

Chapter 1

Advancing the Science of Cancer in Latinos



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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, *Helicobacter 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 women 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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