFS for the entire cohort. We hypothesize that we will further validate these findings with this expanded cohort, and this will support further investigation into potential causes of poor outcome in this vulnerable Latino population.

Steroid-Induced Hyperglycemia and Hispanic Ancestry in Childhood ALL

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Introduction: Glucocorticoids have been a cornerstone of the treatment of childhood acute lymphoblastic leukemia (ALL) for decades. However, glucocorticoids are associated with numerous adverse effects in children including avascular necrosis, growth impairment, and hyperglycemia. Among children with ALL who are exposed to high-dose steroids throughout therapy, steroid-induced hyperglycemia (SIH) is a common problem, with an estimated incidence of 20.4% during induction alone (Lowas, Pediatric Blood Cancer 2009). SIH severity ranges from transient hyperglycemia to secondary diabetes with insulin dependence. In children with ALL, SIH is also associated with increased bacteremia, hospital readmission, and most importantly with diminished survival. Predisposing factors for SIH include a family history of diabetes, age > 10 years, and non-white ethnicity. Although it is known that Hispanic children have some increased genetic vulnerability to several drug-induced toxicities during ALL treatment, previous studies relied on self-reporting of ethnicity to describe these relationships. Therefore, we aimed to evaluate the association between SIH and Hispanic ethnicity in childhood ALL using Hispanic ancestral markers across a predominately Mexican-American patient population in South Texas.

Methods: We performed a retrospective chart review of 46 pediatric ALL patients treated at the South Texas Childhood Cancer and Blood Disorders Center at UT Health San Antonio between 2014 and 2017. Data collected included the following: cancer diagnosis, date of diagnosis, age at time of diagnosis, gender, race/ethnicity, and two highest glucose values recorded. SIH was defined as serum glucose ≥ mg/dL as fasting status was not available. Sixty-four Hispanic SNP ancestral markers, previously validated in the South Texas Hispanic population (Beuten, Annals of Human Genetics 2011), were analyzed using the Arizona Genomics Core: MASSArray. Three of the SNPs failed to capture. Allele frequencies for the remaining 63 Hispanic SNPs were calculated using Qiagen's Ingenuity Variant Analysis tool. Individual Hispanic SNP alleles were mapped to glucose values, and hyperglycemia association was evaluated by regression analysis, adjusting for age and gender, using STATA software.

Results: Overall, 12/46 (26.1%) pediatric ALL patients met criteria for SIH. Most patients (39/46, 84.8%) self-reported Hispanic ethnicity. Among Hispanic patients, SIH was seen in 25.6% (10/39). SIH incidence was similar in non-Hispanic patients, seen in 28.6% (2/7). Ancestral marker analysis and association studies are forthcoming.

Conclusion: Although limited by sample size, our data shows no association between self-reported Hispanic ethnicity and SIH. However, Hispanic ancestral marker associations are still pending analysis. Although well-established that

Hispanic children with ALL have poorer survival outcomes, it is unclear to what degree SIH may contribute, as SIH is known to be an independent risk factor for decreased survival in childhood ALL. Aggressive identification and management of SIH may improve survival outcomes among Hispanic children with ALL.

Adult Hispanic Males Experience a Higher Incidence of Acute Lymphoblastic Leukemia Compared to Non-Hispanic Whites

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Introduction: Acute leukemia is an important cause of morbidity and mortality with differences in incidence and outcomes between patients of different racial/ethnic backgrounds; however, most of the studies have focused on acute lymphoblastic leukemia (ALL) in children. Hence, we conducted this study to examine the racial and ethnic disparities in incidence of ALL as well as other types of acute leukemia, specifically focusing on Latino population in South Texas.

Methods: Data were obtained from the US Surveillance, Epidemiology and End Results 18 (SEER) Program and the Texas Cancer Registry (TCR) under Limited-Use Data Agreements between sources and authors. Adult patients (15 years or older) were identified in both SEER and TCR databases from 2000 to 2014 and ICD-O-3 codes were used to select specific malignancies: ALL (9727–9729, 9835–9837), acute promyelocytic leukemia (APL) (9866), and non-APL acute myeloid leukemia (AML) (9840, 9861, 9867, 9870–9874, 9891, 9895–9897, 9910, 9920, 9930, 9931). Race/ethnicity was classified as Hispanic (H) and non-Hispanic white (NHW) per the North American Association of Central Cancer Registry (NAACR) Hispanic/Latino Identification Algorithm. For each malignancy, cases were obtained from SEER 18 and TCR, including both the State of Texas and the 38 counties which comprise South Texas. Comparisons were made using SEER population of NHW as point of reference. We used SEER∗Stat software v 8.3.4 (SEER∗Stat, National Institutes of Health) to generate 2000–2014 average annual age-specific and age-adjusted acute leukemia incidence rates (per 1,000,000), rate ratios (RR), and 95% confidence interval (CI) for Hispanic and NHW populations in SEER, Texas, and South Texas regions.

Results: Hispanics in South Texas and specifically males had significantly higher RR for the development of ALL ($p < 0.05$) and lower for non-APL AML; there was no statistical difference for APL rates compared to NHW. Within ALL,

greater rates were seen in males and in the AYA (15–39 years) and 70–79 year groups (data not shown).

Conclusion: Latinos in South Texas experience a higher incidence of ALL and a lower incidence of most types of AML compared to NHW. Future studies are needed to identify specific risk factors associated with this higher burden in Hispanic population.

Examining Spatial Differences in Cancer Mortality Among Hispanic Subgroups in Texas

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Introduction: Over the course of 10 years, the Hispanic population in the United States has grown by 43% and is projected to make up 29% of the US population by 2060. Since Texas is a minority-majority state, the demographic make-up foreshadows the make-up of US population in the future where approximately 40% of the Texas population will be classified Hispanic. Hispanic is an umbrella classification for any person of Spanish descent and masks the complexity and heterogeneity within this group. Understanding the complexity of the Hispanic population requires going beyond this umbrella term. Mortality advantages exist in the Hispanic population where both foreign-born and US-born Hispanic populations have better survival outcomes than native, non-Hispanic populations despite experiencing more disparities (i.e., lower SES, education, etc.). Unfortunately, little is understood among Hispanic subgroups in Texas regarding the Hispanic mortality paradox and how it pertains to cancer mortality. Since cancer is the second leading cause of death in United States and first among Hispanics, understanding the complexity and differences within the Hispanic population will add to a growing body of literature regarding subgroup mortality advantages.

Methods: Using data from the Texas Cancer Registry, we will conduct a spatial exploratory data analysis to examine spatial patterns in cancer mortality among Hispanic subgroups in Texas from 2000 to 2014. We will use ARC GIS to map clusters for Texas counties to identify areas with higher and lower than average cancer mortality by Hispanic subgroup.

Results: We expect that cancer mortality outcomes will differ between Hispanic subgroups where mortality advantages will be seen among some groups but not others. Although, in general, a Hispanic paradox exists where mortality outcomes are more favorable among Hispanics despite existing disparities, more data is

needed to understand and develop interventions among different subgroups specific to cancer mortality.

Significance: Understanding the cancer mortality differences among Hispanic subgroups will allow researchers and practitioners the ability to tailor health interventions specific to mitigating the disparities and negative health issues among Hispanic subgroups in the United States.

Examining Environmental Factors and Elevated Cancer Incidence in South Texas

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Introduction: South Texas, defined as Public Health Region (PHR) 11, which includes Aransas, Bee, Brooks, Duval, Jim Hogg, Jim Wells, Kenedy, Kleberg, Live Oak, McMullen, Nueces, Refugio, San Patricio, Webb, and Zapata counties, as well as the Lower Rio Grande Valley (LRGV) counties of Hidalgo, Starr, Cameron and Willacy, is predominately Hispanic and currently experiencing rising cancer rates. Factors underlying specific increases in cancer incidence in this region are not currently well defined.

Methods: To investigate factors and cancer incidence rates in South Texas, we first conducted a systematic literature review focused on search terms related to diet and environmental factors, such as water contamination, air pollution, and pesticide exposure, in relation to cancer incidence in South Texas. We also analyzed data from the Texas Cancer Registry's Web Query Tool for cancer incidence for Hispanics from 2005–2009 to 2010–2014 in PHR11 and LRGV counties.

Results: We identified elevated cancer incidence in comparison to the entire state, for leukemia, cervical, stomach, and liver cancers in PHR11, as well as targeted LRGV counties. Furthermore, based on our review, there is limited literature on the relationship between diet/environmental exposures and cancer incidence in the South Texas.

Conclusion: Little is known about the relationship between diet and environmental exposures and cancer incidence in South Texas. Our work is ongoing to investigate environmental factors and their association with specific cancer incidences mentioned above.

Disparities in Functional Health Trajectories Among Older Adults

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This study examines racial and ethnic disparities in the trajectories of functional health limitations among older adults and explores how chronic conditions, such as cancer and health-related behaviors contribute, to the level and rate of change in functional limitations over time. Using data from the Health and Retirement Study (HRS) and a multiple-group latent growth model of functional limitations, findings reveal significant racial and ethnic disparities in functional status. These disparities are found to result primarily from differences in socio-demographic factors. Specifically, blacks and Hispanics are more likely to suffer functional limitations at the initial time period than non-Hispanic whites. However, net of years of educational attainment and wealth, a "disability crossover" is observed in the baseline odds of functional limitations from higher odds for blacks to higher odds for whites. In addition, non-Hispanic whites tend to have faster increases in the rate of change in functional limitations over time. Results also demonstrate that these observed racial and ethnic disparities in functional health derive from racial/ethnic group differences in the presence of chronic conditions and health-related behavioral factors. Smoking and being overweight/obese is associated with the onset of functional limitations in older adults. Also, whites who are light drinkers had lower functional limitations at onset. None of the health-related behaviors influenced the rate of change in functional limitations over time across all three racial and ethnic groups.

These findings indicate that addressing racial and ethnic disparities in chronic conditions such as cancer and increasing healthful behavioral factors may minimize disparities in trajectories of functional health among older adults. Overall, functional health of older adults can also be improved by implementing health intervention programs such as early detection and screening and pursuing policies that support tobacco use cessation, weight reduction, and other health-related behaviors.

Epidemiology and Surgical Management of Chondrosarcoma: A Case-Based Analysis

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Patient Profile: KA is a 51-year-old Latina female with a chief complaint of left-sided shoulder pain for the last 2 years. Her past medical history includes right-sided pectoral melanoma and septic knee. Past surgical history includes right-sided melanoma excision, total knee arthroplasty, and rotator cuff repair. Her family history includes melanoma, breast cancer, prostate cancer, and colon cancer.

Patient Workup: Her physical exam was notable for left shoulder pain with passive and active range of motion, positive Hawkins, Neer, and O'Brien tests, and tenderness to palpation throughout left shoulder. She previously received an MRI of the left shoulder showing a lesion in the proximal humerus. Biopsy of the lesion by interventional radiology showed cartilaginous proliferation with rare atypia. Based on workup, surgical excision and curettage with bone grafting was planned.

Surgical Procedures: A longitudinal incision in the deltopectoral interval of left shoulder was made and dissected down to proximal humerus. Using a 1/8th in. drill bit, multiple elliptical perforations were made throughout the proximal humeral cortex; the bony flap was removed in order to expose the bony lesion which was currettaged. A specimen was sent to pathology (report: cellular chondrocyte lesion with mild cellular atypia suspicious for chondrosarcoma) confirming pre-operative diagnosis by interventional radiology. Lesion was sprayed with 89% phenol, allowed to cure for 5 min and neutralized with isopropyl alcohol. The surgical site was then irrigated with normal saline and packed with 45 cc of cancellous bone chips and 2 cc of demineralized bone matrix putty. Finally the overlying periosteum was repaired and the wound closed.

Conclusion: Chondrosarcomas can present at any age and are more often axial than appendicular. Prognosis will vary considerably depending on the grade of the lesion. Clinicians should maintain a high index of suspicion for patients aged 50–70 years looking like they suffer from mass lesion-related bone pain—deep, dull, achy pain (especially at night), pathologic fractures, limited range of motion, or neuropathies. Advanced imaging is indicated in these cases. Surgical management can be of the intralesional or wide-excision varieties.

Ancestral Analysis of Uveal Melanoma Patients

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Uveal melanoma (UM) is the most common primary malignancy of the eye and has a propensity for metastasis to the liver. There have been tremendous advancements in understanding the genomics of UM and the development of precision medicine for UM patients over the past decades, but the vast majority of this research has been performed in white populations of northern European ancestry. Hispanics/Latinos represent the fastest growing racial/ethnic minority group in the USA, and they comprise a tremendous genetic heterogeneity due to different migratory patterns from Europe, Asia, Africa, and America, leading to genetically admixed

populations. Our ocular oncology center is in a unique position to elucidate the genetic ancestry of patients with UM, owing to our diverse catchment area. To determine genetic ancestry, we genotyped 48 UM patients, 20 self-reported Caucasian, 23 self-reported Hispanic, 2 self-reported Asian, and 3 self-reported black. European, African, East Asian, and Native American reference populations were obtained from the 1000 Genome project and the Human Genome Diversity Project (HGDP). A SNP overlap of over 300,000 SNPs was used to calculate global ancestral analysis. A PCA analysis of the genotyped data was performed and showed 5% of self-reported Caucasians clustered outside of the European reference and showed a degree of admixture as seen in our Hispanic samples. The PCA analysis also showed that 30% of self-reported Hispanic patients clustered more closely to the European reference population while 70% showed admixture clustering closer to the African, East Asian, and Native American reference populations. These findings confirm that genetic methods are required to accurately assess the contribution of ancestry to UM. This work lays the groundwork for future work in which we will use global and local genetic ancestry to assess the influence of ancestry on the risk, prognosis, and outcomes associated with UM.

Sun Protective Behaviors Among Latinos in the US: A Secondary Data Analysis

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Background: UV radiation is a major risk factor for skin cancer including melanoma, and incidence rates of melanoma have substantially increased over the past decades. Although Latinos have a lower incidence of melanoma compared to non-Latino whites, they tend to be diagnosed at younger ages, have a more advanced stage of the disease, and have lower survival rates. This project aimed at assessing the prevalence of sun protective behaviors and associated factors among Latinos in the USA.

Methods: This is a secondary data analysis of the 2005 Health Information National Trends Survey. Chi-square and Wilcoxon tests were used to detect differences between Latinos and other racial/ethnic groups. Logistic regression was performed to identify associations between sun protective behaviors with selected demographic variables including age, gender, education, income, health insurance status, and geographic location.

Results: Latinos do not regularly use sunscreen as recommended (78%), more than half (51%) do not seek shade, 62% do not wear a wide-brimmed hat, and 75% do not wear a long-sleeve shirt to protect themselves from the sun.

Conclusion: As the largest minority group in the country and given their low rate of sun protective behaviors, Latinos are a critical group to target for skin cancer prevention. Tailored and culturally sensitive interventions are recommended to reduce skin cancer-related morbidity and mortality among Latinos. Public health education initiatives should be aimed primarily at younger, less educated, and lower income groups, and when possible, involve their families and healthcare providers.

Sun Protective Behaviors Among Latinas Living in the US–Mexico Border

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Background: Skin cancer is the most commonly diagnosed cancer in the USA, and melanoma incidence is increasing among the US Hispanic population. Even though the incidence of melanoma is lower for Hispanic than for non-Hispanic whites, when diagnosed Hispanics tend to be younger, have a more advanced stage of the disease and have lower survival rates. This is particularly important because Hispanics are the largest and fastest growing racial/ethnic group in the country and are heavily concentrated in the southern and western states which have among the highest ultraviolet indexes in the country. This study examines the prevalence and correlates of sun protective behaviors among low-income Latinas living along the US–Mexico border.

Methods: A survey was conducted with 200 adult women, living in the predominantly Latino region of South Texas. Participants completed an English or Spanish language phone survey in November 2012. Self-reported sunscreen use, shade seeking, and use of sun protective clothing were the outcomes of interest. Correlates included selective demographic variables, knowledge of skin cancer risk, tanning bed use, past year sunburns, and acculturation.

Results: Multiple logistic regression revealed that sunscreen use was associated with age (OR 3.59, CI 1.08–11.98), education (OR 0.36, CI 0.18–0.73), sunburns last year (OR 2.19, CI 1.16–4.13) but not with cancer knowledge, tanning bed use, or acculturation.

Conclusion: Latinas in the border do not routinely practice sun protective behaviors and are in need of skin cancer prevention interventions. Further research is warranted to design and evaluate intervention to increase sun protective behaviors and reduce the risk for skin cancer among this population group.

Addressing Tobacco Regulation in the Retail Environment with Community Voices

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Background: Engaging Latinos in cancer prevention research is necessary to reduce the burden of tobacco-related cancers use among ethnic minorities, since many disparities continue to exist in tobacco use and exposure. Exacerbating this is that tobacco control actions and regulatory messages are not always conveyed in culturally specific ways or in the most linguistically appropriate manner, particularly for ethnically diverse communities such as African-Americans, American Indians, Koreans, and Latinos. To obtain relevant information to support appropriate approaches, Community Health Workers (CHWs) or Key Opinion Leaders (KOLs) may be helpful as sources. CHWs and KOLs are potentially central in addressing the effects of the tobacco retail environment as they are aware of their strengths, needs, and vulnerabilities.

Methods: This presentation discusses two studies within a project conducted in Los Angeles that use both CHWs and KOLs to inform regulatory practices. We present data from eight focus groups conducted with KOLs ($N = 70$) to explore the role that KOLs could play as potential channels for the FDA in delivering tobacco regulatory messages to retailers. We recruited KOLs who represented different industries and agencies to gain a broad understanding of the tobacco retail environment in different ethnic communities. We also present data and lessons learned from working with CHWs in a study conducted in tobacco retail outlets ($N = 800$). The data collection methods include store employee interviews and observations.

Results: Most of the KOLs felt that retailers were moderately to well-informed of tobacco laws. Less than half of the KOLs, however, believed that retailers were aware of FDA authority over tobacco products. When shown materials for a regulatory message, most of the KOLs expressed concern that the materials may not be effective given the language, colors, and content used. While most retailers, 70.8%, reported that they had no barriers to compliance, less than half, 43.5%, believed that the FDA had regulatory authority over tobacco products.

Conclusions: The findings from this project highlight how KOLs and CHWs each provide an independent window into their communities. The information gained from these different channels in turn creates a stronger foundation for future tobacco control messages and educational campaigns that are likely to be received well in ethnically and linguistically diverse populations.

Quitxt: A Text-Based Smoking Cessation Service for Young Adults in South Texas

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Background: Smoking among Latino young adults (18–29) in South Texas is high (23.2–25.7%), representing a serious public health problem. Yet few are reached by services to help them quit smoking. Young adults are heavy users of mobile devices for texting and access to mobile media. These have an extraordinary potential for assisting smoking cessation by providing peer modeling and eliciting social reinforcement for behavior change. We present preliminary results of Quitxt, a bilingual text messaging and mobile media service to help young adults quit smoking.

Methods: We constructed a bilingual texting and mobile media system that was promoted in South Texas via social media advertising and other recruitment channels. The ads, which featured couples with different themes (disgust with cigarettes or confidence in quitting success) and styles (cowboy, metro/urban, geek, punk, and graphic novel), asked potential participants who showed interest in quitting smoking to text a code to our system corresponding to the channel of recruitment. Text messages include links to web pages with additional content and YouTube videos with peer modeling of reasons and skills to quit smoking.

Results: Results showed that enrollments were achieved for 798 participants with a mean age of 29.3 years and 55% were below the age of 30 years. More men (57%) than women (43%) enrolled and 36% identified themselves as Hispanic or Latino. The mean number of cigarettes consumed per day was 11.5. Seven-month texted follow-up found that 21% (171) of the enrollees reported abstinence at that point. This is consistent with high rates of success found in studies of telephone counseling for young adults and confirms that text and mobile media service specifically designed for young adults provide a feasible and cost-effective approach to promoting cessation.

Conclusion: Preliminary results provide evidence that young adult smokers in South Texas can be reached via mobile media service. The anticipated outcome is a scalable, culturally relevant, evidence-based, and cost-effective service with broad national reach to help young adult Latinos stop smoking, with the potential to reduce healthcare costs, reduce chronic disease burden, and improve quality of life among this young, fast-growing, at-risk population.

A Bilingual Mobile Application Prototype to Promote Endocrine Hormone Therapy Adherence in Breast Cancer Patients

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Background: Adjuvant endocrine hormonal therapy is highly effective and appropriate for nearly all women with hormone receptor-positive tumors, making such treatment the most widely prescribed therapy for patients with this type of breast cancer. Despite the proven benefits in reducing cancer recurrence and improving survival, hormone therapy adherence is suboptimal (less than 80%). About 33% of patients do not take their medication as prescribed and are at increased risk of disease recurrence and increased mortality.

Objective: We present the design and development process of a theory-based, culturally tailored, interactive mobile app to improve adherence to endocrine hormone therapy among breast cancer patients as the initial phase of a two-group randomized clinical trial study.

Methods: Four focus groups (n = 21) were conducted with breast cancer patients and personal semi-structured interviews (n = 8) with oncologists, nurses, and patient navigators to assess barriers and facilitators to endocrine hormone therapy adherence, key symptoms, app content, and features. Qualitative data informed the initial design and development of app mock-ups; these were assessed with two additional focus groups (n = 10) and based on formative research a functional phone app prototype was developed for beta testing.

Results: Inputs from patients and healthcare team members helped to identify specific app content and features. Key themes included the importance of increasing patient education, enhancing self-efficacy, facilitating communication with the medical team, and helping patients to develop self-care skills to promote optimal adherence to hormone therapy. Specific app features included notification pop-ups, reminders, motivational messages, symptom tracking and management tips, educational content, social networking among patients, communication with a patient navigator, local resources, including support groups, and technical support. In addition to colors, background, and icon preferences, patients emphasize the need for a user-friendly app that is easy to navigate with simple and clear educational content.

Conclusions: We followed an iterative and patient-centered design process to develop a bilingual, culturally tailored, and interactive mobile app prototype to be used in a randomized control trial. The anticipated outcome is a scalable, evidence-based, and easily disseminated intervention with potentially broad use to patients using oral anticancer agents.

Provider's Perceptions of Genetic Cancer Risk Assessment for Latina Women at Risk of Hereditary Breast and Ovarian Cancer

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Background: BRCA1/2 mutations are the most commonly identified Hereditary Breast and Ovarian Cancer (HBOC) mutations. Latinas have the second highest prevalence of BRCA1/2 mutations after Ashkenazi Jews. However, compared to non-Hispanic whites, Latinas have a lower use of HBOC cancer risk assessments (GCRA) (genetic counseling and testing if appropriate). While some studies have identified barriers for GCRA use in this population, few studies have focused on healthcare providers' perspectives or provided insights into the counseling process for Latinas. The study aimed to examine provider's perceptions on barriers and facilitators for at-risk Latina women use of GCRA services as well as their experiences providing services to this population.

Methods: We conducted semi-structured interviews with 20 healthcare providers (e.g., genetic counselors, patient navigators) recruited nationally through snowballing. Interviews were transcribed verbatim. Two coders independently coded each interview and then met to reconcile the codes using Consensual Qualitative Research guidelines.

Results: We identified 16 barriers and five facilitators to participate in GCRA. Barriers included financial (e.g., cost, lack of insurance), structural (suboptimal referrals), and psychosocial factors (e.g. limited awareness about GCRA, cancer stigma). The most frequently identified facilitators included the availability of low cost/no cost resources and motivation to inform the risk of relatives, especially given the importance of family in the Latino culture. The awareness about safety net programs and other resources to cover GCRA varied among providers. Genetic counselors described several challenges they faced during counseling with Latinas including language barriers, challenges obtaining accurate family histories, addressing misconceptions, limited communication among relatives, addressing emotional concerns, and barriers testing relatives outside the USA.

Conclusions: This project adds to the very small literature on providers' perspectives on GCRA participation in ethnic minorities. Increasing providers' awareness about GCRA low cost/no cost resources and developing interventions to improve

the referral process will be important to enhance GCRA uptake among this population. Exploring other genetic counseling modalities to overcome language barriers and targeting counseling to address cancer stigma and communication barriers among Latino families are warranted.

Programa de ÁRBOLES Familiares: An Innovative Training Program for Community Outreach and Educational Professionals to Assess Risk of Hereditary Breast and Ovarian Cancer in Latinas

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Background/Introduction: Latinas at increased risk of hereditary breast and ovarian cancer (HBOC) participate in genetic counseling and testing at strikingly lower rates than non-Hispanic whites and other minority groups. Increasing awareness of cancer risk and promoting uptake of appropriate risk reduction and management strategies, including use of genetic services, can help reduce cancer disparities. There is an urgent need for alternate models to facilitate risk appropriate referral to and navigation through genetic services that address socioeconomic, language, and cultural barriers.

Methods: We developed Programa de ÁRBOLES Familiares, an innovative training program to help bridge the gap between Latinas at risk for HBOC and genetic services. Our program targets 250 bilingual English and Spanish community outreach and educational professionals (CORE-P). We aim to develop a trained network of CORE-P with referral-level competence to facilitate risk appropriate uptake of genetic services among Latinas at risk for HBOC.

Results: Programa de ÁRBOLES Familiares will consist of a 1.5 day in-person workshop followed by eight online modules. In-person training includes didactic and interactive activities related to family history, risk assessment, genetics and genetic testing, HBOC, risk management, HBOC in Latinas, communication, and ethical, legal, and social issues related to genetic testing. The eight online modules include topics related to identifying community members at risk for HBOC, educating

about genetic risk, identifying genetics professionals, accessing resources, providing referrals to and navigating Latinas through genetic services.

Significance/Impact: We will assess the effectiveness and impact of our training program by evaluating changes in trainees' knowledge, self-efficacy, and skills related to referral of high-risk Latina women to appropriate genetic services. We will assess community impact by trainee self-report regarding implementation of risk assessment procedures and education and referral of high-risk women to genetics services. If successful, the ÁRBOLES Familiares training program can serve as a model for training CORE-P about other hereditary health conditions and provide a strong platform on which to expand trainees' knowledge, self-efficacy, and skills related to genomic risk and technologies in the future.

Breast Cancer Characteristics and Survival Among Different Indigenous American Communities in Peru

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Background: Breast cancer prognosis depends on stage at diagnosis and varies by intrinsic tumor subtype. In the USA, the distribution of tumor subtypes has been shown to differ between racial/ethnic groups with African American and Latina women more likely to be diagnosed with the more aggressive "triple negative" breast cancer (TNBC) compared to non-Latino white women. Latinos in the USA originate from different countries with different cultures and ancestral genetic backgrounds, demonstrating the heterogeneity that exists. Information about the distribution of tumor subtypes in Latin American regions is limited.

Methods: Data for these analyses come from The Peruvian National Cancer Institute (INEN), which include clinical information for 303 patients diagnosed with breast cancer between 2010 and 2015 and who are members of Indigenous American communities. We analyzed women from different groups: the Quechuas (Group 1; $N = 223$), Aimara (Group 2; $N = 9$), Ashankinka/Nomatsigenga/Yenesha (Group 3; $N = 17$), Awajun/Kichwa/Shawi/Shipibo-Konibo (Group 4; $N = 29$), and other communities (Group 5; $N = 20$). Some communities were combined based on previous literature describing their genealogical proximity. We compared tumor characteristics and survival between these groups using Fisher exact tests, *T*-tests, and a Cox Proportional Hazards model with predictors' age at diagnosis, stage,

tumor subtype, and treatment. Breast cancer subtype was defined as luminal A (ER/PR+/HER2−), luminal B (ER+/HER2+), HER2 overexpressing (ER/PR− HER2+), and triple negative (ER/PR− HER2−) based on immunohistochemistry.

Results: Overall, tumors from the 303 Indigenous American women included in the present study were 37% luminal A, 20% luminal B, 23% HER2 overexpressing and 19% triple negative. Our analyses showed that women from group 1 were diagnosed at an older age (55 vs. 48–50 years, $p < 0.0001$) and less frequently with TNBC compared to women from other groups (45% vs. 55–78%, $p = 0.06$). Compared to group 1, women from the other groups show a nonsignificant trend toward higher mortality (hazard ratio 1.5–1.9, $p = 0.272$). In the full model, including age, stage, tumor subtype, and treatment, the trend was no longer apparent. Whether the women had surgery had the strongest effect on survival ($p = 0.001$) followed by stage ($p = 0.0012$) and TNBC ($p = 0.0023$).

Conclusion: Differences in survival between the women of different indigenous communities with breast cancer in Peru are most likely due to differences in access to care. There could be environmental factors or subtle sub-continental genetic differences influencing the risk of TNBC. However, the lower frequency of TNBC among the Quechuas could also be due to a reduced set of logistic barriers to reach INEN. The limited power of this study demonstrates the need for larger data sets for subgroup analysis in Latinas. The more we learn by analyzing diverse populations and subpopulations and revealing heterogeneity within Latin American women, the better equipped we will be to provide adequate care for all women.

Increasing Uptake of Genetic Counseling Among Hispanics at Increased Risk for Inherited Breast Cancer

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Background: Despite the established role of BRCA and other high to moderate penetrance genes in increasing breast cancer (BC) risk in Hispanics, this group is less likely to participate in genetic counseling (GC) and testing compared to non-Hispanic whites. Guided by our prior work documenting barriers for utilization of genetic services among Hispanic women and the Behavioral Model of Health Services Utilization, we developed and pilot tested an educational intervention to increase the uptake of telephone GC.

Methods: High-risk Hispanic female BC survivors without prior GC and/or testing were recruited using community-based approaches in Tampa, Florida, and Ponce, Puerto Rico. Eligible participants were consented and completed a baseline survey. Participants were then randomized to receive (1) a brief fact sheet about BC survivorship and the option to receive a survivorship care plan (SCP) (control), or (2) an educational booklet about GC and testing (developed based on multiple rounds of cognitive debriefing and targeted to Hispanic women based on preferences) with the option to receive telephone GC and testing free of charge (intervention). After randomization and mailing of educational materials, we followed up with participants 1 month after baseline to assess changes in knowledge and GC uptake. Quantitative data were analyzed using frequency distributions and independent sample *T*-tests.

Results: From the 82 women assessed for eligibility, 66 met inclusion criteria, and 51 (77.2%) consented and were randomized to the study conditions ($n = 25$ intervention; $n = 26$ control). Most women at both sites were between the ages of 51 and 60 years (52%), identified themselves as Hispanic white (68%), college graduates (48%), and had health insurance (88%). One month after baseline participants completed the follow-up assessment, knowledge in the intervention group increased compared to control group ($t(45) = -1.909$; $p = 0.045$). The majority of women in both groups opted to receive the offered resources (76% of the participants in the intervention group opted to receive GC and 89% of the participants in the control group opted to receive an SCP). The most common reasons for declining GC included lack of time ($n = 5$) and anxiety ($n = 1$). Control group participants did not seek genetic counseling and/or testing during the study period.

Conclusions: Results from this pilot study show significant increases in GC knowledge and utilization of genetic services, thus providing one approach to reducing disparities through the use of genetic and genomic services targeted to Hispanic populations.

A Spatial Analysis of the Breast Cancer Incidence Rates in Texas Counties, 2009–2013

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Background: During 2009–2013, 73,563 new breast cancer cases were reported in the State of Texas. During this 5-year period, the age-adjusted breast cancer incidence rates averaged 113.3 per 100,000 population at risk for the disease. The State of Texas is one of the states with the lowest breast cancer incidence rates in the USA. However, when comparing these same rates between Texas counties, the values

show a great variability that cannot be fully understood by only considering the age structure of the population. To date the influence of specific behavioral and environmental risk factors on the breast cancer incidence rates for Texas counties has not been accurately established. Thus, focusing on the effects of certain population and ecological characteristics distributed at these counties may help identify high-risk areas within the State of Texas. This study examines the ecological relationship between the breast cancer incidence rates and a series of known potential and proxy risk factors for the disease across Texas counties.

Data and Methods: The 2009–2013 Age-Adjusted Breast Cancer Incidence rates from the Texas Cancer Registry and data from the 2016 County Health Rankings were employed. A negative binomial model and an alternative regime linear model were fitted in order to measure the effect of potential and proxy cancer-related risk factors on breast cancer incidence rates in Texas counties and to identify high-risk areas.

Results: The effects of the risk factors for the disease is not stationary and tend to vary in magnitude across Texas counties with different sociodemographic characteristics. Counties located along the US–Mexico border showed lower breast cancer incidence rates, although these counties could be more vulnerable to the disease due to the high concentration of potential risk factors for the disease.

Significance: Promoting more health education programs and tailored interventions designed for reducing the impact of potential risks factors for the disease in high-risk areas could help moderate disparities and reduce the burden of breast cancer for the Texas families.

Systematic Review of Mammography Screening Educational Interventions for Hispanic Women in the United States

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Background: In the United States (US), breast cancer disparities persist for Hispanics compared to other ethnic groups. Breast cancer is the leading cause of cancer-related death among Hispanic women, and Hispanic women receive mammography screening at lower rates than other ethnic groups, which are associated with increased risk for possible late-stage diagnosis and lower survival rates.

Methods: This systematic review aims to synthesize the current literature on educational interventions to increase mammography screening among Hispanic women. The review included studies with experimental and quasi-experimental designs published between May 2003 and September 2017, which focused on diverse Hispanics in the US to increase the rates of mammography screening. Five studies met inclusion criteria for the review.

Results: All studies used an interpersonal intervention strategy employing community health workers, or promotoras, to deliver the intervention. For each study, odds ratios (OR) were calculated to estimate the intervention effectiveness based on similar follow-up time periods. The study ORs resulted in a narrow range between 1.02 and 2.18, indicating a low to moderate intervention effect for these types of interpersonal cancer education interventions. The summary OR for the random effects model was 1.67 (CI 1.24–2.26).

Conclusion: Hispanics exhibit lower levels of adherence to screening mammography. Interpersonal cancer education interventions such as the use of promotoras help to mediate the impact of major barriers to receiving a mammogram such as socioeconomic disadvantage, low health literacy, and lack of access to health care.

Racial/Ethnic Disparities in Patient-Reported Quality of Care Measures Among Medicare Breast Cancer Patients: Analysis of the SEER-CAHPS Data Set

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Background: Hispanics are less likely to receive appropriate adjuvant breast cancer treatment, which partially contributes to racial/ethnic disparities in cancer mortality. Excellent patient experiences with care, a measure of quality of care, is associated with receipt of recommended treatment for patients with chronic conditions; however, little is known about whether these measures are important for patients diagnosed with breast cancer. Therefore, the objective of this study was to identify racial/ethnic and socioeconomic differences in patient-reported experiences with care at the time of cancer diagnosis.

Methods: We used the SEER cancer registry and patient surveys from the Consumer Assessment of Healthcare Providers and Systems (CAHPS)-linked dataset to identify Medicare breast cancer patients diagnosed between 1997 and 2011, over the age of 65 years, and who completed a CAHPS survey prior to the date of diagnosis. CAHPS survey responses were used to generate five composite measures of patient experiences with (1) getting needed care, (2) getting needed prescription drugs, (3) getting care quickly, (4) physician communication, and (5) customer service. We created a binary measure for each composite score of 90–100 as excellent versus 80–100. In the multivariable logistic regression analyses examining racial/ethnic differences in the proportion of patients reporting excellent experiences with each composite measure, we included variables for age at survey, marital status, census tract-level poverty and education, SEER region, Medicare type (fee-for-services, Medicare advantage), survey mode (mail, telephone), comorbidities (0, 1, 2+), and survey year.

Results: Of the 10,144 patients, 80.7% were non-Hispanic white, 7.6% black, 7.1% Hispanic, and 4.6% Asian. The proportion of patients that reported excellent experiences for each composite measure are: (1) 70.2% for getting medical care when needed, (2) 76.5% for getting prescription care when needed, (3) 58.9% for getting access to medical care quickly, (4) 65.4% for communicating with their physician, and (5) 62.4% for customer service. After controlling for potential confounders, Hispanics had lower odds of reporting excellent experiences with getting needed medical care (OR: 0.75, 95% CI: 0.63–0.91) and with getting prescription drugs (OR: 0.79, 95% CI: 0.65–0.97) compared to non-Hispanic whites. More importantly, this pattern persisted in the stratified analysis by cancer stage (0, I–III, IV) for Hispanics versus non-Hispanics whites diagnosed with stage I–III breast cancer.

Conclusion: Among Medicare breast cancer patients, Hispanics compared to non-Hispanic whites reported poorer experiences with getting needed care and prescription drugs prior to their diagnosis. Research is needed to determine whether these racial/ethnic differences in patient experiences with care are associated with receipt of appropriate cancer treatment.

Racial/Ethnic Differences in Long-Term Adjuvant Endocrine Therapy Adherence and Mortality Among Medicaid-Insured Breast Cancer Patients in Texas: A TCR-Medicaid Retrospective Cohort Study

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Background: Racial/ethnic disparities in breast cancer mortality may be attributed to differences in adherence to adjuvant cancer treatment. Our purpose was to determine whether the mortality disparities could be explained by racial/ethnic differences in long-term adherence to adjuvant endocrine therapy (AET).

Methods: We conducted a retrospective cohort study with the Texas Cancer Registry and Medicaid claims-linked dataset of women (20–64 years) diagnosed with local and regional breast cancer who filled a prescription for AET from 2000 to 2008. Adherence to AET was measured at three time points (1-, 3-, and 5-year adherence) using a value for the percentage of medication filled for each period divided by the total number of possible prescriptions prescribed (medication possession ratio, MPR). We created a binary variable of adherence (MPR $\geq$ 80%). We performed multivariable logistic regressions to assess racial/ethnic differences in the odds of AET adherence and Cox proportional hazard models to determine the risk of mortality adjusting for AET adherence, potential confounding variables of area-level socioeconomic status, comorbidities, tumor prognostic factors, and other cancer treatment.

Results: Of the 1497 women with breast cancer who initiated AET, 56.9%, 42.3%, and 33.3% were adherent for 1, 3, and 5 years, respectively. The cohort was comprised of 37.8% non-Hispanic white, 18.6% black, 38.9% Hispanic, and 4.0% other race/ethnicity women with breast cancer. Hispanics compared to non-Hispanic whites did differ significantly in the proportion that were adherent to 5 years of AET (36.8% versus 35.3%). In the adjusted analysis for long-term adherence to AET, Hispanics did not have significantly increased risk of death compared to non-Hispanic white patients (HR: 1.13, 95% CI: 0.58–2.21). However, black compared to non-Hispanic white women had significantly lower odds of 3-year adherence (OR: 0.45, 95% CI: 0.28–0.73) and after controlling for 5-year adherence to AET in the fully adjusted model, the disparity in the risk of death between black versus non-Hispanic white women was reduced and no longer significant (HR: 1.86, 95% CI: 0.94–3.66).

Conclusions: Long-term adherence to AET in the Medicaid population is suboptimal and racial/ethnic differences in AET adherence may partially explain disparities in mortality since Hispanics were not less likely than non-Hispanic whites to be adherent to AET. This study underscores the critical need to ensure long-term adherence to AET for all racial/ethnic groups.

County-Level Socioeconomic Deprivation and Late-Stage Breast Cancer Diagnoses Among Hispanic Women in the USA

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Background: Annually, more than 230,000 women are diagnosed with breast cancer in the USA. Among Hispanic women, invasive breast cancer is the leading cause of cancer death in the United States. Further, Hispanic women are more likely to be diagnosed with regional and distant breast cancer than non-Hispanic white women. Timely diagnosis and treatment initiation are key in achieving best outcomes for these women; however, differences continue to exist in access to screening and diagnosis particularly among rural and minority populations. Despite lower overall mortality among Hispanic women who have breast cancer, having health insurance remains the most significant predictor of utilizing mammography services, with insurance rates being lowest for Hispanics. This research aims to examine the role that living in disadvantaged neighborhoods have on the likelihood of being diagnosed with late-stage breast cancer in Hispanic women in an attempt to understand disparities in accessing health care.

Methods: Using 2007–2014 data from the Surveillance, Epidemiology and End Results (SEER) Cancer Registry, the Texas Cancer Registry, and the Area Health Resource File, we construct a county-level deprivation index to examine disparities in late-stage breast cancer diagnoses among Hispanic and non-Hispanic women and net individual level characteristics. We use multilevel logistic regression models adjusting for spatial and temporal clustering.

Results: Preliminary results for women diagnosed with breast cancer between 2000 and 2013 in the SEER registry data show that Hispanic women (OR = 1.18; $p < 0.01$), women living in rural areas (OR = 1.12; $p < 0.01$), and women living in counties with higher levels of deprivation (OR = 1.06; $p < 0.01$) had higher odds of being diagnosed with late-stage breast cancer. Subgroup analysis for Hispanic women only showed that while rural/urban status did not impact their odds of late-stage diagnosis, the effect of the deprivation index remained unchanged.

Impact: Timely diagnosis of breast cancer is key in providing patients with chances for best outcomes, as late-stage diagnosis dramatically reduces 5-year survival rates. Identifying factors that limit timely diagnosis both on the individual and contextual level and how these factors differ among vulnerable patients (i.e., minority and rural women) can inform policy and program makers to design targeted interventions to improve access to care and treatment.

UPTAKE Study: Uptake of Preventive Surgeries Among Latinas with BRCA1/2 Mutations

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Background: Germline testing for BRCA1/2 genes provides an opportunity to reduce mortality and morbidity by adopting appropriate risk reduction and screening options, in particular risk-reducing bilateral salpingo-oophorectomy (BSO). There is a paucity of data on Latinas and prophylactic measures among BRCA1/2 carriers. Existing studies are limited either by the small number of Latinas or to a specific geographic location. Factors related to decision-making have also not been evaluated.

Methods: The UPTAKE study is an observational study of 100 Latinas with germline BRCA1/2 mutations. Subjects were recruited nationally and, by telephone interviews, reported uptake of prophylactic surgeries (BSO, bilateral mastectomy in unaffected women, and contralateral mastectomy in carriers with breast cancer (BC)). Women with ovarian cancer were ineligible. All women had to have been informed that they carried a deleterious BRCA1/2 mutation at least 1 year prior to completing the interview. Objectives of this study were (1) to examine the rate of uptake of prophylactic surgeries; (2) to identify acculturation and attitudinal factors related to decisions made; (3) to examine relationships between primary language, receipt of genetic counseling (GC) and in which language it was provided and uptake of prophylactic surgeries.

Results: Our population was diverse in terms of country of origin: 57% were born in the USA, 23% in Mexico, 6% in Puerto Rico, 4% in El Salvador, 3% in Ecuador, and 7% in other countries of Latin America. Seventy-seven percent of patients received genetic counseling before undergoing genetic testing. The majority of the patients received their genetic test results from the genetic counselor (45%) or the medical oncologist (36%). Most patients did not undergo multigene panel testing (77%). Forty-three patients had a deleterious BRCA1 mutation; 45 had a deleterious

BRCA2 mutation and 12 had both. Sixty-eight percent of women opted to undergo BSO and 61% were satisfied with the decision. Non-US-born women were more likely to be dissatisfied with their decision to proceed with BSO ($p = 0.03$). In a logistic regression model, uptake of BSO was related to young age ($p < 0.001$), being US born ($p = 0.03$) and higher annual household income ($p = 0.06$).

Conclusions: To our knowledge, this is the largest study that evaluates uptake of prophylactic measures in Latinas known to be BRCA1/2 carriers. Our study included a heterogeneous group of participants in terms of country of origin, income, and level of education including English knowledge and was conducted across various academic and community centers in the country. The uptake of prophylactic surgeries among Latinas with germline BRCA1/2 mutations was slightly lower (68%) than what has been reported in non-Hispanic whites (71–74%) but higher than in African Americans (32–50%). Our findings suggest the need for targeted interventions in this minority group to increase the uptake of measures with a reduction in mortality.

Interventions Addressing Latinas with Breast Cancer-Related Lymphedema (BCRL): A Review

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Background/Introduction: For Latina breast cancer survivors, breast cancer-related lymphedema (BCRL) is a treatment sequela with the potential to negatively impact physical and psychological function. Research has demonstrated that theory-based interventions can positively impact health behaviors that address BCRL development risk. Ethnic and cultural considerations can influence the outcome of such interventions, but may not be well understood in minority populations. With the increase in the Latino population in the United States, it is critical for the cancer care community to discover and address the factors which increase BCRL risk and may negatively impact long-term quality of life for this population. This literature review undertook to identify successful intervention strategies that address BCRL in the Latina population.

Methods: MEDLINE, Scopus, CINAHL, ONS website, and Google Scholar databases were searched. PRIMSA guidelines were used to assess and select articles for review. The review yielded 11 intervention studies from 2005 to 2017 addressing physical activity, diet, and quality of life concerns for the Latina breast cancer survivor.

Results: Most interventions using a theoretical framework were guided by social cognitive theory. For Latina breast cancer survivors, three strategies were found to be important for mediating healthful behavior change: overcoming language barriers,

observing social modeling, and enhancing self-efficacy. This review suggests that family involvement, peer mentoring, culturally tailored educational materials, and time to practice self-care skills are important elements of a behavior intervention that can lead to successful adoption of BCRL-risk reducing behaviors.

Conclusion: The literature suggests that more theory-based, culturally tailored interventions addressing BCRL risk in the Latina community are needed. An increasing Latina population makes such research highly pertinent in today's cancer care environment. Future studies could identify additional population factors and clarify behavior themes to provide stronger guidance for researcher activities and healthcare professionals who care for these survivors. Understanding the unique factors that influence health behavior for Latina survivors at risk for or living with BCRL could improve long-term behavior maintenance. Implications for practice: Healthcare professionals may benefit from more education about BCRL risk factors in Latina breast cancer survivors. Survivorship care plans should be culturally tailored and address interventions and assessment for long-term surveillance for BCRL. Culturally tailored assessment tools, education sources, and interventions should be developed and tested to address health behavior barriers. Family involvement in BCRL risk reduction and management activities should be considered for this population.

Dietary Intervention Among Breast Cancer Survivors Increased Adherence to an Anti-inflammatory Dietary Pattern: The Rx for Better Breast Health Randomized Controlled Trial

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Background: It is imperative to identify lifestyle interventions to reduce the risk of recurrence in breast cancer survivors (BCS). Pro-inflammatory dietary patterns have been associated with elevated cancer risk. The Mediterranean diet (MD) is an anti-inflammatory (AI) dietary pattern consisting of high intake of fruits, vegetables, whole grains, nuts, legumes, fish, and monounsaturated fats such as olive oil; moderate intake of dairy and alcohol; and limited red and processed meat. Additionally, the variety of antioxidant containing spices and herbs (SH) used in the

MD may contribute to its AI activity and health protective role. The majority of dietary interventions among BCS have been conducted in non-Hispanic white (NHW) women; thus, there is a need to test the efficacy of interventions in more diverse BCS populations. The aim of this analysis was to determine if a 6-month, culinary-based, dietary intervention increased adherence to an AI dietary pattern in NHW and Latina BCS.

Methods: Overweight and obese, early stage (0–III), English-speaking BCS who had completed treatment at least 2 months prior to study enrollment were randomized to the intervention (I; $n = 76$) or control (C; $n = 77$). The sample was recruited from the San Antonio, Texas area; over 50% of the baseline sample was Latina. The I consisted of individualized, AI dietary guidelines and behavior-change cues delivered during six monthly in-person workshops, monthly motivational interviewing telephone calls by trained patient navigators, and monthly newsletters tailored to individual change readiness. Each workshop consisted of a didactic portion, a cooking demonstration with a chef skilled in AI food preparation, a tasting, and interactive discussion. C participants received monthly informational brochures and no navigational services. At baseline and 6 months, participants completed an MD adherence questionnaire, an assessment of SH use, and a 3-day food diary. MD and SH questionnaire scores and 3-day food record variables were analyzed with a 2×2 repeated measures ANOVA. McNemar's test identified changes in adherence to individual MD guidelines and frequency of use of individual SH, between baseline and 6 months.

Results: MD scores in the I but not the C group significantly increased. The I group increased adherence to MD guidelines related to reduced red meat consumption ($p = 0.008$), increased fish and shellfish consumption ($p = 0.001$), and reduced consumption of commercial sweets and baked goods ($p = 0.007$). No significant changes in MD guideline adherence occurred in the C group. SH scores significantly increased in the I but not the C group. The I group significantly increased the use of cinnamon, turmeric, garlic, ginger, black pepper, and rosemary (p's < 0.05); only cinnamon use significantly increased in C group ($p = 0.039$). Although calorie reduction was not a focus of the I, the I group significantly reduced caloric intake ($p = 0.037$).

Conclusion: An evidence- and theory-based dietary intervention in BCS successfully increased adherence to an AI dietary pattern. These results can inform the design of future AI dietary interventions in diverse BCS samples as well as other cancer populations.

Nutrition Communication for Cancer Prevention Among Latinas: Toward a Dynamic Conceptualization of Acculturation

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Background: Health communication strategies, increasingly including mobile health strategies, have been effective at improving cancer-related behaviors; however, conceptualizations of "culture" in health communications and research have generally meant African-American culture or Spanish language translations. Thus, how acculturation—the process of adapting to mainstream US culture—interacts with communication influence processes is unknown. US Latinos hold particular beliefs, values, and attitudes, and these may be related to the ways in which information is processed. Explicating the dual processes of acculturation and media influence is critical to improving the efficacy of cancer communication strategies and eliminating Latino disparities. Diet behaviors provide an opportunity to examine how acculturation may complicate communication strategies, since epidemiological studies have demonstrated a "Dietary Acculturation Paradox": as Latinos acculturate, their risk for poor dietary behaviors increases. Specifically, acculturation to mainstream US culture is associated with increased consumption of high-fat foods including fast foods and decreased consumption of fruits and vegetables, making improved understanding of cultural influences on communication effects especially important for health communicators.

Purpose: This study—a work-in-progress at the time of abstract submission—aims to develop and test a set of culturally appropriate healthy diet text messages, extrapolating theoretical constructs that guide the integration of acculturation and cultural values and integrating these with the principles of message design and behavior change theories. The present study builds on findings from qualitative interviews with young adult Mexican-American women, which found that although feeling "Mexican" was a source of pride and that food was an important way to express one's Mexicanness, that food was perceived as unhealthy. Stated in another way, participants felt that to be healthy, they felt they had to reject traditional ways of eating. Thus, while appeals to culture may be necessary to garner the attention of bicultural Latinos, messages that simply advise Latinos to eat their cultures' "traditional" foods may backfire.

Methods: A team of bilingual, bicultural researchers developed original nutrition communication text messages using principles of cultural relevance and empowerment derived from the Decolonize Your Diet movement and cookbook. Development included a process of "transcreation" that has been previously employed. The messages will be tested with bicultural Mexican-American women aged 18–29 years and ultimately packaged as part of a mobile-enabled healthy diet intervention.

Discussion: This project will advance understanding of the dynamic influence processes of acculturation and communication on diet behaviors to inform effective nutrition communication interventions for cancer prevention among bicultural Latino/as.

The LLEAD Study (Latinas Learning About Density): A Three-Arm RCT to Examine Psychological and Behavioral Effects of Density Inform Legislation in a US Federally Qualified Health Center

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Background: Among Latinas, breast cancer is the most common cancer and the leading cause of cancer mortality. As more is known about the association between breast cancer risk and mammographic breast density, an increasing number of US states have adopted legislation that mandates written notification of breast density as part of the mammogram results letter. Examination of this notification has shown variability in content, understandability, and readability. The purpose of this study is to determine whether educational enhancement of mandated breast density notification results in increased knowledge of breast density as a breast cancer risk factor, decreased anxiety, and adherence to mammography among Latinas (primary cognitive, psychological, and behavioral outcomes).

Methods: LLEAD is an ongoing three-arm RCT comparing behavioral and psychological outcomes in Latinas who receive mandated mailed notification per current clinical practice (usual care) vs. two educationally enhanced approaches that are theory informed, culturally consistent, and novel in this context. Two thousand Latinas undergoing screening mammography in a federally qualified health center will be randomized 1:1:1 to mailed notification (usual care); mailed notification plus written breast density educational materials (enhanced); or mailed notification, written breast density educational materials, plus verbal explanation by a promotora (interpersonal). The study will examine the potential mechanisms through which written or verbal information influences motivation and continued screening behavior as well as potential moderating factors such as depression and breast cancer worry that have been linked to diagnostic delays among Latinas. The study includes multiple psychological measures (anxiety, depression, knowledge/understanding of breast density, perceived risk of breast cancer, breast cancer worry,

self-efficacy) and behavioral outcomes (continued adherence to mammography, discussion of breast density with a healthcare provider, uptake of supplemental screening). Measurement time points include baseline/enrollment, post-density notification, and 1 and 2 years post enrollment. Qualitative inquiry related to process and outcomes of the interpersonal arm and cost analysis related to its implementation will be undertaken to understand the intervention's delivery and transferability.

Results: This study is currently under way, thus trial results are unknown. Participant characteristics will be described for those presently enrolled; study measures (patient-reported, process, and outcome) and intervention materials will be presented along with challenges and "lessons learned" in implementing this trial and engaging Latinas in clinical research.

Significance/Impact: The effect of providing women with written notification of their breast density and its impact on breast cancer risk, absent other contextual information, may have unintended consequences, particularly among Latinas with lower health literacy and limited resources. Our study is intended to build the evidence base in the area of cancer risk communication and offer empirically tested, generalizable educational strategies for delivering density information to Latinas in limited-resource settings.

Applying a Community Engaged Model to Community-Clinic Linkages: Trial and Error in a Small Rural Town

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Introduction: Latinas continue to experience one of if not the highest rates of cervical cancer compared to other racial/ethnic groups in the United States. Latino parents seem to accept provider recommended HPV vaccines for their children, but continue to fall far below the Healthy People 2020 goal of 80% vaccination, especially for young boys. In 2016, up-to-date HPV vaccinations for Latino adolescents in the US was 49.9% (with 55.3% of females and 44.6% of males up-to-date). Furthermore, although national studies suggest higher vaccine rates among Latino children compared to other racial/ethnic groups, these national rates may be obscuring rural Latino rates, especially in states or areas that have higher than national averages of foreign-born Latinos, and lower than average rates of educational attainment and health insurance; all factors that can contribute to lower odds of vaccination status. For small rural towns, these factors may be exacerbated by economic, geographic, and social barriers to vaccine access. The Midwestern state in which the project was conducted does not have data available on Latino HPV vaccination rates.

This project is a description of the process used by our research group to build partnerships, identify major barriers to access based on community input, and to implement a project to link community education and clinic resources to increase access to the HPV vaccine in a rural Latino population.

Methods: This project was guided by principles of community-based participatory research (CBPR). We describe the adaption of the step-by-step process to a small town setting. We framed the project into three phases: (1) community approach and entry, (2) assessment and development, (3) implementation and evaluation.

Results: In Phase 1, we contacted and began building relationships with several civic and social organizations in the town, most notably the local Catholic Church, but also several informal Latino community leaders. We conducted a Photovoice project, a community forum, and had dozens of informal conversations with Latino residents. Two main objectives were identified as next steps: (1) develop tailored education for the community and (2) provide access to the HPV vaccine in town. Phase 2 began with the development of a group-based health education intervention, that for a variety of important reasons failed to reach many community members and was determined an ineffective method to increase vaccination rates. Through conversation with community advisors and partners, it became apparent that education did not have the necessary reach into the community and created confusion if we could not also provide access to the vaccine. This realization led to Phase 3 and the development and implementation of a community–clinic linkage to provide both HPV education and vaccination in a local setting.

Conclusion: The rural Latino population continues to grow around the country; however, the fastest growing Latino populations are often in rural or frontier areas and often in areas that have little experience serving Latinos. These emerging communities often lack access to health services and/or grassroot community organizations. Thus, it is important that we begin to examine, develop, and implement strategies that build on local resources and capital linked to resources in community settings. This project has been an attempt to develop such a process. Several important challenges were encountered and lessons learned that will provide important information for other similar communities across the Midwest and other rural areas.

Building a Health Temple Primary Cancer Prevention Program Among Latinos

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Introduction: The Building a Healthy Temple (BHT) Primary Cancer Prevention Program is a translational research program adapting and implementing "Body and Soul," an evidence-based cancer prevention program created for African-American churches, into Latino churches. BHT aims to reduce cancer risks through the promotion of healthy lifestyles among Latinos.

Methods: BHT was a 4-month program adapting the four pillar model of B&S. BHT intervention components included Health Sermons, Health Bible Study, Nutrition Education and Cooking Demonstrations, Active Living Competition, Health Ministry Committee (HMC), church health-conducive environmental changes, and Peer Counseling by trained health lay leaders. The program was implemented in 17 churches and reached approximately 3422 individuals in San Antonio's low-income neighborhoods between 2014 and 2017. Using a one group pre/post-test design, BHT measures both congregational and individual level changes. Congregational level outcomes (i.e., nutrition and physical activity environment) were measured by the Congregational Health Index. Individual level eating and physical activity behavior were measured using the National Cancer Institute Dietary Screener Questionnaire and the International Physical Activity Questionnaire short form, respectively. Self-reported body mass index and waistline, as well as social demographics, were also assessed. Data were collected at baseline, endpoint, and 1-year follow-up.

Results: At the church level, BHT significantly improved churches' nutrition environmental/policy. Examples of nutrition environmental/policy improvements made by church HMCs include church provision of nutritious meals and refreshments; increase in healthy beverage availability; church provision of low-fat options; and church practice of food purchasing and preparation to reduce fat content of foods. BHT also improved church physical activity (PA) environmental and policy. Examples of PA environmental/policy improvements made by church HMCs include improved church-built environment to support PA; increased PA equipment availability at church; church promotion of PA; improvement in safety of church PA facilities. At an individual level, BHT was effective in reducing added sugars and added sugars from beverages, as well as increasing dairy and calcium consumption. BHT also increased the proportion of participants who met dietary guidelines for fruit and vegetables from 8.3% baseline to endpoint with 13.9% ($n = 110, \chi^2 = 22.87$, $p < 0.05$) of participants meeting USDA guidelines for fruit and vegetable consumption. The percentage of participants meeting the Physical Activity Guideline (150 min of moderate or 75 munities of vigorous activity per week) significantly ($n = 149, \chi^2 = 16.4, p \leq 0.001$) increased from 57% at baseline to 75% endpoint. In addition, BHT significantly decreased mean BMI and waist circumference among overweight and obese participants.

Conclusion: The BHT program targets three preventable cancer risk factors, i.e., poor nutrition, physical inactivity, and obesity, among Latinos. BHT has significantly improved both church environment and individual lifestyle leading to reduced

cancer risks. BHT has the potential to be disseminated on a broad scale to meet community needs, impact practice and policy, and ultimately lead to the reduction in cancer risks among underserved Latinos.

Culturally Relevant and Appropriate Cancer Risk Counseling and Education for Underserved Latinas

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Background: Research demonstrates that Latinas are highly likely to have cancer risk associated with genetic predisposition to breast cancer and ovarian cancer. In addition, underserved Latinas have a compelling need for access to genetic cancer risk assessment (GCRA) and cancer screening and prevention measures, along with culturally appropriate education.

Objectives: The primary purpose of this project was to evaluate the effectiveness of a culturally relevant GCRA educational intervention for Latinas.

Methods: Four focus groups were conducted consisting of Latinas that have undergone GCRA. Participants completed a demographic questionnaire that included items assessing perceived cancer risk and patient satisfaction. The focus groups entailed a facilitated discussion of the key study variables and other culturally relevant issues that may impact the GCRA intervention. Descriptive statistics and thematic analysis were used and analyzed.

Results: Findings show that there is a perceived sense of lack of information, education, and uncertainty about what to expect appeared to play a key role in distress. Most women initially had negative expectations (expecting the worse or bad outcome), but ultimately felt hopeful that they could learn more about the GCRA process and what it meant for them. Information was cited as the primary contributor to positive psychosocial outcomes specifically increased locus of control and self-efficacy. Cultural themes identified were destiny, religious, and spiritual coping mechanisms, how cultural attitudes and beliefs influence lack of information, community awareness, and public health issues.

Conclusions: Findings indicate that the pre-GCRA window may be most distressing for this population indicating that this may be the most appropriate time for psychological intervention.

Disseminating Cancer Education and Navigation Training to CHWs

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Background/Introduction: The Access to Cancer Training, Information, Outreach and Navigation (ACTION) project engages Community Health Workers (CHWs) and organizations to deliver culturally competent cancer education to vulnerable communities in Texas. By disseminating CHW training on Breast, Cervical, and Colorectal Cancer prevention, detection, treatment, survivorship, and cancer navigation, the ACTION project aims to reduce disparities in cancer knowledge, screening, and outcomes.

Methods: With funding from the Cancer Prevention Research Institute of Texas, the team of CHWs and instructors prepared ten CHW training modules in-person and online, in English and Spanish. All modules are available at no charge to CHWs. In addition to training modules, the ACTION project provides print and online resources for cancer education and outreach for CHW use in their home communities. For organizations, the ACTION project provides packaged curricula, technical assistance, and supporting materials to assist with the implementation of new CHW cancer training and outreach programs across the state.

Results: Over 1000 CHWs received training and resources in the first 21 months of the 2-year project. Through partnerships with CHW organizations in Laredo, Harlingen, Rio Grande City, Corpus Christi, Tyler, Bryan, Austin, and Houston, ACTION CHW instructors trained 341 CHWs in person. An additional 746 CHWs received training through self-paced, online courses. As measured through pretests, baseline cancer knowledge for CHWs participating in-person was 80% and 84% for online. Posttest scores indicate an increase in 9.7% points for online participants and 10.9% points for in-person trainings.

Significance: Training and supporting CHWs is a promising strategy for improving cancer education and navigation knowledge. More informed CHWs and better-equipped CHW organizations can effectively promote behaviors to prevent, detect, and manage cancer diagnoses in their communities. Disseminating bilingual, community-based resources through in-person and online channels to CHWs and organizations has the potential to reduce disparities in accessing cancer information, screening, treatment, and survivorship services.

Improving Cancer Screening Outcomes in Latinos Through Culturally Appropriate Navigation Services

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Background/Introduction: For over a decade University Health System has promoted healthy behaviors, such as early cancer detection and screening, in South Texas Latino communities using the A Su Salud model which combines aspects from Social Cognitive Theory, the Stages of Change, and the Health Belief model. We focused on screening for colorectal, breast, and cervical cancer because Latinos are more likely to be screened later and diagnosed with advanced stages of these cancers compared to non-Latino whites. Access to screening services is particularly difficult for uninsured and underinsured Latinos, who experience barriers to care such as transportation, financial limitations, fear, and cultural concerns. We aimed to motivate, initiate, and sustain health-seeking behavior changes by increasing patient knowledge about colorectal, breast, and cervical cancers and the benefits of preventive care, addressing cultural factors, and reinforcing a relationship of trust with the Health System.

Methods: Our patient navigation approach used a combination of culturally tailored, social cognitive theory-based techniques to educate patients, dispel myths, provide social support and initiate system changes to remove organizational, financial, and other major barriers associated with the completion of colonoscopies, mammograms, and Pap tests. The navigators served as liaisons between the community and patient care services to increase screening rates. Through face-to-face interactions, they created a link with patients which removed barriers to screening by providing support during the period between scheduling and completing the procedure, as well as on the scheduled screening date. Transportation to and from colonoscopy appointments and a companion for the ride home were provided for those who needed it, eliminating a common barrier for this population.

Results: A total of 11,292 patients were navigated to screening services, 2079 to colonoscopies, 4714 to mammograms, and 4499 to Pap tests. In addition to navigation services, our program funded a total of 38,403 screenings for colon, breast, and cervical cancers, reducing the financial burden on our community. Of those who completed cancer screenings, four patients were diagnosed with colon cancer, five women were diagnosed with breast cancer, 205 women received abnormal Pap results, and 21 women were diagnosed with cervical cancer. Program satisfaction was high, with 98% indicating the navigator worked with them to overcome challenges to receiving care, they were satisfied with the navigator program, and they would recommend this program to others.

Conclusion/Significance/Impact: We successfully addressed financial, systemic, and cultural barriers to cancer screenings for Latino men and women. Results from a system change evaluation confirmed the program was cost-effective, integrated suitably into University Health System, improved the Health System's ability to serve its patients, and earned high patient satisfaction. Use of the A Su Salud model to promote and sustain healthy behaviors in underserved Latino communities enabled the transformation of navigators into community champions who facilitated access to care where it may not have been possible previously.

Outcome Evaluation of a Community Health Worker-Delivered Breast and Cervical Cancer Screening Intervention Targeting Low-Income Hispanics

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Background: Hispanic women are less likely to receive preventive breast and cervical cancer screenings, leading to later stage breast cancer diagnoses and lower survival rates, as well as higher cervical cancer incidence and mortality among Hispanics compared with non-Hispanic whites. We adapted an evidence-based community health worker (CHW)-delivered screening education and referral intervention (Cultivando la Salud) developed for rural Hispanic migrant farmworkers, to deliver to medically underserved Hispanic women in urban settings. CHWs delivered the adapted intervention using new outreach and implementation strategies, including conducting group education rather than one-on-one education sessions. We examined the effect of the adapted intervention on increasing Pap and mammography screenings.

Methods: We conducted a community-based randomized controlled trial to assess the effectiveness of the CHW-delivered screening education and referral program targeting low-income Hispanic women non-adherent to screening recommendations. Women were eligible if they were over-due for mammography and Pap screening based on age-specific American Cancer Society recommendations and had no history of cancer or hysterectomy (for the Pap screening group). Bilingual data collectors conducted baseline and follow-up surveys 6 months after baseline. Logistics regression was conducted using both intent-to-treat and per-protocol analysis to evaluate the effect of the intervention on mammogram and Pap screening, adjusting for covariates significant at the $P < 0.20$ in univariate analyses, as well as adjusting for time to follow-up in the per protocol analyses.

Results: We enrolled 1025 women in need of a breast and/or cervical screening. Women were randomized to mammography and Pap screening intervention and

control groups, according to screening needs. Among women followed up, 39.9% received a mammogram in the intervention group compared with 20.3% in the control group ($P = 0.001$) and 55.8% received a Pap screening in the intervention group compared with 27.4% in the control group ($P = 0.001$). Among the breast screening cohort, compared with the control group, women in the intervention group had 2.02 increased odds of receiving a mammogram compared with women in the control group, based on the adjusted intent-to-treat analysis (adjusted OR = 2.02, 95% CI: 1.42–2.87) and 2.17 times greater odds of screening in the adjusted per protocol analysis (adjusted OR = 2.17, 95% CI: 1.48–3.18). Among the cervical screening cohort, compared with the control group, women in the intervention group had 1.84 increased odds of completing a Pap screening based on the adjusted intent-to-treat analysis (adjusted OR = 1.84, 95% CI: 1.21–2.78) and 3.09 increased odds based on the adjusted per protocol analysis (adjusted OR = 3.09, 95% CI: 1.88–5.08).

Conclusion: The adapted CHW-delivered intervention effectively increased breast and cervical cancer screenings among Hispanic women. Future research is needed to further strengthen the intervention effect among those who did not overcome personal and environmental barriers to complete needed screenings.

Appendix C: Engaging Latinos in Research Across the Cancer Continuum

Challenges and Opportunities Using Mobile Technology for Data Collection in Biomedical Research: An Observational Discovery Science Investigation with Spanish-Speaking Latinas

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Background/Introduction: Mobile devices including phones offer significant contributions to improve reach and convenience of research participation and data collection. Technological advancements have enabled smartphone devices to track health behaviors such as physical activity and provide convenient feedback as well as survey data. High usage of mobile devices, i.e., smartphones among both US-born and immigrant Latinos may not similarly translate to mobile technology utility for research participation among Latinos and other ethnic minority populations. Among Latinos, smartphones are primarily used for communication as only 50% use the data application capabilities. The acceptability and application of mobile data harnessing tools can present both opportunities and challenges for engaging this population in research. We report our observations of the challenges Latinas face using mobile technology for data collection.

Methods: Latina mothers were recruited from school to participate in a behavioral nutrition and physical activity study for cancer and chronic disease risk reduction. A total of 38 enrolled and 32 participated in the intervention.

Results: Sixty-three percent were Spanish speakers, 59% were foreign-born, 66% had ≤high school education, 91% reported income <$40,000. Participants used a mobile device to perform two tasks: (1) complete a REDCap online survey on a

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tablet and (2) download and install a fitness tracker mobile application. Latinas rated their confidence in their ability to use mobile technology using a 4-point Likert scale. Participants with little/no confidence requested paper versions of the survey. Eighty-eight percent required individualized research staff assistance to complete the survey and set up their fitness tracker. Monolingual Spanish-speakers were more likely to report little/no confidence connecting to Wi-Fi ($\chi^2 = 13.175$, $p < 0.01$), downloading an app ($\chi^2 = 11.277$, $p = 0.01$), creating an electronic account ($\chi^2 = 7.882$, $p < 0.05$).

Conclusion/Significance/Impact: Our findings suggest that lower-income, Spanish speakers require more assistance and ongoing guidance with technology applications and devices for research data collection. In fact, we found that about 20% shared the device (Fitbit) with family members, especially children to facilitate the participants' use of the device. However, this threatened data accuracy. Therefore, studies using mobile technology should account for the added staffing and resources required to conduct studies with this population. Addressing this barrier may require a pre-study session to train research participants on the study's technology applications. Further research is needed to evaluate and improve the applicability of mobile technology for increasing reach and participation, as well as validation of data accuracy for medically underserved and understudied populations.

A Bigger Voice: Hispanics Increasing Diversity to Enhance Advocacy in Science (H-IDEAS)

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Background and significance: Breast cancer is the most common cancer type and the number one cause of cancer death among women in Puerto Rico. Historically, breast cancer survivors have played an important role as advocates in advancing science. Moreover, there is a lack of representation of Hispanics in scientific review panels, and clinical studies increasing the need of representation in important forums to advocate for studies in Hispanics with breast cancer. The specific aim for the project is to create a scientific advocate group of trained Hispanic cancer survivors who will participate (1) in research proposal reviews, (2) as part of key personnel within research studies, (3) in patient recruitment from clinical studies, and (4) in cancer research information dissemination in Puerto Rico and abroad. By increasing minority populations trained to serve in review panels, engage in cancer research, and help in patient recruitment, this project ensures that everyone, including Hispanics, will have an equal opportunity to live long, healthy, and productive lives.

Methods: This educational project will be conducted in a 1-year period. A group of 15 breast cancer survivors were recruited. The inclusion criteria included: being a woman between the ages of 18 and 65 years, resident of Puerto Rico for at least 10 years, being diagnosed with breast cancer, be bilingual (written and spoken, English and Spanish), and have an interest in the science of cancer and peer review research process. The participants were recruited through word of mouth, email, social media, and flyers. After the initial contact by the potential candidate, they had to complete an application, and a telephone interview was conducted. Once the participant was chosen, a written agreement was signed by each of them. The training began with an intensive 3-day curriculum with topics on cancer and breast cancer overview, introduction to genetics and immunology basics, experimental designs and evidence-based medicine, ethics, good clinical practices, and breast cancer clinical trials in Puerto Rico. Follow-up sessions are conducted every other month to increase and reinforce scientific advocacy knowledge as well as hand on activities such as poster development, oral presentations, and mock study sessions.

Results: Preliminary evaluation suggests that participants acknowledge the need of this projects to allow them to be proactive in their role as advocates. Also, they have demonstrated to be highly engaged and motivated to continue their journey as scientific advocates. Data in progress.

Conclusion: This innovative project is unique in addressing the needs for bigger voice of Hispanics as scientific advocates. To our knowledge, this is the first advocacy training to Hispanics adapted to their culture and language.

Éxito!: Increasing Latino Representation in Cancer Control Research

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Background: Cancer is now the top leading cause of death among Latinos, making it critical to develop the next generation of researchers who can tackle and solve Latino cancer issues. However, few Latinos seek doctoral degrees. Exito! Latino Cancer Research Leadership Training aims to increase ethnic diversity in the field of Latino cancer health disparities (CHD) by encouraging minority master's-level students and master's-trained health professionals to pursue a doctoral degree and a career in cancer health disparities.

Methods: Twenty-five participants attend a 5-day Summer Institute (SI). The SI is led by recognized Latino researchers, faculty, and role models. During the SI, participants are exposed to interactive activities, tips/tools for applying and completing a doctoral degree, information on funding, mentorship, and Latino CHD research. Ten, 6-month internships in Latino CHD research are also awarded annually.

Results: From 2011 to 2017, 151 individuals have come through the SI and 37 internships have been awarded. Results from the SI show a significant improvement in academic self-efficacy in attendees. Improvements in confidence toward applying to a doctoral program in the next 5 years are also seen. Results for internships show significant improvements in students' research skills across all measured domains. Twenty-four percent (n = 36) of our alumni are currently enrolled in a doctoral program.

Conclusion: Exito! results indicate an improvement in master's-level students' and master's-level health professionals' confidence and capacity to pursue and complete a doctoral degree leading to careers in cancer control research. The Éxito! program provides the necessary encouragement to build a new pipeline of Latino doctors and cancer researchers.

Fostering Cancer Education and Participation in Research Among Immigrant Latinos

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Background: Cancer is the leading cause of death among Latinos in the USA. Louisiana has one of the highest cancer mortality rates and a Latinos' growth rate higher than the national one. Although research has shown that Latinos have low health literacy and English skills, no study had focused on measuring or addressing cancer literacy in immigrant Latinos in Louisiana, where majority come from Centro America and have low education and English skills.

Objectives: To identify and address barriers to cancer screening, participation in cancer research, and donation of biospecimens among immigrant Latinos in Louisiana.

Methods: The Cancer Health Literacy Test (CHLT-30) was translated to Spanish, culturally adapted, pilot-tested, and validated among Latinos in Louisiana. Results of the assessment of cancer literacy were used to identify misconceptions and knowledge gaps regarding cancer risks, screening, and research. Focus groups assessed the applicability of educational materials selected from the literature review and that addressed the gaps identified. The training "Cancer 101: A Cancer Education and Training Program" (Briant et al.), available in Spanish, was selected, adapted, and pilot-tested with ten Latinos from different age-ranges and educational backgrounds. The resulting training "Cancer 101 for Latinos" was developed using three different delivery options (print, video-based, and face-to-face). A field test of the feasibility and preliminary comparative effectiveness of the three interventions was conducted

with a stratified sample (by gender, age range, and education) of 54 Latinos, who were randomly assigned to the different arms (18 in each arm). All participants completed the same pre-post tests before and after the intervention and also completed evaluation of the training.

Results: A total of 500 Latinos (half women) completed the CHLT-Spanish version. In general, participants were young (42% 25–40 years old; 30% 41–55; 28% older than 55+) and had low educational levels (37% less than high school; 49% high school or some college; 14% advanced degrees). While 17% scored in the lower level of CHL (0–10), 49% scored in the medium level (11–20), and 34% in the higher one (21–30). Although majority of participants (>70%) were willing to participate in studies requiring to complete a survey, attend an educational intervention, or give samples (saliva, cheek cells, urine, or blood), lower percentages (<45%) were willing to take an experimental natural supplement or drug, donate skin or tissue, or undergo a minor or major experimental procedure. For the field tests of the three interventions, 54 Latinos (24 males, 30 females) completed the study. There were no significant pre-post test differences by education, gender, or intervention type; but there was a slight difference ($p = 0.06$) in the interaction between difference scores and age. Ultimately, the difference scores proved that overall participants learned more about cancer after receiving an intervention, regardless of type. In the learning process, there was a significant difference ($p < 0.05$) with education in the posttest scores.

Conclusion: Addressing cancer literacy in immigrant Latinos is becoming critical for increasing their participation in cancer screening and research. Results show that educational interventions may be the best approach to address lack of knowledge and trust about cancer research. However, considering that no intervention method (print, video-based or face-to-face) produced higher knowledge changes, we recommend the use of hybrid educational methods to address the learning needs of immigrant Latinos.

Hispanic Patient Navigation: Improving Cancer Care and Clinical Trial Participation

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Introduction: Hispanics are the fastest growing population in North Carolina and have unique healthcare needs related to culture and language. To meet their needs and address the historically low participation in cancer clinical trials, we developed a bilingual Hispanic Clinical Trial Navigator (HCTN) position to support Hispanic adult and pediatric patients treated at Wake Forest Baptist Comprehensive Cancer

Center (WFBCCC). The HCTN is a novel approach to integrate culturally and linguistically competent navigation with support around clinical trial decision-making. The purpose of this analysis was to evaluate the services provided during the program's first year and its impact on clinical trial participation.

Methods: Retrospective data from November 1, 2015 to October 31, 2016 was obtained from a navigation database, WFBCCC cancer registry, and clinical trial system. Data were reported in the aggregate, and clinical trial participation rates were compared to data prior to the hiring of the HCTN (November 1, 2014 to October 31, 2015).

Results: There were 108 pediatric and adult patients navigated during the first year; 55 breast screening/diagnostic, and 53 cancer treatment. The majority of patients were female (87%) with a mean age of 45 years. The most common diagnoses among treatment patients were breast (47%), hematologic (34%), and gastrointestinal (6%) malignancies. Major patient barriers identified by include treatment logistics/transportation (87%), financial/insurance (70%) information/education (55%), and continuity of care (53%). In addition to education and referrals, the HCTN was able to remove potential barriers to trial participation through transportation assistance (31%), meal vouchers (21%), and parking validation (40%). In the year prior to the HCTN, there were 88 newly diagnosed Hispanic patients with a clinical trial participation rate of 20% in treatment/non-treatment intervention studies. With HCTN navigation, clinical trial participation among Hispanic patients navigated was 34%.

Conclusions: Navigation is now available in a majority of community cancer centers and is an opportunity to provide culturally and linguistically appropriate patient support around cancer and clinical trials. Our initial data indicates a success in increasing Hispanic participation in cancer clinical trials utilizing a HCTN. Future data analysis is planned after completion of the second year of the program. Placing HCTNs in cancer treatment settings could be a cost-effective and efficient method of providing navigation, while also facilitating state-of-the-art care through clinical trials. Opportunities exist for additional studies of navigation to increase clinical trial participation in underserved populations. Increased and equitable participation in clinical trials is necessary in ensuring that the future of cancer care is applicable to all.

Localized Translation and Real-Time Interpretation of Informed Consent Forms in Pediatric Oncology Clinical Trial Participation

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Background: Pediatric oncology patients and Limited English Proficiency (LEP) parents commonly experience language, social, and cultural barriers throughout the course of treatment, particularly at the time of diagnosis. Hispanic linguistic and cultural studies combined are essential to positively impact health services and trial participation for LEP families.

Methods: The cohort consisted of 42 LEP families. We (1) collected recurrent questions and clarifications during initial consenting with a Mexican Spanish (es-MX) language variant under the Spanish Language Family text corpus and (2) categorized the patients' and LEP parents' lexical variations at follow-up visits by clarifying geographical origin.

Results: We observed that (1) 93% of Spanish LEP parents and patients responded positively to the es-MX translation of consent forms, (2) 61% favored lexical variations of northern Mexico, (3) 29% favored lexical variations of central Mexico, (4) 7% favored lexical variations of Central and South America, (5) 3% of patients opted to not enroll in a clinical trial based on other sociolinguistic challenges.

Conclusion: Our data indicated that (1) localization of the consent form translation and (2) vocabulary with a high regional affinity in interpretation interactions alleviated difficulties and engaged the parent as an active member of the child's clinical trial participation.

Impact: This retrospective analysis was conducted to validate the applicability of knowledge of patient linguistic preferences as essential for interpretation and translation of clinical trials to ensure full participation. We hope to add sociocultural, sociolinguistic, and treatment compliance measurements to future analysis and see this work as a first step toward cognitive debriefing analysis.

Appendix D: Living with and Beyond Cancer: Taking Action to Improve Outcomes

Development and Feasibility Testing of the My Guide Intervention for Hispanic Breast Cancer Survivors

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Background: Breast cancer (BC) is the most commonly diagnosed type of cancer among Hispanic women living in the USA, and relative to non-Hispanic white women, Hispanic women report poorer quality of life (QOL) after treatment. Smartphone interventions are a viable approach for addressing healthcare accessibility issues and improving QOL outcomes among cancer survivors, especially among Hispanics with documented increased levels of Internet use for accessing health information. This study describes the development and iterative testing process of My Guide, a culturally tailored smartphone-based intervention for Hispanic breast cancer survivors.

Methods: To develop the My Guide content, we conducted semi-structured field interviews with English- or Spanish-speaking Hispanic breast cancer survivors ($n = 9$). Transcribed interviews were coded for prevalent themes using NVivo software. Next, our study team conducted preliminary usability testing on participants and community stakeholders ($n = 9$). Finally, Hispanic breast cancer survivors ($n = 25$) were enrolled in a 4-week feasibility study to assess the initial satisfaction and demand for My Guide.

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Results: The most prevalent themes in the semi-field interviews were fear of recurrence (mentioned in 89% of interviews), patient–provider communication and social support (mentioned in 100% of interviews), and side effects of cancer treatment, psychological well-being, and breast cancer knowledge (mentioned in 78% of interviews). Eighty-five percent of eligible participants enrolled in the My Guide feasibility trial, and the retention was 90%. The mean number of hours spent using the application across the 4 weeks was 8.54 h (SD = 4.44). The mean score on the satisfaction survey was 4.59/5 (SD = 0.76), in which higher scores reflect more favorable reviews of the application. Results from feasibility trial revealed additional content and features that women wanted in future versions of the My Guide application. These data were used to improve the My Guide application, which is currently being testing in a randomized clinical trial.

Conclusions: Study findings underscore the relevant needs and concerns for Hispanic breast cancer survivors and suggest that the My Guide Smartphone application may be a feasible application. Considerations for developing a culturally and linguistically adapted smartphone application will be discussed.

Disparities in Financial Hardship Among Hispanic and Non-Hispanic White Colorectal Cancer Survivors

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Introduction: With rising cancer care costs and a growing burden of out-of-pocket cost-sharing requirements, patients diagnosed with cancer have become increasingly financially vulnerable. Yet racial/ethnic variation in the financial experiences of individuals with cancer remains largely understudied. The objective of this study was to assess financial hardship among Hispanic and non-Hispanic whites in a population-based sample of colorectal cancer survivors.

Methods: Individuals diagnosed with localized or regional colorectal cancer from 2004 to 2012 were identified from the population-based New Mexico Tumor Registry, a member of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. Potential participants were asked to complete a survey (in English or Spanish), by mail (paper) or telephone, to assess the experiences of colorectal cancer survivors in New Mexico. Hispanic and rural cancer survivors

were oversampled. Information on ethnicity and primary language spoken was used to form three exposure groups: (1) primarily English-speaking Hispanics, (2) Spanish-speaking Hispanics, and (3) non-Hispanic whites. Financial hardship was measured by four items asking participants if they ever (1) had to borrow money or go into debt, (2) had to file for bankruptcy, (3) were unable to cover their share of medical care costs, or (4) made other financial sacrifices because of cancer, its treatment, or lasting effects of treatment. We created a dichotomous measure of any financial hardship based on responses to these four measures. Multivariable logistic regression was used to estimate adjusted odds ratios (ORs), adjusting for participant sociodemographic, geographic, and health literacy characteristics.

Results: Among 277 colorectal cancer survivors, 40% ($n = 111$) identified as Latino or Hispanic ($n = 67$ English-speaking and $n = 44$ Spanish-speaking). Financial hardship was reported by 68% of Spanish-speaking Hispanics, 42% of English-speaking Hispanics, and 38% of non- Hispanic whites. In multivariable analyses, Spanish-speaking Hispanics were significantly more likely to report treatment-related financial hardship (OR 3.09, 95% CI 1.39–6.87), compared to non-Hispanic whites; although, no significant difference was observed between English-speaking Hispanics and non-Hispanic whites (OR 0.83, 95% CI 0.42–1.64). Rural county residence, health literacy and marital status were also found to be significantly associated with financial hardship, in multivariable adjusted analyses.

Conclusions: Our findings highlight important disparities in the financial hardship from cancer between Spanish-speaking Hispanic and non-Hispanic white colorectal cancer survivors. Given that prior evidence suggests cancer survivors who experience financial hardship are more likely to delay or forgo care and may have poorer health outcomes, future research is needed to assess the unique financial experiences among Spanish-speaking Hispanic cancer survivors. Such efforts may inform the development of interventions to reduce financial hardship from cancer in this at-risk population and potentially prevent widening disparities in cancer outcomes.

Going Through Cancer Together as a Family: The Experiences of Hispanic Mothers Diagnosed with Cancer

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Background: Approximately 1.5 million cancer survivors are parents of minor children, with approximately 80% of these survivors being women under the age of 50 years. Approximately one third of these mothers are in the early phases of cancer treatment and recovery. Most of what is known about the challenges of parenting dependent children following a cancer diagnosis is based on studies with NHW mothers. However, relatively little is known about the experiences of Hispanic mothers diagnosed with cancer and their families, particularly those residing along the US–Mexican border. This is unfortunate given that Hispanics demonstrate significant disparities in cancer care, outcomes, and overall disparities compared to NHWs. The purpose of this study was to describe, in their own words, the lived experiences of Hispanic mothers who were in the early phases of cancer treatment and recovery while concurrently rearing dependent children.

Methods: Nine cancer-diagnosed Hispanic mothers of Mexican descent participated in focus groups or individual interviews, responding in their preferred language. Study questions assessed parent–child communication surrounding cancer, parenting experiences while managing the cancer, family support, and the impact of cancer on the family. Study data were transcribed verbatim, translated to English, and coded using inductive content analysis within a framework of grounded theory. Trustworthiness of study results was protected by coding to consensus, systematic peer debriefing, and maintaining an audit trail.

Results: The core construct that organized the data was "Going through Cancer Together as a Family" which consisted of 48 categories organized across 15 domains. The data were organized into four key areas: (1) the advantages of being open and honest about the cancer with the children; (2) what and how much to share with her children about the cancer; (3) mom's evaluation of her maternal role and the impact of her cancer on her children; and (4) the children's choice to take care of the mother even as they retained her identity as mom.

Conclusion/Significance: Mothers and children mutually assisted and protected each other from the negative impact of cancer. This study highlights the importance of research examining the dimensions of relational coping among Hispanic women diagnosed with cancer and their families.

Health Behavior Engagement, Obesity, and Symptom Management in Latina Breast Cancer Survivors: A Qualitative Study

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Background: Breast cancer survivors are at risk for weight gain, obesity, and diabetes. Relative to other ethnic groups, Latinas are at even greater risk of diabetes and obesity and are more likely to experience other breast cancer-related symptoms, including fatigue and negative mood. Symptom burden is further compounded in this population by lower socioeconomic status and limited access to resources (e.g., car transportation, specialty medical care). Importantly, engaging in health behavior change to achieve weight loss can significantly reduce the number symptoms and their severity among breast cancer survivors. Thus, understanding the complex interplay of obesity, health-behavior engagement, and symptom experience among a group of high-risk, under-resourced Latina breast cancer survivors is a critical next step for addressing this disparity.

Purpose: To obtain an in-depth understanding of Latina breast cancer survivors' perception of factors that contribute to their own health, and the potential connection between their engagement in particular health behaviors and whether these behaviors alleviated symptoms.

Methods: We conducted 17 focus groups in both English and Spanish with 70 Latina women who had undergone treatment for breast cancer to further understand the role of Hispanic culture in the breast cancer survivor experience, cultural-specific motivators and barriers, as well as symptom burden, to engaging in a healthy lifestyle during survivorship.

Results: A common theme that emerged from the focus groups was that a healthy lifestyle helped alleviate some of their symptoms. Some quotes to provide direct examples include: "For me, the more that I exercise the more active I feel. I also want to be healthier and to feel better. When I do not exercise I feel more fatigued, more tired. The body is not the same after you have been through a lot." In response to asking what made her start walking another patient said: "Well, because I was feeling like I was not feeling good with myself. I was feeling bloated and the doctor said that it would probably help. So I did and I just felt better, you know. I know, so I started walking a lot and like 30–40 minutes a day."

Conclusions: Findings suggest under-resourced, high-risk Latina breast cancer survivors recognize a potentially important link between healthy behavior and symptom management. This awareness has the potential to be leveraged to create meaningful lifestyle modification programs.

Latino Adolescent and Young Adult Childhood Cancer Survivorship

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Background: Survivorship concerns of Latino adolescents and young adults may be different from those of the general population due to varied understandings of the disease and illness, age, language barriers, cultural beliefs, and values; therefore, engaging this population in research is vital to successful care delivery and survivorship. About 5000 adolescents are diagnosed with cancer each year in the USA. Adolescents and young adults with cancer are usually treated by pediatric cancer specialists if they have a type of cancer more common in children, and by adult cancer specialists if they have a type more common in adults. Either way, they are unlikely to run into other patients like themselves and often feel out of place. This research is essential because of the need to address cancer care needs and concerns post treatment of diverse ethnic populations in the state of Texas to create an optimal Survivorship Care Plan (SCP). This research will explore the experiences and concerns of adolescents and young adults (AYA), and their parents, post childhood cancer treatment, in order to determine their understanding of follow-up care and then to determine the optimal format and content of a survivorship care plan. Results of this inquiry will reveal common themes experienced by the participants and provide information about the impact of childhood cancer after completion of treatment. Findings may be used to improve the transition of care from the tertiary cancer care setting to the community, after treatment, for this specific patient population.

Methods: A qualitative descriptive analysis approach will explore participants' experiences and concerns as a childhood cancer survivor. This inquiry will employ focus group semi-structured interviews as well as one-to-one interviews as tools of data collection as per the qualitative approach. Purposive sampling of participants will be employed to recruit participants aged between 15 and 39 years, male or female, and have lived more than 5 years post active treatment from the UHS South Texas Pediatric Blood and Cancer Center in San Antonio, Texas. Verbal informed consent will be obtained from all adults and assent will be obtained from children. Semi-structured interviews will be audio recorded and later transcribed, cross-checked for accuracy, and analyzed to identify common themes that emerge.

Significance: Unique factors are associated with a cancer diagnosis in the Latino AYA population. In addition to cultural, physical, and biological differences, adolescents and young adults face a unique range of psychosocial issues that may affect their care and transition into survivorship. Data gathered during these interviews will provide valuable information that may be used to develop survivorship care plans and help improve follow up care for this population. The Institute of Medicine reports the needs for SCP to "summarize the potential late effects, their prevention,

symptoms and treatment, recommendations for cancer screening, psychosocial effects, financial issues, recommendations for a healthy lifestyle, genetic counseling, referrals for follow-up care and a list of support resources (2017)." However, gaps in existing knowledge related to SCP, particularly in the Latino population, interfere with the provision of quality health services. This research will fill the gaps in Latino adolescent and young adult survivorship care plan development.

Latino/a Adolescents Coping with Parental Cancer Within a Cultural Context

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Background: Parental cancer has a strong influence on the psychological well-being of children at all ages. Children and adolescents whose parents have more distress and advanced disease tend to have lower rates of healthy psychological adjustment. Children from the US Latino/a population may face additional challenges, such as racism and acculturative stress that compound the stress of having a parent with cancer. At the same time, facets of the Latino/a culture may play a crucial role in how Latino/a adolescents adapt to parental cancer, specifically the Latino/a cultural values of familismo (familism), espíritu (spirit), and respeto (respect). This cross-sectional study examined the relation of Latino/a cultural values to coping and psychological adjustment among adolescents and young adults (AYAs). Specific aims were to examine (1) the associations between AYA's stress and coping responses and psychological adjustment to their mother's cancer; (2) the direct and moderation effect of three Latino/a cultural values—familismo, espíritu, and respeto—on the coping-adjustment association; (3) the effects of age and gender on coping responses, cultural values, and psychological adjustment outcomes; and (4) the associations between severity of the parent's cancer and the parent's level of distress with AYA's psychological adjustment.

Methods: The sample included 38 Latino/a AYAs who were coping with their mother's breast cancer (n = 24). AYAs and mothers completed questionnaires in English or Spanish in-person or by mail. A subsample of seven AYAs completed an optional interview. Psychological adjustment was measured by symptoms of depression (Center for Epidemiological Studies Depression Scale (CES-D); Eaton et al. 2004; Faulstich et al. 1986) and anxiety (adults: Generalized Anxiety Disorder scale; Spitzer et al. 2006; AYAs: Spence Children's Generalized Anxiety Scale, Spence 1998). Stress appraisals and coping responses were measured with six subscales from the Response to Stress Questionnaire (RSQ; Connor-Smith et al. 2000) and the religious subscale from the Brief COPE (Carver 1997); Latino/a cultural values of familismo and respeto were measured with the Mexican-American

Cultural Values Scale (MACVS; Knight et al. 2009); the espíritu value was measured with the Systems of Belief Inventory (SBI-15; Holland et al. 1998).

Results: Results demonstrated that stress appraisals and the coping responses of secondary control, disengagement, involuntary disengagement, and involuntary engagement coping were positively correlated with symptoms of depression and anxiety. The Latino/a cultural values of familismo and espíritu were associated, both directly and indirectly, with fewer symptoms of depression and anxiety. Higher endorsement of these values was associated with lower symptoms of depression and anxiety and greater primary control and religious coping use. Protective patterns of familismo and espíritu were evident in their interactions with coping responses. At higher levels of familismo, secondary control coping was negatively associated with symptoms of depression, but at lower levels of familismo, secondary control coping was positively associated with symptoms of depression. A similar pattern was also found for the espíritu value with both primary and secondary control coping. However, this buffering effect was less evident for involuntary modes of coping (disengagement and involuntary disengagement coping). AYAs whose mother was in active treatment had greater anxiety. Age, gender, severity of mother's cancer, and mother's distress were unrelated to coping or adjustment outcomes.

Conclusion: The findings suggest that Latino/a AYAs experience significant distress, but those with higher levels of familismo and espíritu may fare better than those with lower levels of these values. The creation of psychosocial interventions for Latino/a AYAs should incorporate or strengthen Latino/a values; however, these culturally tailored interventions need to be based on needs assessments of Latino/a AYAs and their families, and their communities.

Preliminary Insights into the Impact of the Affordable Care Act on Breast Cancer Care and Outcomes Among Patients Receiving Care at an Urban Safety-Net Hospital: Work in Progress

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Introduction: Non-Latina (nL) black and Latina women are diagnosed with breast cancer at a younger age and at later stages than nL-white women. Furthermore, compared to nL white women, the breast cancer mortality rate is higher in nL-black women, and quality of life is lower for Latina breast cancer patients. The etiology of these breast cancer disparities is multifactorial. However,

poor access to health care and lack of adequate insurance coverage are often implicated. Through its various provisions, the Patient Protection and Affordable Care Act (ACA) has the potential to (1) increase access to cancer care, particularly among the most vulnerable and (2) reduce racial/ethnic disparities in cancer care and outcomes. It is critical to understand the degree to which healthcare policy can help improve these two factors. The current project will carry out a preliminary assessment by using medical record and cancer registry data to quantify the impact of ACA provisions on cancer care access and outcomes among minority breast cancer patients.

Methods: The study population will include women diagnosed (2010–2016) with breast cancer at Mount Sinai Hospital, a safety-net institution in Chicago. The following information is being abstracted from medical records and the hospital cancer registry: demographics (race, ethnicity, age), insurance status (Medicaid, private, uninsured), mode of detection (screen detected vs. symptomatic), tumor characteristics, and treatment information. Descriptive statistics will be calculated to compare patient, tumor, care, and treatment characteristics between the pre- and post-ACA periods overall and by racial/ethnic group. Logistic regression models will be used to report proportions and estimate differences with bias-corrected bootstrapped 95% confidence intervals.

Results: At present, data from 2012 to 2015 has been abstracted (n = 167). The study population consists of 41% Latina, 46% nL-black, and 5% nL-white breast cancer patients. The pre- and post-ACA periods were defined as 2012–2013 and 2014–2015, respectively. Among nL-black and Latina women, the proportion of Medicaid-enrolled patients increased, while the proportion of uninsured decreased post-ACA, with Latina women experiencing a greater shift (p = 0.076). In addition, the proportion of screen-detected breast cancers increased while symptomatically presented cancers decreased post-ACA (p = 0.216). At completion of data collection, we will examine changes in insurance status, mode of detection, timeliness to breast cancer care, and cancer stage pre- and post-ACA, appropriately adjusting for disease characteristics (i.e., stage, grade, hormone receptor status).

Discussion: The provisions of the ACA aim to decrease the number of uninsured, particularly targeting minorities, and increase access to appropriate cancer care. It remains unclear the extent to which such provisions will impact breast cancer-related care and outcomes in underserved black and Latina populations. Furthermore, little is known of the differences in improvements of the breast cancer care continuum between Latina and black women as a result of the ACA. Efforts aimed at evaluating the impact of the ACA on cancer outcomes and disparities should be supported, as they will help inform future policy recommendations.

Utilization of Palliative Therapies Among Hispanics with Stage IV Non-small Cell Lung Cancer

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Background: Racial disparities in the treatment of lung cancer are well documented. However, research in disparities in palliative care is limited. Early integration of palliative care in advanced non-small-cell lung cancer (NSCLC) has been proven to improve quality of life and overall survival in this subset of patients. We proposed to study the use of palliative treatments for stage IV NSCLC among Hispanic patients.

Methods: Using the National Cancer Database (NCDB), we identified all Hispanic patients (self-reported) diagnosed with stage IV NSCLC from 2005 to 2013. Cases with incomplete data, unknown life/death status or classified as Hispanic by surname only were excluded. Hispanics were grouped based on place of origin. Pearson chi-square tests were used to estimate differences in categorical data; predictors of palliative care referral/use were determined by logistic regression analysis.

Results: Ten thousand four hundred forty-one patients were included. The median age was 66 years. Regarding place of origin: 15.5% of patients were from Mexico, 8% from South/Central America, 7% from Cuba, 6% from Puerto Rico, 2.4% from the Dominican Republic, and 57.6% were no-otherwise specified. When all Hispanic patients were included, 3.5% received surgery, 45% radiation, and 52.9% chemotherapy. Overall, 2.2% of patients received a referral for palliative pain management ± other palliative therapies. When divided by place of origin, Dominican patients had the highest percentage of pain management referrals at 5.5% ($p < 0.01$) followed by Puerto Rican patients (2.4%). On the other hand, only 1.3% of patients from South/Central America were referred to pain management. In multivariate analysis, Dominican Republic origin (OR: 3.30, 95%CI: 1.69–6.44, $p < 0.01$), bone metastasis (OR: 1.98, 95%CI: 1.17–3.3, $p < 0.01$), and a Charlson comorbidity index ≥2 (OR: 2.07, 95%CI: 1.11–3.85, $p < 0.02$) were significant predictors of receiving a pain management referral. We observed an increased number of pain management referrals over time with 1.4% of Hispanic patients getting a referral in 2004 vs. 2.9% in 2013 ($p < 0.02$).

Conclusions: We observed that only a small percentage of Hispanic patients with metastatic NSCLC cancer are receiving referral for palliative care/pain management. Several cultural beliefs and barriers may play a role in these findings. Providers should offer early referrals to pain management/palliative care to all patients with metastatic NSCLC independent of their race or ethnicity.

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