

MEETING SUMMARY PRESIDENT'S CANCER PANEL

AMERICA'S DEMOGRAPHIC AND CULTURAL TRANSFORMATION: IMPLICATIONS FOR THE CANCER ENTERPRISE

October 27, 2009
Los Angeles, California

OVERVIEW

This meeting was the second in the President's Cancer Panel's (PCP, the Panel) 2009-2010 series, *America's Demographic and Cultural Transformation: Implications for the Cancer Enterprise*. The agenda for the meeting was organized into two discussion panels.

PARTICIPANTS

President's Cancer Panel

LaSalle D. Leffall, Jr., M.D., F.A.C.S., Chair

Margaret Kripke, Ph.D.

National Cancer Institute (NCI), National Institutes of Health (NIH)

Abby Sandler, Ph.D., Executive Secretary, PCP

Speakers

Stefan Ambs, Ph.D., M.P.H., Principal Investigator, Laboratory of Human Carcinogenesis, Breast and Prostate Unit, NCI

Barri M. Blauvelt, M.B.A., Adjunct Faculty, Institute for Global Health, School of Public Health and Health Sciences, University of Massachusetts

Tim Byers, M.D., M.P.H., Associate Dean, Public Health Practice, Colorado School of Public Health, University of Colorado Denver

Jorge Gomez, M.D., Ph.D., Director, Office of Latin American Cancer Program Development, NCI

Beth A. Jones, Ph.D., M.P.H., Research Scientist, Division of Chronic Disease Epidemiology, Yale School of Public Health

Laurence Kolonel, M.D., Ph.D., Deputy Director, Cancer Research Center of Hawaii

Upendar Manne, M.S., Ph.D., Associate Professor of Pathology, University of Alabama at Birmingham School of Medicine

Susan Neuhausen, Ph.D., Associate Director, Genetic Epidemiology Research Institute, University of California, Irvine

Wael A. Sakr, M.D., Vice Chair, Anatomic Pathology, Department of Pathology, Wayne State University School of Medicine

Amr S. Soliman, M.D., Ph.D., Associate Professor, Epidemiology, School of Public Health, University of Michigan

Cheryl L. Willman, M.D., Director and CEO, University of New Mexico Cancer Center

Elad Ziv, M.D., Associate Professor of Medicine, University of California, San Francisco

OPENING REMARKS—LaSALLE D. LEFFALL, JR., M.D., F.A.C.S.

On behalf of the Panel, Dr. Leffall welcomed invited participants and the public to the meeting. He introduced Panel members, provided a brief overview of the history and purpose of the Panel, and described the aims of the current series of meetings.

Dr. Kripke reported that the President's Cancer Panel Working Group on America's Cultural Transformation in Cancer met on September 22, 2009, to discuss the format of the 2009–2010 series and other logistical considerations. The Working Group recommended that future open meetings in this series conform to the logistics of the first meeting. Dr. Kripke's motion to accept the Working Group's recommendations was unanimously passed.

PANEL I

DR. LAURENCE N. KOLONEL:

ETHNIC VARIATIONS IN CANCER INCIDENCE AND SURVIVAL IN HAWAII

Background

Dr. Kolonel is a Researcher in the Epidemiology Program of the Cancer Research Center and a Professor of Public Health in the John A. Burns School of Medicine at the University of Hawaii. From 1977 to 2007, he was Director of the Epidemiology Program at the Cancer Center; from 1991 to 2009, he also served as Deputy Director of the Center. His research focuses on the epidemiology of nutrition and cancer in diverse ethnic populations, migrant studies, and associations between lifestyle, genetic susceptibility, and cancer risk. Dr. Kolonel was among the earliest epidemiologists to study the role of diet and nutrition in cancer and to explore changing patterns of cancer incidence in migrant populations. He has served on many national and international committees, including the Food and Nutrition Board of the U.S. National Academies of Science, the NCI Board of Scientific Counselors, award selection committees of the American Association for Cancer Research, and two Expert Panels of the World Cancer Research Fund. In 2002, he received a MERIT award from NCI. Dr. Kolonel is an author on more than 350 peer-reviewed scientific publications as well as several reviews, monographs, and book chapters.

Key Points

- Hawaii has a very diverse population. The state has no majority ethnic group. Caucasians, the largest group, account for less than one-quarter of the population.
- In the mid 1970s, breast cancer and colon cancer surveillance data showed a wide range of incidence rates among ethnic groups, with higher rates among Caucasians than among other groups. The Japanese population had the highest rate of stomach cancer. Native Hawaiians had the highest rate of lung cancer.
- The University of Hawaii Cancer Research Center decided to determine whether these differences reflected genetic or inherited factors. A study of age-adjusted cancer incidence among migrants to Hawaii was conducted, focusing on the large Japanese-American population. Comparisons were made between migrants and their home populations, between first- and second-generation migrants, and between migrants and the Caucasian population.
- Adult migrants had lower stomach cancer incidence than adults in Japan, indicating that changes occurring in adulthood can alter cancer risk. Risk was reduced further for the offspring of migrants, emphasizing the effect of environment on cancer risk. An opposite trend was found in breast cancer. Rates were low in Japan, higher in migrants, and higher still in second-generation Japanese, approaching the rates in Caucasians.

- Because Hawaii is not heavily industrialized and has little water pollution, the researchers focused on diet and other lifestyle factors. Hawaii's ethnic diversity contributes to a wide variety of health-related behaviors.
- Overall cancer incidence rates have not changed dramatically in Hawaii since 1975. However, a comparison of breast cancer incidence between the 1975–1980 period and the 2000–2005 period shows that increases in incidence have been much greater among Hawaiians, Chinese, Japanese, and Filipinos than among Caucasians.
- Age-adjusted data on relative breast cancer risk from the population-based Multiethnic Cohort (MEC) study—which focuses on Caucasians, Hawaiians, and Japanese in Hawaii and African Americans and Latinos in Los Angeles—have shown that Hawaiians and Japanese are at much higher risk for breast cancer than the other ethnic groups, with a particularly high risk level for Hawaiians. These data were also adjusted for eight well-known breast cancer risk factors. The researchers concluded that other risk factors must be contributing to the high risk among Hawaiians.
- Lung cancer incidence rates in the 1970s were significantly higher for Hawaiians than for other groups. Since then, rates have dropped for all groups except Filipinos, whose lung cancer incidence is now higher than that of Hawaiians. A population-based survey of smoking habits in the 1970s found that smoking did not explain this pattern in lung cancer. Smoking levels were similar in Japanese and Hawaiians, while lung cancer incidence among Hawaiians was twice as high as that for Japanese. After additional analysis adjusted for age, education, extent of smoking, occupational exposures, and intake of beta carotene and cholesterol, the differences in lung cancer incidence remained. It was suggested that Hawaiians were genetically predisposed to lung cancer or that protective dietary factors among the Japanese population might account for these differences.
- More recent analyses using MEC data showed that among those who smoked half a pack of cigarettes daily, lung cancer incidence was much higher among African Americans and Hawaiians than for other groups. Higher smoking levels were associated with higher rates and smaller differences among all groups. For those smoking one and a half packs daily, the differences were not significant. This suggested that overwhelming exposure to carcinogens reduces the importance of predisposition and places all populations at equal risk. Other factors contributing to different incidence rates need further study; for example, recent studies have suggested that Japanese metabolize nicotine at a lower rate than other groups.
- In the 1970s, Caucasians had the highest rate of prostate cancer in Hawaii; however, over the past three decades, disproportionate increases in prostate cancer rates have occurred among Filipino, Japanese, and Chinese populations in the state, all of which now exhibit higher rates of prostate cancer than their white counterparts. The reasons for the observed disparities in prostate cancer risk are unknown. The only environmental factor that has been associated with reduced prostate cancer risk using MEC data is high intake of legumes.
- Japanese have the highest colorectal cancer incidence rates in Hawaii. Rates among first-generation migrants in Hawaii have been much higher than for residents of Japan, suggesting the involvement of environmental factors in Hawaii that do not exist in Japan. The role of heterocyclic amines in colorectal cancer carcinogenesis is being studied; heterocyclic amines are formed in meats that are cooked at high temperatures, particularly red meats, and they are metabolized by the enzymes NAT2 and CYP1A2. Using MEC data, high-risk forms of the *NAT2* and *CYP1A2* genes have been found to be more prevalent in Japanese, who consume well-done meats in larger quantities than other groups.
- Native Hawaiians now have the highest rate of endometrial cancer in Hawaii. In the 1970s, cervical cancer rates among Caucasian women were the highest of all the ethnic groups, but rates among Caucasian as well as Chinese women have decreased over the past 30 years; in contrast, cervical cancer rates have increased among Native Hawaiians, Japanese, and Filipino women in Hawaii. After adjusting MEC data for known endometrial cancer risk factors, the differences among ethnic groups remain unexplained.

- The ratio of breast cancer mortality to incidence in Hawaii is higher among Native Hawaiians than in the Japanese population. Japanese have higher incidence of *in situ* breast cancer, but Hawaiians have higher incidence of breast cancer in distant locations. Much of the difference in the mortality-to-incidence ratio could be the result of diagnosis at later stages among Hawaiians. Biologic differences in disease progression may be a factor, but evidence supports the likelihood that delayed diagnosis is associated with beliefs and behaviors related to cancer—fatalism and other cultural factors among Hawaiians are being studied by research projects targeting special populations.
- Hawaii has the highest rate of health insurance coverage in the nation; more than 90 percent of Hawaiians have third-party coverage. Thus, disparities in insurance coverage are likely not as much of a factor as they may be in other parts of the country.
- Caucasians have the highest mortality-to-incidence ratio for prostate cancer, for reasons that are not clear. Ratios for colorectal cancer are similar among all groups.
- Variations in cancer incidence by ethnicity have persisted over several decades in Hawaii, but the ethnic incidence patterns have changed over time for some cancer sites. The Westernization of Hawaii has not caused intergroup differences to disappear.
- Most of the ethnic variation probably reflects different levels of exposure to causal factors, although some of the variation probably reflects differences in genetic susceptibility. Studying ethnic variations can offer insights into cancer etiology.
- Mortality-to-incidence ratios vary among ethnic groups by cancer site. Some of the variation can be explained by later stage at diagnosis. Research into other possible explanations for this variation (e.g., biologic differences) is needed. Social, cultural, and behavioral factors related to early diagnosis and adherence to treatment need more study.
- Hawaii has the highest cancer survival rates in the country; the reasons for this are unknown. High rates of insurance coverage may play a part, as well as environmental and lifestyle factors.

DR. AMR S. SOLIMAN:

CANCER EPIDEMIOLOGY IN SPECIAL POPULATIONS: CHALLENGES AND OPPORTUNITIES FOR UNDERSTANDING THE DISEASE ETIOLOGY

Background

Dr. Soliman's research and educational activities are focused on international cancer epidemiology. He directs the University of Michigan's Cancer Epidemiology Education in Special Populations (CEESP) program, which trains M.P.H. students in cancer epidemiology in minority settings in the United States and in other countries. Dr. Soliman has developed multidisciplinary molecular and genetic epidemiologic investigations of cancer in different ethnic and racial groups through national and international comparative studies. Furthermore, he is exploring the effect of migration to the United States on cancer risk modification. These studies are being pursued through interaction and collaboration with U.S. clinicians and scientists as well as institutions in Egypt, Tunisia, Algeria, Morocco, Uganda, Tanzania, and other countries in Africa and the Middle East.

Key Points

- Michigan has the largest Arab-American population in the United States—approximately 400,000 Arab Americans live in the state. The CEESP is conducting international studies to understand cancer in this population, especially in the areas of epidemiology and molecular pathology. CEESP research also addresses opportunities for cancer control and prevention in U.S. ethnic minorities. This presentation focused on studies of breast cancer, including inflammatory breast cancer, in the Middle East and Africa. Understanding gained through international studies could be applicable to understanding breast cancer in Michigan's Arab-American and African-American populations.

- Challenges in conducting international studies include developing collaborative relationships, building multidisciplinary teams, creating research infrastructure (e.g., registries), and standardizing clinical criteria. Cultural and logistical issues are also barriers to international research.
- Breast cancer is the most common cancer in women. There is a huge disparity in breast cancer incidence and mortality rates between the U.S. population and foreign populations or ethnic minorities in the United States. As a result of demographic shifts, increased life expectancy, and Westernization, cases of breast cancer are increasing in lower- and middle-income countries and are expected to continue to increase in the coming decades. It has been projected that by 2020, 63 percent of all new breast cancer cases will be diagnosed in developing countries.
- In developing countries, most breast cancer cases are diagnosed at advanced disease stages for which treatments are not effective. Breast cancer mortality is much higher in developing countries than in the United States and other Westernized areas. As a result of migration, the United States can expect to see increases in diagnoses of late-stage breast cancers.
- CEESP has conducted several studies on the incidence and distribution of breast cancer in North Africa. Other studies have focused on the molecular epidemiology of inflammatory breast cancer, predictors of advanced-stage breast cancer, and survival of inflammatory breast cancer patients.
- Working with the NCI-funded Middle East Cancer Consortium, CEESP helped establish population-based cancer registries in this region. The Consortium is a collaboration among Israel, the Palestinian National Authority, Jordan, Egypt, Turkey, and Cyprus.
- The African and Middle Eastern areas studied by CEESP combine two areas with very low breast cancer incidence rates (sub-Saharan Africa and Oman) with an area that has moderate rates (North Africa). Israel has the highest breast cancer incidence in this region. In Egypt, urban areas have breast cancer incidence rates four times higher than those in rural areas. Similar differences between urban and rural areas have been observed for gynecologic malignancies.
- Inflammatory breast cancer (IBC) is an aggressive form of the disease that accounts for less than 1 percent of breast cancer cases in the United States. However, 10 to 15 percent of breast cancers in Egypt and Tunisia are IBC. This disease is usually diagnosed in premenopausal women. It is difficult to diagnose and is often mistaken for lactation mastitis. In North Africa, the three-year survival rate for IBC is 15 percent, compared with 42 percent in the United States.
- A study comparing IBC in Egypt and the United States found that Egyptian patients were younger at disease onset and had a higher frequency of tumor emboli. The Egyptian women's tumors had greater overexpression of *RhoC*, an oncogene associated with IBC.
- CEESP uses questionnaires to collect information on environmental exposures and also studies biomarkers of exposure. Africa and the Middle East present a wide variety of risk factors, such as reproductive, lifestyle, and dietary factors. Many women in these regions work in agricultural settings and are thus exposed to carcinogenic agents, including organochlorine pesticides and xenoestrogens. Rates of disease presentation in these regions may also be affected by exposure to infectious agents; the effects of infectious agents may vary between ethnic groups.
- Current CEESP studies are examining a variety of topics, including epidemiology of IBC in North Africa, molecular diagnosis of IBC, rural-urban comparisons, cultural barriers to seeking medical care, the effects of prepubertal xenoestrogen exposure on breast development and future breast cancer risk, and international variation in IBC incidence and risk factors. Two studies in Uganda and Tanzania are obtaining specimens from IBC and non-IBC patients to collect data on *RhoC* overexpression and tumor emboli.
- CEESP depends on its relationships with collaborators at NCI, the University of Michigan, the M.D. Anderson Cancer Center, the International Agency for Research on Cancer (IARC), the African Organization for Research and Training in Cancer (AORTIC), and a wide variety of organizations in

North African and Middle-Eastern countries. The program also depends on its students, who travel to Africa and the Middle East as part of their training in public health.

DR. CHERYL L. WILLMAN:

CANCER INCIDENCE, MORTALITY, DISPARITY, AND CULTURAL BELIEFS IN THE MULTI-ETHNIC POPULATIONS OF NEW MEXICO

Background

Dr. Cheryl Willman received her B.A. in chemistry from St. Olaf College in Northfield, Minnesota and her M.D. in 1981 from The Mayo School of Medicine in Rochester, Minnesota. Awarded one of the first NIH Physician Scientist Awards in 1984, Dr. Willman completed her residency and postdoctoral training in cancer research and pathology at NIH in Washington, DC, the University of New Mexico (UNM), and the University of Washington-Howard Hughes Medical Institute in Seattle. Today, Dr. Willman is an internationally known leukemia researcher and Director and CEO of the University of New Mexico Cancer Center, the Official Cancer Center of the State of New Mexico. The UNM Cancer Center received designation as an NCI-Designated Center in 2005 and was ranked as one of “America’s Best Cancer Hospitals” by *U.S. News & World Report* in 2006.

Key Points

- New Mexico is the only state in the U.S. with a minority majority population and has a higher percentage of Hispanics and American Indians than any other state. The 2 million citizens in New Mexico are 45% non-Hispanic white, 42% Hispanic, 10% American Indian, 2% black, and 1% Asian and other ethnic minorities.
- New Mexico is rich in Hispanic and Native American culture; the state is home to over 195,000 Native Americans comprising 19 Pueblo, Apache and Ute tribes, and the sovereign Navajo Nation.
- Despite a large technology industry in the state, New Mexico has a very low per capita income and high rates of under- and uninsured citizens.
- About 90 to 95 percent of children with cancer in the U.S. are captured in the context of clinical trials; unfortunately, less than 5 percent of adults with cancer participate in clinical trials.
- Recent NCI Surveillance, Epidemiology and End Results (SEER) data indicate an increase in acute lymphoblastic leukemia (ALL) incidence in Hispanic/Latino and non-Hispanic white children in the U.S. in recent years.
- Supported through an NCI TARGET (Therapeutically Applicable Research to Generate Effective Treatments) Project, UNM Cancer Center investigators, in collaboration with St. Jude Children’s Research Hospital, NCI, and the Children’s Oncology Group (COG), have made considerable discoveries in pediatric ALL, particularly in relation to recurring genetic abnormalities in children of different ethnic backgrounds.
- With progressive intensification of therapy, 75 to 80 percent of children with ALL achieve long-term survival. However, these therapies are associated with serious short- and long-term toxicities.
- Nearly 30 percent of children with ALL with “high-risk” features—older age, more ethnically-mixed, and higher white blood cell counts—fail to respond to the therapeutic regimens currently used to treat this disease and require a different approach for a cure.
- UNM investigators focused on a cohort of 207 children with high-risk ALL uniformly treated on COG 9906, a COG clinical trial testing an intensive regimen from Europe, augmented Berlin-Frankfurt-Munster (BFM) therapy.

- The cohort of children was predominantly male and poorly genetically characterized. Of the 207 children, 51 reported themselves to be Hispanic and 3 were American Indian/Alaskan Native. The mean age of the cohort was 13.5 years.
- Using comprehensive molecular technologies—gene expression profiling, single nucleotide polymorphism (SNP) and loss of heterozygosity analysis to identify polymorphisms and copy number changes, racial admixture mapping, and targeted DNA sequencing—the investigators determined that the most significant predictor of outcome among these high-risk pediatric ALL patients was genetic ancestry.
- Principal components analyses were used to differentiate African-American, Asian, and Native American/Hispanic ancestries among ALL patients and control groups. Of note, Native American and Hispanic/Latino ancestry were significantly associated with relapse. Even among self-reported non-Hispanic whites, increasing degrees of American Indian/Hispanic genetic admixture predicted a higher likelihood of ALL relapse.
- Standard hierarchical clustering of the gene expression profiling data yielded eight cluster groups: children with MLL gene structural rearrangements in their leukemic cells; children with 1;19 translocation; and six other distinct cluster groups. The underlying genetic abnormalities associated with each of these six cluster groups serve as potential targets for therapy.
- Investigators discovered that tumors in cluster 8 were characterized by high expression of distinct outlier genes (*BMPRI1B*, *CRLF2*, *GPR110*, *MUC4*), frequent deletion of *EBF1*, *IKAROS/IKZF1*, *RAG1-2*, and Hispanic/American Indian race. All cluster 8 patients experienced a relapse within five years.
- Specific recurrent DNA mutations identified in the leukemic cells of cluster 8 patients—including mutations in the genes for the *JAK* tyrosine kinase and a type I cytokine receptor, *CRLF2*—are potential new therapeutic targets.
- When introduced into cultured cells, the identified *JAK* mutations induced transformation; this transformation could be blocked by treatment with *JAK* inhibitors. Approximately half of the cluster 8 tumors housed *JAK* mutations.
- Virtually all of the cluster 8 tumors exhibited structural genomic rearrangements (e.g., translocation, interstitial deletion) that resulted in *CRLF2* overexpression. High expression of *CRLF2* was strongly associated with *JAK1* or *JAK2* mutations, Hispanic/American Indian race, and very poor survival.
- Recent studies suggest that 10 to 12 percent of adult and young adult ALL patients also have *CRLF2* and *JAK* mutations.
- NCI has approved a COG Phase I trial that will test *JAK* inhibitors in pediatric cancers. A Phase II trial is also being designed to test a *CRLF2* inhibitor; eligibility will likely be determined by screening for *CRLF2* mutations.
- These findings indicate that ethnic background may predispose an individual to the acquisition of specific ALL-associated genetic abnormalities and/or that genetic admixture contributes to a poorer outcome, regardless of the presence of specific abnormalities, for reasons yet unknown.
- With the changing demographics of the U.S., it is essential to consider genomic assessments of genetic/racial ancestry rather than self-reported race in all cancer investigations, and to conduct studies to determine the relationships among genetic ancestry, cancer-promoting mutations, and the effectiveness of targeted cancer therapies.

DR. TIM BYERS:

DIFFERENCES BETWEEN HISPANIC AND NON-HISPANIC WHITE WOMEN IN BREAST CANCER INCIDENCE AND OUTCOMES

Background

Since 1995, Dr. Byers has held the position of Professor at the University of Colorado. He is now the Interim Director of the University of Colorado Comprehensive Cancer Center and Associate Dean for Public Health Practice at the Colorado School of Public Health. He was formerly Chief of the Chronic Disease Prevention Branch of the Nutrition Division at the Centers for Disease Control and Prevention in Atlanta. Dr. Byers is an expert in cancer prevention research. He has worked in various settings in clinical medicine, public health, and academic medicine. He has a particular interest in epidemiologic studies of the role of early detection, diet, and nutrition in the prevention of cancer, and in the application of disease prevention in community settings. He has published over 300 papers in peer-reviewed scientific journals. His current research includes epidemiologic and clinical studies of nutrients as protective factors in prostate, colon, breast, and lung cancer; studies of cancer treatment decision-making by patients and physicians; studies of cancer genetics; and studies to promote the early detection of cancers of the breast and colorectum. He is now developing a new center in the Colorado School of Public Health to improve the effectiveness of public health agencies and programs.

Key Points

- There is ample evidence that sociological and biological factors are important in breast cancer and many other cancers. Historically, the sociological reasons underlying health disparities have been ignored in favor of biological factors; however, in recent years, there has been a shift away from considering biological factors because many equate this approach with racism. There needs to be an evidence-based approach to health disparities that includes consideration of both biological and sociological factors.
- The NCI-funded Study of Hormones, Insulin, Nutrition, and Exercise (SHINE), also called the Four Corners Study, is a population-based, case-control study conducted by investigators from Arizona, Utah, New Mexico, and Colorado. SHINE included multiple in-home interviews of each of its nearly 5,000 participants. The study set out to determine why breast cancer incidence rates are considerably lower among Hispanic women than non-Hispanic whites in the four-corners states, while Hispanic women have higher breast cancer mortality rates.
- SHINE identified a number of risk factors that did not differ by ethnicity, including parity, age at first birth, breastfeeding, and age at menarche. However, several risk factors did differ by ethnicity: height, increased postmenopausal adiposity, hormone replacement therapy, and alcohol use were associated with increased risk of breast cancer among non-Hispanic white women, but not among Hispanic women. Attributable risk estimates further highlighted differences between the two ethnic groups—while information on all risk factors measured accounted for nearly two-thirds of breast cancer cases among non-Hispanic whites, known risk factors accounted for a relatively small amount of the cancer risk for Hispanics (21 percent among premenopausal and 7 percent among postmenopausal women).
- Based on the risk factor profiles observed, SHINE investigators hypothesized that differences in risk factors between Hispanics and non-Hispanic whites were due to differences in estrogen effects. Examination of SHINE participants diagnosed with breast cancer found that 80 percent of breast tumors from non-Hispanic whites expressed estrogen receptor (ER) compared to only 72 percent of those from Hispanic women. Similar trends were observed among cohorts of breast cancer patients from other studies.

- Additional analysis revealed that risk of developing ER-negative breast cancer is similar between Hispanic and non-Hispanic white women; however, Hispanic women are less likely to develop ER-positive breast cancer. This explains the lower overall incidence of breast cancer among Hispanic women and, at least in part, accounts for their increased mortality (they have a higher proportion of ER-negative tumors, which are more aggressive and less responsive to current treatments).
- Levels of estrogen metabolites are highly dependent on the activities and polymorphisms of various estrogen-metabolizing enzymes. There is some evidence that the ratio of two of these metabolites—2-hydroxyestrone and 16 α -hydroxyestrone—might play a role in breast cancer risk. Estradiol and other estrogen metabolite levels were measured in a small subset of postmenopausal SHINE participants as part of a pilot study. While estradiol levels were equivalent between Hispanic and non-Hispanic white women, Hispanic women exhibited higher levels of 2-hydroxyestrone, which is thought to be associated with lower breast cancer risk. In contrast, non-Hispanic white women had higher levels of 16 α -hydroxyestrone, which is thought to be associated with higher risk of breast cancer. Thus, the ratios of these two estrogen metabolites were substantially different between the two ethnicities. This study needs to be repeated in a larger subset of SHINE participants.
- Follow-up interviews are being conducted with approximately 1,100 SHINE participants from Arizona and Colorado through the SUNSHINE (Survivorship Update Network from SHINE) study. The purpose of this study, which is funded through the American Cancer Society (ACS), is to look at the impact of various behavioral and psychosocial factors on the survivorship experience of these women. Long-term outcomes after breast cancer are generally worse among Hispanics than non-Hispanic whites and it is possible that this may be due to behavioral and/or psychosocial factors.
- Early results of SUNSHINE indicate that Hispanic breast cancer survivors report higher levels of cognitive impairment than their non-Hispanic white counterparts. Additional analysis will be done on spiritual and social outcomes as well as cancer recurrence.
- Data from Colorado indicate that breast cancer survival rates are lower among women who live in poorer neighborhoods. This pattern is consistent when the data are stratified by age, stage of disease, or race/ethnicity. The one exception is that black women living in the most affluent neighborhoods actually exhibit lower five-year survival rates than black women in other neighborhoods; this phenomenon may be driven by the fact that the black population in Colorado is very small. However, overall, social class is a driver of breast cancer outcomes in Colorado. The gap in breast cancer survival among various socioeconomic groups lessens if the data are adjusted for stage, grade, and completeness of treatment. This indicates that there are things that could be done to improve outcomes for poorer women.
- In conclusion, Hispanic women in the Four-Corners states have a lower incidence of breast cancer because they have a lower incidence of estrogen-induced cancers relative to non-Hispanic whites; this may be due to differences in estrogen metabolism between the two groups. Poorer survival among Hispanic women is due at least in part to the higher proportion of ER-negative tumors. Poverty is a predictor of poorer outcomes within various racial/ethnic groups. Thus, it appears that there are both biological and sociological factors affecting breast cancer risk and outcomes among Latinas.

DR. JORGE GOMEZ:

PARTNERING FOR CANCER RESEARCH IN LATIN AMERICA

Background

Dr. Jorge Gomez is Director of the NCI Office of Latin American Program Development (OLACPD), an exciting new partnership between NCI and the NIH Fogarty International Center for Advanced Study in the Health Sciences. Dr. Gomez founded OLACPD in 2008 with the goal of supporting and advancing international collaboration and partnerships in scientific and clinical cancer research, training, and

infrastructure development in Latin America. He first joined NIH in 1992 as a postdoctoral trainee at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and later joined the NCI Organ Systems Branch (OSB). In 1998, he became Chief of OSB, where for 10 years he oversaw the management and administration of the Specialized Programs of Research Excellence (SPORes). As Chief of OSB, Dr. Gomez was responsible for a \$130-million portfolio of grants that comprised over 600 research projects, 200 research cores, and 255 clinical research studies, including 150 clinical trials. Dr. Gomez was honored with the 2006 Medical Advancement in Breast Cancer Award from the Avon Foundation for his work on the Patients Award Program, which provides grants for innovative research focused on breast cancer.

Key Points

- The National Cancer Act of 1971 provides NCI with a mandate to “support research in the cancer field outside the United States by highly qualified foreign nationals which can be expected to benefit the American people; collaborative research involving American and foreign participants; and training of American scientists abroad and foreign scientists in the United States.”
- Hispanics will soon become the largest minority group in the United States. As of 2006, the U.S. population included 44.3 million Hispanics, or 14.8 percent of the total population. The Hispanic population’s 24.3 percent growth rate is more than three times the overall U.S. rate. The top five states in Hispanic population size are California, Texas, Florida, New York, and Illinois.
- The U.S. Hispanic population is younger than the general population. As this population ages, its cancer incidence is expected to increase. Hispanics earn less than the general population and are less likely to have health insurance. Access to health care is also affected by the fact that many Hispanics work in the United States on a seasonal basis, returning to their countries of origin for several months each year.
- The fact that 40 percent of Hispanic residents were born outside the United States is an important factor in planning studies of cancer in this population. The cancer burden is increasing in Latin America, and the types of cancer that affect U.S. Hispanics are similar to those seen in their countries of origin. A number of studies have shown that ethnic biological differences, as well as socioeconomic disparities, have an impact on cancer among U.S. Hispanics. There are limited data to aid in understanding the cancer burden for various U.S. Hispanic subgroups.
- Hispanics in the United States experience disparities in certain types of cancer (e.g., liver, stomach, cervical, acute lymphocytic leukemia, and gall bladder). Some of these cancers are associated with infectious agents. Breast cancer presents differently in Hispanic women compared with non-Hispanic white women, even when taking into account differences in access to health care.
- A number of common assumptions and beliefs about cancer among U.S. Hispanics (e.g., the belief that Hispanics often fail to comply with treatment recommendations) are not fully supported by evidence, suggesting areas for future research.
- Factors that should be studied to address questions concerning cancer among U.S. Hispanics include acculturation, genetic ancestry, susceptibility genes, environmental exposures, regional differences, differences in country of origin, lack of representation in clinical trials, and varying definitions of the terms “Latino” and “Hispanic.”
- The NCI Office of Latin American Cancer Program Development was created to study questions about cancer in Hispanic populations in partnership with Latin American countries. Its research program builds on the principle that working with Latin America will provide insight into cancer trends among the growing Hispanic population in the United States. OLACPD is initiating research projects based on common interests and high bioethical standards that will elevate the quality and credibility of cancer research conducted in Latin America. Building research capacity in Latin

America will lead to independent, sustainable infrastructure to support first-rate clinical research around the globe. U.S. investigators will have more capable partners in cancer research.

- In March 2009, OLACPD developed a model for partnerships and collaborations. Agreements to cosponsor research projects have been signed with five Latin-American countries—Mexico, Brazil, Uruguay, Argentina, and Chile—to create the United States-Latin America Cancer Research Network (US-LA CRN). Partnerships involve governments, research institutions, individual investigators, and nongovernment organizations. Other countries will be added as they develop health care systems and research infrastructure that meet network criteria.
- This network is developing programs in three broad scientific areas: basic and clinical research; training programs; and technology and capacity building for sustainable cancer research activities. Areas identified for development include clinical trials management and biospecimen banking. A number of pilot research projects are planned; the first will focus on breast cancer.
- Challenges for the future include conducting parallel clinical research in the United States and Latin America, involving Latin-American investigators in research focused on their populations, and incorporating cultural appropriateness into peer review.
- NCI should take a leadership role to ensure that research on important questions is not postponed due to lack of support. A Hispanic/Latino Cancer Task Force should be constituted in order to make appropriate recommendations to NCI and develop an implementation plan. Hispanic/Latino leaders should be given appropriate resources and support to coordinate studies in this area and to follow up to ensure that the implementation plan is carried out. Research on cancer's impact on Latinos should be a national priority at all levels and an integral component of the National Cancer Program.

MRS. BARRI M. BLAUVELT:

U.S. ETHNICITY AND CANCER: LEARNING FROM THE WORLD

Background

Barri Blauvelt is Adjunct Faculty in the University of Massachusetts (UMass) Institute for Global Health (IGH) and School of Public Health and Health Sciences. She conducts qualitative studies involving medical, policy, and advocacy developments globally, specializing in horizon-scanning research, a relatively new method of qualitative research. In addition, she is the author of *Powerful Medical Presenter™*, a medical presentation skills curriculum developed for Harvard faculty at Massachusetts General Hospital, and *From Clinical Research to Publication*. Raised and educated internationally (Asia, Canada, Europe, U.S.), Mrs. Blauvelt worked in international patent and trademark law with Pennie and Edmonds and held managerial positions with Exxon Corporation, Pfizer, and American Cyanamid, eventually rising to become responsible for Asian and then global commercialization of Lederle and Davis & Geck Divisions. She also founded and leads Innovara, Inc., a leading company in global medical thought leadership development, and one of the top five in the world in health care industry training and development. Mrs. Blauvelt has a B.A. degree in international education and pre-law from Hampshire College. She holds an M.B.A. in marketing from the Graduate School of Business, Columbia University in New York City, where she also studied law and postdoctoral-level management sciences.

Key Points

- Cancer is the second leading cause of death in the world. In the past 30 years, the worldwide burden of cancer has doubled and there is expected to be a 30 percent increase in new cancer cases by 2020. Two-thirds of new cancer cases are from lower- and middle-income countries, which illustrates the influence of socioeconomic status on cancer. Current estimates indicate that the global economic impact of cancer exceeds \$300 billion.

- Only 5 percent of the resources devoted to cancer research and care are being invested in the developing world. Less than 15 percent of all clinical research spending is in developing nations. The U.S. federal government accounts for 34 percent of research funding worldwide, with large pharmaceutical companies and European Union (E.U.) health care and university systems also being large sources of research funding.
- Funding for breast cancer exemplifies the inequitable allocation of resources. In the U.S. and E.U., breast cancer is effectively controlled in up to 80 percent of women in some populations. However, breast cancer is the leading cause of cancer death among most nonwhite female populations around the world, including in the U.S. In general, guidelines for breast cancer are driven by research on white women of European ancestry.
- The UMass/Johns Hopkins Horizon Scanning Study encompassed 30 countries across three regions of the world—Asia, Latin America, and the Middle East/Africa. The populations studied account for approximately 60 percent of the world population, and 90 percent of the cohort is nonwhite. A key finding of the study was that non-Caucasian ethnic groups present with breast cancer at significantly younger ages and with more aggressive tumors than their white counterparts. Differences between ethnic groups are attributed to lifestyle and cultural attitudes, lack of prevention and early detection, lack of education and advocacy, issues related to access to care, affordability, environmental factors, and genetics.
- Of the 30 countries studied, only one had organized national advocacy; however, as a result of the study, an additional country, Canada, has initiated national advocacy efforts, and more resources are going toward national advocacy in Taiwan, Korea, and other countries.
- Most countries involved in the study noted they lacked the resources and know-how to conduct adequate research.
- Many countries depend on National Comprehensive Cancer Network (NCCN) guidelines; however, these and most other guidelines are based mainly on research done on white populations and may not be appropriate for ethnically diverse and economically challenged populations around the world or in the United States. Significant need and opportunity exist for greater diversity in cancer epidemiology, socioeconomics, and related research in order to formulate successful strategies and policies to control cancer in America's increasingly culturally and ethnically diverse populations.
- Compared with non-Hispanic whites, Hispanic men and women are twice as likely to have and die from liver cancer. Hispanic women are 2.7 times more likely to have stomach cancer, twice as likely to have cervical cancer, and 1.5 times more likely to die from cervical cancer.
- Compared with non-Hispanic whites, Asian/Pacific Islander (API) men are twice as likely and API women, 2.6-times as likely to die from stomach cancer. API men and women have triple the incidence of liver and intrahepatic bile duct cancer of non-Hispanic whites.
- African Americans have the highest mortality rate of any racial/ethnic group in the U.S. for all cancer combined and for most major cancers. African-American men are twice as likely as white men to have new cases of stomach cancer, and African-American women are 34 percent more likely to die from breast cancer, although they have lower risk of breast cancer diagnosis than white women.
- Liver cancer is the fifth or sixth leading cause of cancer death in the world (depending on the data used for calculation) and has the third highest rate of mortality. Most people diagnosed with liver cancer die within one year. In the U.S., it is suspected that 70 percent of liver cancer deaths occur among Asian or Hispanic populations.
- In the U.S., nonwhite women have lower ages of breast cancer diagnosis, which is consistent with what was observed internationally. African-American, American Indian, and Hispanic women have 1.7- to 2.5-fold increased risk of stage III and IV breast tumors and a 1.3- to 2-fold increased risk of breast cancer-related mortality. Among stage I and II breast cancer patients with tumors smaller than

5 centimeters, African-American, API, Mexican, and Puerto Rican women were 20 to 50 percent more likely to receive inappropriate primary surgical and radiological breast cancer treatment.

- There are ethnic and cultural challenges related to cancer research and care in diverse populations. There are several examples of mistrust and fear. Some individuals fear genetic research because they think certain results will make them unmarriageable. Some leaders—including Mexico’s Deputy Minister of Health—have expressed concern that if individuals knew they had “cancer genes,” they would consider cancer inevitable and not try to adopt healthier lifestyles. Chinese individuals may be reluctant to participate in cancer research for fear of learning that they have, and being rejected because of, hepatitis, which is very common in Chinese populations because of low rates of vaccination. In Africa, people are reluctant to participate in research because of fear of learning that they have HIV and other diseases. In some countries, women choose to delay or avoid seeking treatment for breast cancer for fear of surgical disfigurement or losing their hair.
- Studies on communication with patients have shown that oncologists appear to communicate differently with breast cancer patients depending on the woman’s race, age, and other factors. Poor communication of mammogram results may also help explain disparities in breast cancer diagnosis and outcomes.
- Socioeconomic status and race impact access to screening and treatment for cancer. Poor, minority, and uninsured individuals have reduced access to screening and surgery for colorectal cancer. Furthermore, minority women are less likely to receive adjuvant therapies following breast cancer surgery and there are disparities in the receipt of chemotherapy following ovarian cancer surgery. Socioeconomic barriers also hinder timely diagnosis and treatment of prostate cancer in black men.
- Fewer than 10 percent of U.S. clinical trial participants come from nonwhite populations. Clinical trials could help low-income, uninsured individuals obtain free access to care and drugs, but very few adult cancer patients participate in clinical trials. An ongoing study has found that individuals involved in clinical trials are likely to have Internet access, at least a high school education, and fluency in English. Documented barriers to clinical trial participation include mistrust, lack of awareness, cultural barriers, language/linguistic differences, socioeconomic obstacles, cost/lack of insurance, and study eligibility criteria. Physicians often fail to refer their patients to clinical trials, in part because they are not aware of available options.
- There is a lack of minority investigators in clinical cancer research, which is important because physician race may be an important factor in influencing patient participation in a clinical trial.
- Health insurance and socioeconomic status play a role in cancer care. Only 11 percent of white Americans lack health insurance, compared with 30 percent of legal Hispanic immigrants in the U.S. A study of men with prostate cancer from the North Carolina Cancer Registry showed that although black and white men had to travel similar distances to receive health care for their cancer, black men had poorer health insurance coverage, had less continuity of care, used more public clinics and emergency wards, and expressed less trust in their physicians. The study concluded that barriers to early diagnosis and appropriate care for prostate cancer among black men were related more to SES than to lack of education or cultural misunderstanding.
- Efforts to prevent cancer should include a focus on smoking and obesity.
- Immigrants to the U.S. have increasing risk of cancer the longer they are in the country. This is likely due in large part to changes in lifestyle.
- The Johns Hopkins taxonomy for cancer control is based on analysis of data from the UMass/Johns Hopkins study and may serve as a framework to assess strategies to improve cancer control in the United States. The taxonomy includes four areas—removing barriers, building capacity, developing evidence, and promoting advocacy. The first step to improving cancer control is to remove barriers to access; this includes addressing out-of-pocket costs, high costs to payers, and issues surrounding reimbursement. Building capacity involves issues related to research, registries, national statistics,

and public education; it also relates to workforce issues (e.g., researchers, nurses). Developing evidence will require more international networks and study of local environments. Finally, advocacy efforts need to be encouraged and supported.

- There is much that the United States could learn from the rest of the world to help achieve better control of cancer across its rich and diverse population. If the U.S. succeeds in this effort, the whole world will benefit.

DISCUSSION AND CONCLUDING COMMENTS:

PANEL I

Key Points

- There has been extensive intermarriage between ethnic groups in Hawaii, particularly in recent years, and many Hawaiians are of mixed ancestry. The data presented by Dr. Kolonel were based on self-reported ethnicity, but he and his colleagues are beginning to use ancestry markers to define ethnicity. It is striking that ethnic differences in cancer risk are evident despite high levels of ethnic mixing.
- Native Hawaiian breast cancer patients have higher mortality rates than breast cancer patients of other ethnic groups in Hawaii. It is not known whether there is a biological basis for this difference. Like white women, Native Hawaiian women have high proportions of ER-positive tumors, so the increased mortality rates are not due to increased incidence of ER-negative tumors, as is the case for African Americans and some other ethnic groups. Furthermore, most Native Hawaiians do have health insurance; however, there are still social and cultural barriers that may keep them from obtaining optimal care for their cancers. For example, there are few Native Hawaiian oncologists.
- Several decades ago, Filipino women in Hawaii had high breast cancer mortality rates, similar to those of Native Hawaiians. However, their mortality-to-incidence ratio has improved dramatically since that time. This is likely due to changes in sociocultural factors.
- Cancer risk conferred by obesity depends in part on where the fat tissue is deposited. In general, central adiposity carries more risk than peripheral adiposity. Studies in Hawaii are working to distinguish between these two types of obesity, in part by using MRI to measure fat deposits.
- Rural-urban differences in cancer incidence and mortality have been documented in some developing countries, including Egypt. The reasons for these disparities are not clear. One hypothesis was that rural women in Egypt were not seeking medical care for their cancer and were thus dying without being diagnosed and were underrepresented in registries. However, focus groups revealed that rural and urban women seek medical care at similar rates. Interestingly, many rural women do not trust their local primary care doctors, so they travel to and are often diagnosed in urban areas. It is also possible that higher rates of cancer in urban areas are due to increased exposure to estrogenic compounds (e.g., from plastic bags, cosmetics, waste mismanagement).
- There are high rates of inflammatory breast cancer in North Africa. It is not known whether risk of this disease persists when North African women migrate to other countries. Many North Africans migrate to France, but it is difficult to study migration effects among the French population because France does not record patients' ethnic background. There may be opportunity to study North African immigrants to Canada, California, and Michigan.
- There is ancestral and genetic variation within ethnic groups, particularly Hispanics. It was noted that many of the Hispanic men who traveled with the Spanish conquistadors to what is now the U.S. Southwest were Crypto-Jews. As a result, some Hispanic subpopulations in the Southwest exhibit significant Jewish admixture. Hispanic women in northern New Mexico have high rates of breast cancer, which are often associated with *BRCA* mutations similar to the Jewish founder mutation. This illustrates the importance of understanding racial/ethnic admixture.

- Hispanic pediatric leukemia patients with significant American Indian genetic admixture exhibited very high frequency of mutations in the *CRLF2* and *JAK2* genes. *JAK2* inhibitors have been FDA-approved for other cancers and are in clinical trials for leukemia. The *CRLF2* gene was first discovered by asthma researchers and there are already FDA-approved drugs that target *CRLF2*.
- It is not yet clear why Hispanic children have a predisposition to acquiring *CRLF2* and *JAK2* mutations. Dr. Willman's group has discovered a locus that appears to be linked to leukemia predisposition among Hispanic children, but it is not yet clear whether the increased susceptibility of individuals with high-risk polymorphisms is due to environmental exposure, sociobehavioral factors, diet, or some other factors.
- Dr. Willman's group is extending its study of *JAK2* and *CRLF2* mutations into adolescent and young adult ALL patients in conjunction with adult Cooperative Groups. Initial studies indicate that approximately 15 percent of these patients house *JAK2* mutations. Similar studies are also being pursued for acute myeloid leukemia; however, this disease is much more heterogeneous, which makes studying it more complicated.
- Hispanic women with breast cancer have higher rates of mortality than their stage-matched white counterparts. However, it is also important to consider whether mortality rates for women with ER-negative breast cancer differ between ethnic groups or whether the increased mortality risk among Hispanic women is due largely or in part to an increased proportion of ER-negative cancers.
- Linguistically and culturally appropriate advocacy needs to be conducted in local communities regarding the importance of early detection, screening, and risk factors. Currently, very little advocacy exists in non-English-speaking communities in the United States. Advocacy efforts in other countries may need to be different than those in the United States, depending on cultural issues and other factors.
- Alternative approaches to screening have been attempted and discussed. In Taiwan, the percentage of the target population being screened for breast cancer is quite low, but Taiwan has lowered its breast cancer mortality rates; this may be in part because an effort has been initiated to teach young girls about breast health and the importance of seeking medical care early. Strategies to improve screening and early detection need to be developed based on the target population—a strategy that works in one country may fail in another country. The U.S. should work with other countries, particularly Latin-American countries, as they develop their cancer screening strategies. Although the strategies may not be directly transferable to the United States, the U.S. could gain insights into what works within various ethnic populations. The U.S. has to deal with the added complexity that its ethnic populations are very heterogeneous.
- One approach to screening being discussed within Johns Hopkins is to conduct more focused outreach for screening, such as targeting family members of cancer patients for more aggressive screening. This may be a more productive approach than promoting massive public screening.
- Changes in screening guidelines or strategies will likely have implications for insurance reimbursement.
- Some people are concerned about undergoing genetic testing for fear that if a high-risk gene is identified they may be prevented from buying health insurance. Current health reform efforts under consideration would prohibit insurance companies from denying coverage based on preexisting conditions. This change would help progress related to genetic testing and personalized medicine because people would likely be more willing to learn about their genetic background.
- Cancer risk and cancer health disparities are due to both genetic and environmental factors.
- Genetic background can influence treatment outcomes in some cases. Nonsmall cell lung cancer patients with EGFR mutations tend to respond better to Tarceva than those who do not harbor mutations in this gene.

- A study recently published in *Cancer* reported that mammary tumor virus was detected in 70 percent of breast tumors of Tunisian women and 30 percent of breast tumors of U.S. women. Viral DNA was not detected in normal mammary tissue of women without breast cancer.
- Many U.S. students, including medical students and public health students, are interested in international studies and global health, and several take advantage of opportunities to study abroad. There should be an effort to attract these students to cancer research.
- There are clear genetic differences related to disease susceptibility among different populations. Although studying these differences creates some ethical concerns, if differences in susceptibility are ignored, a significant fraction of the population will continue to be poorly served by available treatment options. By focusing on genetic differences, it has been possible to identify novel mutations that may respond to targeted therapies, thus advancing the quest for personalized medicine.
- Comprehensive population-based studies are needed to identify cancer risk factors and potential therapeutic targets. However, progress in the U.S. has been hindered by the fragmentation of the health care system and lack of adult participation in clinical trials. These types of trials are progressing more quickly in European countries that have socialized medicine and higher rates of clinical trial accrual.
- In Australia and New Zealand, all clinical trial protocols must be reviewed by a panel of consumer advocates, which ensures community input into research.
- It is important to discuss race as a social construct when addressing cancer health disparities because disparities are likely largely due to social and cultural factors. However, it is also necessary to develop less-polarizing ways to discuss genetic and other biological factors that contribute to racial/ethnic differences in disease. It was suggested that the term “genetic ancestry” be used in lieu of “race” and “ethnicity.”
- In choosing partners for the US-LA CRN, NCI utilized criteria that included whether the country has an established health care system, ongoing scientific research and supporting technological infrastructure, an existing cancer research network, and a central government agency responsible for health care policy and research funding. It was noted that NCI is a research-sponsoring organization and cannot provide funding to support health care in US-LA CRN partner countries.
- The Johns Hopkins taxonomy for cancer control was developed based on results of the 30-country horizon-scanning study. It drew on priorities identified by community, policy, advocacy, and medical leaders.
- U.S. studies should develop inclusion/exclusion criteria that facilitate international collaboration. Factors such as consent forms and institutional issues must be considered.

PUBLIC COMMENT

Key Points

- Consideration needs to be given to the terminology used when studying genetic and biological contributors to health disparities. Race and ethnicity are often used interchangeably, but should not be. There is extensive admixture even within African-American populations. Greater attention should be paid to neighborhoods and environments and exposures incurred over a person’s lifetime.
- Breast cancer is the most common cancer among U.S. women and most women diagnosed do not have a family history of breast cancer. This needs to be taken into account when changes in screening strategies are discussed.
- Communities are valuable sources of information. Researchers could often avoid spending money to answer questions if they talked to the community first.

PANEL II

DR. SUSAN L. NEUHAUSEN:

ASSOCIATION OF GENETIC VARIATION AND CANCER RISK IN ETHNIC SUB-POPULATIONS

Background

Dr. Susan Neuhausen is Professor in the Department of Epidemiology and Program Leader of Population Sciences in the Chao Comprehensive Cancer Center at the University of California (UC), Irvine. She also holds a joint appointment in the Department of Pediatrics, where she serves as a mentor to genetic counseling students. From 2004 until July 2009, she served as the Associate Director of the Genetic Epidemiology Research Institute at UC Irvine. Dr. Neuhausen recently accepted the Morris and Horowitz Families Endowed Professorship in Cancer Etiology and Outcomes Research in the Department of Population Sciences at the Beckman Research Institute of the City of Hope. She serves on the Steering Committees of the NCI Breast Cancer Family Registry and the California Teachers Study.

Key Points

- Breast cancer is the most common cancer in women and the second most common cause of cancer death. A woman has a 1 in 8 chance of developing invasive breast cancer and a 1 in 35 chance of dying from the disease once it has developed. Two-thirds of breast cancer cases are in women age 55 years or older.
- Breast cancer statistics differ depending on the population being studied. For example, the highest incidence of breast cancer is in non-Hispanic white women, with the lowest incidence in American Indian women.
- Some breast cancer risk factors are modifiable. These include reproductive history; use of oral contraceptives and hormone replacement therapy; alcohol use; weight; and physical exercise. Nonmodifiable risk factors include race, menstrual history (i.e., age at menarche and menopause), personal or family history of breast cancer, and genetic susceptibility.
- People who share a common ethnic ancestry (i.e., individuals from the same population group) have more similar DNA sequences than people of diverse ethnic ancestry. Based on analysis of several regions of the genome, DNA sequences are estimated to be 99.9 percent identical between different individuals. However, with a 3 billion nucleotide genome, the 0.1 percent difference translates to several million nucleotide differences between individuals.
- Increasing population admixture blurs many genetic distinctions between individuals. Nevertheless, the memory of an individual's ancestry is retained in the genome and can be used to identify disease susceptibility loci.
- Certain genetic diseases occur more frequently in some population groups than in others. Awareness of these facts may be valuable in designing diagnostic and prevention strategies. The objective of obtaining ethnicity information from patients is to improve health care for diverse populations who differ in their risk to develop specific genetic disorders and their response to treatment.
- Association studies are used to identify genetic links to disease. These studies aim to test whether single-locus alleles or genotype frequencies are different between two groups (usually those with and without the disease of interest).
- A marker locus is associated with a disease if the distribution of genotypes at the marker locus in disease-affected individuals differs from the distribution in the general population. A specific allele may be positively associated (overrepresented in affected individuals) or negatively associated (underrepresented) with a disease trait.

- An association between an allele/genotype and a disease phenotype may be direct or indirect. A direct, or causal association means the identified SNP directly affects the function/expression of a gene involved in cancer. In contrast, an indirect association involves a SNP that does not directly drive cancer risk but is genetically linked to a polymorphism that does; an indirect association of a certain polymorphism with a disease may be more robust in some populations than in others.
- African Americans are an understudied population with a much higher age-adjusted breast cancer mortality rate than whites. UC Irvine investigators conducted a population-based study to assess the role of variation in genes in the IGF (insulin-like growth factor) signaling pathway—a pathway linked to cancer—in breast cancer in African-American women. Previously published data indicate that African Americans have higher circulating serum levels of IGF-1, which is associated with higher risk of premenopausal breast cancer.
- Using DNA from 460 African-American women with breast cancer and 280 controls, the investigators discovered significant associations between breast cancer risk and polymorphisms at gene loci for two IGF binding proteins. These associations were replicated using 600 samples from a Nigerian case-control set established by Dr. Olufunmilayo Olopade, University of Chicago Medical Center. Interestingly, other genome-wide association studies (GWAS) have identified another SNP near these genes that is associated with breast cancer risk.
- Parise et al., have identified variation in breast cancer subtypes by ethnic group. In both whites and Asians/Pacific Islanders, approximately 11 percent of total breast cancers are triple negative (i.e., ER/PR/HER2-negative). The rates of triple-negative breast cancer are higher among other ethnic groups—18 to 19 percent of breast cancers in Hispanics and 29 percent in African Americans. The high percentage of triple-negative breast cancers in African Americans likely contributes to the poor prognosis and more aggressive disease in that population.
- The differing proportions of breast cancer subtypes could be due to genetic variation. A study investigating the top GWAS-identified SNPs by subtype found that associations for some of the loci varied by subtype.
- Risk factors sometimes differentially influence breast cancer subtypes. Early age at first full-term pregnancy and high parity are protective against luminal breast cancer, whereas they increase risk for basal-like breast cancer. However, it was noted that breastfeeding can negate the risk of basal-like cancer conferred by high parity. African-American women, who are diagnosed with basal-like breast cancer at disproportionately high rates, should be encouraged to breastfeed in order to reduce their risk of this type of cancer.
- Certain intermediate phenotypes that lead to increased breast cancer risk, such as early-onset menarche and abdominal adiposity, are heritable as well as modifiable (i.e., diet, physical exercise).
- Ethnic/racial differences in response to cancer treatment reflect underlying genetic variation. Differences in pharmacokinetics may be driven by variation in the genes for phase I and II metabolizing enzymes and drug transporters. Variation in inflammatory or immune genes may also affect response to treatment.
- Breast cancer is complex, heterogeneous and develops through multiple pathways. Differences between subpopulations in incidence, clinical presentation, and response to treatment are likely due to genetic differences and their interactions with environmental exposures.
- Individualized medicine is the ultimate goal in cancer care; but until that goal can be reached, it would be beneficial to take into consideration patient subpopulations when recommending treatments.

DR. STEFAN AMBS:

PROFILING TUMORS TO IDENTIFY FACTORS THAT CONTRIBUTE TO CANCER HEALTH DISPARITIES

Background

Dr. Stefan Ambs is a tenure-track investigator and head of the Laboratory of Human Carcinogenesis Breast and Prostate Cancer Unit within the NCI Center for Cancer Research. He received his master's degree in biochemistry from the University of Tübingen (1988) and completed his Ph.D. at the Institute of Toxicology, University of Würzburg, Germany (1992). He also earned a Master of Public Health degree (epidemiology) from Johns Hopkins Bloomberg School of Public Health (2005). Dr. Ambs was trained in translational research as a postdoctoral fellow at NCI under the mentorship of Dr. Curtis Harris (1992-1997). He continued his research at a biotechnology company in California and at the Aventis Genomics Center in Cambridge, Massachusetts. In 2001, he returned to NCI as an investigator in the field of molecular epidemiology.

Key Points

- According to the American Cancer Society, of all the ethnic groups in the U.S., African Americans have the highest death rates from malignancies of the lung, colon, rectum, breast, prostate, and cervix.
- Cancer health disparities are an ongoing research focus at the NCI Laboratory of Human Carcinogenesis (LHC). African-American and European-American patients from the greater Baltimore area are being recruited into case-control studies to examine the contribution of environmental and inherited factors to the excess cancer burden among African Americans.
- Racial disparities in prostate and breast cancer survival among African Americans and European Americans persist in randomized clinical trials, raising the possibility that intrinsic differences in tumor biology influence disease aggressiveness and response to therapy.
- Cancer epidemiology and genetic studies also suggest that the prevalence of endogenous risk factors can differ between population groups. For example, basal-like breast tumors, which are ER negative, are most common among young African-American women. The higher prevalence of this specific subtype among African-American women accounts for some of the overall survival disparity between African-American and European-American breast cancer patients; however, racial disparities in outcomes are observed even if women are stratified by ER status.
- Recent studies report that 70-80 percent of breast cancer patients in West Africa present with ER-negative disease, and over 50 percent present with triple-negative disease. These numbers are much higher than in the U.S., Europe, or Asia. These patterns indicate that women of African ancestry tend to develop tumors with different biology than women of European descent.
- The LHC used genome-wide expression profiling of breast and prostate cancers to identify differences in tumor biology between African Americans and European Americans. Investigators analyzed gene expression profiles of primary prostate tumors resected from 33 African-American and 36 European-American patients. These tumors were matched on clinical parameters and the resulting data sets were analyzed for expression differences on the gene and pathway level.
- The analysis revealed 162 genes to be differently expressed among African Americans and European Americans. These genes were found to be associated with pathways related to immune response, host defense, B- and T-cell function, antigen presentation, and inflammation. An analysis of nontumor tissue from the two patient groups did not generate these biological pathway associations, indicating that the detected gene signature is specific to the tumor microenvironment.
- A prediction analysis was also conducted to determine which of the 162 differently expressed genes best separate African Americans from European Americans. Surprisingly, only two of the genes—

CRYBB2 and *PSPHL*—could predict ancestry with great accuracy. The *PSPHL* gene is being studied for cancer-related function due to its upregulation in tumors versus normal tissue.

- In a second study, epithelial and stromal portions of tumors from 18 African-American breast cancer patients and 17 European-American breast cancer patients were subjected to gene expression profiling. Numerous genes were differentially expressed between the two patient groups, but a two-gene signature in the tumor epithelium was able to distinguish between them. Several biological processes identified through this analysis, including angiogenesis and chemotaxis, may contribute to enhanced disease aggressiveness in African Americans.
- The role of angiogenesis in the tumor biology of African-American patients was further validated by measuring the extent of vascularization and macrophage infiltration in an expanded set of 143 tumors from African Americans and 105 tumors from European Americans. Immunohistochemistry revealed that microvessel density and macrophage infiltration is significantly higher in African-American tumors than in European-American tumors.
- *AMFR* (autocrine motility factor receptor) was one of the genes differentially expressed among African-American and European-American patients. Its expression was increased in breast tumors of African-American patients, independent of ER status. *AMFR* increases tumor metastasis by targeting the tumor suppressor gene *KAI1* for degradation; it is a predictor of poor survival outcome in many cancers. The *AMFR* gene was also found to be overexpressed in African-American primary prostate cancer epithelial cells and tumors.
- A prominent interferon signature was detected in African-American tumors that may relate to an unknown etiologic agent in disease pathology. This signature may also influence therapeutic outcome as it is homologous to a recently discovered interferon-related DNA damage resistance (IRDR) signature, which predicts resistance to chemotherapy and radiation in breast cancer. Future research should examine whether the IRDR signature is prevalent in tumors of African-American patients and how it influences the response to therapy.
- In an upcoming study, the transcriptomes, proteomes, and metabolomes of breast tumors and paired normal surrounding tissue from African-American and European-American patients will be analyzed to investigate biological differences between the two patient groups. The goal of this study is discovery of novel biomarkers for prognosis and to elucidate factors that drive the aggressiveness or resistance to therapy of breast cancer in African-American patients.

DR. WAEL A. SAKR:

ETHNIC DISCREPANCIES IN PROSTATE CANCER INCIDENCE AND OUTCOME: A PATHOBIOLOGICAL PERSPECTIVE

Background

Dr. Sakr is Professor and Chairman of the Department of Pathology at Wayne State University (WSU). He received degrees in basic medical sciences and clinical medical sciences from the University of Damascus in 1977 and 1980, respectively. Following an internship at Al Mowassa University Hospital in Damascus, Dr. Sakr did a residency in anatomic pathology at Booth Memorial Medical Center and a fellowship in surgical pathology at Wayne State University. He is Director of the Human Tissue and Pathology Core at Karmanos Cancer Institute, Wayne State's NCI-funded comprehensive cancer center. He is also co-principal investigator on an NIH grant devoted to studying racial differences in prostatic carcinoma.

Key Points

- Approximately 600,000 new cases of prostate cancer are diagnosed annually worldwide. Prostate cancer accounts for nearly 10 percent of all cancers and is the fourth most common cancer among

males. North America, Scandinavia, Western Europe, Australia, and New Zealand are among the regions with the highest burden of prostate cancer; however, Jamaican men of African-Caribbean descent have the highest incidence. Asia, particularly Japan, has significantly lower than average rates of prostate cancer, while moderate rates are observed in Latin America. Data on prostate cancer in Africa are sparse and often conflicting.

- In the U.S., African-American men have the highest incidence of and mortality due to prostate cancer. White and Hispanic men also have relatively high incidence and mortality, while API and AI/AN men have lower incidence. API men have the lowest prostate cancer mortality rates, while mortality rates of AI/AN men are similar to those of white and Hispanic men. Mortality from prostate cancer has decreased in recent years, but significant disparities persist between white and African-American men.
- Potential reasons for ethnic discrepancies in prostate cancer incidence and outcomes include biological/genetic characteristics, lifestyle factors, inflammation/oxidative stress, socioeconomics, education, and differences in treatment.
- Prostate cancer incidence rates vary dramatically among countries, with a 30-fold difference between the countries/regions with the highest and lowest rates of the disease (the United States and Shanghai, China, respectively). However, the prevalence of subclinical disease appears to be less variable (differences ranging from two- to fourfold worldwide). This suggests similar rates of prostate cancer initiation but different rates of disease progression.
- Autopsy data indicate that at any given time, approximately 1 million U.S. men harbor subclinical prostate cancers. An important question is which of these subclinical tumors will progress to become clinically significant. Also of interest is how this progression differs among different population groups.
- Wayne State University serves an urban area with a large African-American population. The University's tissue bank includes cells from approximately 12,500 prostate needle biopsies, close to 3,000 radical prostatectomy specimens, and approximately 1,600 prostate glands procured from autopsies. A high proportion of these samples are from African-American men.
- Prostate glands were collected from just over 1,000 autopsies conducted by the Wayne County coroner's office. These included glands from young men who died due to reasons unrelated to prostate cancer. This collaboration facilitated examination of younger men with fewer comorbidities than were included in previous hospital-based prostate autopsy studies. The entire prostate was sectioned and evaluated to document cancers and precursor lesions. Age and race were extracted from medical examiner records. Data from this study revealed that 20 percent of men between 20 and 50 years of age harbored prostate cancer. Premalignant prostatic lesions were also observed in many young men and increased in prevalence with increasing age.
- High-grade prostatic intraepithelial neoplasia (PIN) is a precursor lesion, but its presence in a needle biopsy sample suggests that malignant cancer may be present elsewhere in the gland (i.e., biomarker for cancer). Analysis of the WSU autopsy samples revealed that African-American men have a higher prevalence of extensive PIN than white men, particularly between the ages of 40 and 70 years.
- Of the prostate cancers identified in the WSU autopsy study (most of which were very small), tumors of African-American men tended to have higher Gleason scores and higher volume relative to those of their age-matched white counterparts. There was no difference in cancer multifocality by age or ethnicity.
- Currently available screening tools for prostate cancer—including prostate specific antigen (PSA) levels and digital rectal examination—are not effective for all patients. Some patients have aggressive cancers that progress to an incurable stage between annual screenings; others are treated for slow-growing tumors that would not become clinically relevant in their lifetimes. Furthermore, PSA levels

do not always correspond with cancer—some men with high-grade prostate cancer have low PSA levels.

- Biopsy of the prostate gland is an imperfect procedure for cancer detection, in part because it provides only a sampling of tissue. The goal is to maximize detection of clinically important cancers while avoiding detection of benign or nonaggressive lesions.
- Needle-biopsy samples exhibit increasing Gleason scores with increasing patient age. Among patients 70 years of age and older, African Americans have higher Gleason scores on average than white patients. In addition, of patients undergoing radical prostatectomy, African-American men are more likely than whites to have metastatic disease.
- An M.D. Anderson study of biopsies from PSA-level-matched patients found that African-American men had larger tumors than whites and tended to have tumors with higher Gleason scores. The investigators state that these results support adoption of a lower PSA threshold of 2.5 ng/ml for biopsy of African-American men.
- In recent years, the average size of the tumors detected via prostate biopsy has decreased. This poses some challenges and requires changes in biopsy approaches. Doctors now sample more heavily from the peripheral zone of the gland than before to help diagnose the small cancers that occur in this region.
- One study found that PSA and PSA density were able to effectively detect cancer in patients who had had a digital rectal exam.
- It has been suggested that there may be differences in tissue testosterone levels between whites and African Americans, but a recent study found no differences in testosterone or dihydrotestosterone between these two populations.
- Efforts are underway to use gene expression profiling to identify genes differentially expressed in radical prostatectomy tissue collected from white and African-American men.
- In conclusion, there is a persistent higher incidence and mortality of prostate cancer among African-American men that is not well understood. There are many indications that this is at least in part due to biological factors.

DR. ELAD ZIV:

GENETICS OF CANCER SUSCEPTIBILITY IN POPULATIONS OF MIXED ANCESTRY

Background

Dr. Elad Ziv is Associate Professor of Medicine and Epidemiology and Biostatistics at the University of California, San Francisco (UCSF). Dr. Ziv completed his undergraduate degree at Yale University. He attended medical school at UCSF, where he also completed his internship and residency training in internal medicine and his fellowship in general internal medicine/epidemiology. He joined the faculty at UCSF in 2001. His research fellowship focused on genetic susceptibility to complex disease, particularly breast cancer. Currently, a major theme of his work is exploring the ways in which complex genetic ancestry can be used to understand population differences in disease. In particular, he is studying breast cancer susceptibility among Latina populations in the U.S. and collaborating on international studies of breast cancer in Latin-American populations. He is also studying genetic susceptibility to breast cancer among African-American populations. Dr. Ziv's group has been a leader in applying the technique of admixture mapping to identifying genes.

Key Points

- There are differences among racial/ethnic groups in incidence and mortality of many cancers, including breast and prostate cancers and multiple myeloma.
- The most common type of genetic variation is single nucleotide polymorphisms. These are regions of DNA in which the identity of a nucleotide at a certain position varies among individuals within a population. SNPs sometimes lead to differences in protein sequence or expression levels, which can lead to differences in biology. Other types of variation include variable number of tandem repeats (VNTRs, also called microsatellites), presence/absence of transposable elements (e.g., *Alu* repeats), and structural alterations such as deletions, duplications, or inversions.
- Modern human populations originated in Africa and over the last 100,000 years migrated to the Middle East and Europe and then throughout the world. As these populations migrated, there have been bottleneck effects—usually a small group left a larger group, resulting in a decrease in genetic variation within the migrating population. Most of the time, migrating populations did not travel far, but regional genetic differences arose because they did not come into contact with the population they left behind. A study published in *Nature* showed that there was a linear correlation between the geographic distance between populations and their genetic differences.
- More recently, there has been an increase in admixture between populations (i.e., mixture between populations genetically distinct because they had been separated for tens of thousands of years). The result is populations with variable proportions of ancestry from each parent population. Chromosomal recombination events over subsequent generations result in chromosomes with genetic material from multiple ancestral populations. This allows geneticists to conduct admixture mapping to link ancestry loci to disease traits.
- Admixture mapping has been used to help study the epidemiology of benign neutropenia. This disease, which is characterized by low white blood cell counts but no excess risk of infection, is present in Africans, Yemeni Jews, and Bedouins. It has a familial component, suggesting that it is a genetic disease.
- The U.S. Health and Body Composition Study included healthy men and women aged 70 years and older. Measurements revealed that African Americans on average have slightly lower white blood cell counts than Caucasians. To determine whether this observation was due to genetic differences, researchers collected information on more than 1,300 ancestry informative markers. Analysis of those who were identified as African American revealed that individuals with greater than 90 percent African ancestry tended to have lower neutrophil counts than those with less than 60 percent African ancestry. Additional experiments were able to map an association between benign neutropenia and the DARC locus on chromosome 1. African Americans homozygous for a certain genotype at this locus had significantly lower white blood cell levels than those who were homozygous for another variant or heterozygous.
- NCI SEER data indicate that European-American women have the highest rates of breast cancer while Native Americans appear to have the lowest rates. Interestingly, Latinas—who are a mixture of European and Native American populations—have intermediate risk of breast cancer.
- Samples from the San Francisco Bay Area Study were utilized to analyze the DNA of self-reported Latina women ages 35 to 79, including healthy women and women who had been diagnosed with breast cancer. A total of 106 ancestry informative markers linked to Native American and European ancestry were genotyped, revealing that the Latina women had a wide range of ancestries.
- An analysis was done to determine whether genetic ancestry was associated with breast cancer risk. When the data were not adjusted for risk factors, women with 76 to 100 percent European ancestry had nearly four times the risk of breast cancer as women with 0 to 25 percent European ancestry. The analysis was repeated after adjusting for a number of risk factors, including reproductive variables, calorie intake, alcohol use, education, hormone use, body mass index, foreign-born status, family

history, and benign breast disease. Using adjusted data, women with 76 to 100 percent European ancestry had 2.2 times the risk of breast cancer as women with 0 to 25 percent European ancestry.

- These data indicate that some of the differences in risk are associated with nongenetic risk factors, but breast cancer risk is also associated with ancestry. Similar results were obtained in a follow-up study conducted with Mexican women. Efforts are under way to use SNP arrays to identify genes responsible for these genetic differences.
- Potential genetic contributions to breast cancer were also studied in African-American women. African Americans are known to have extensive admixture; on average, an African American has 80 percent African ancestry and 20 percent European ancestry, although this ratio varies significantly among individuals. DNA samples from over 1,400 African-American women with breast cancer were used to assess the association between ancestry and estrogen receptor status. After adjusting for all known risk factors, ER-positive breast cancer was associated with high European ancestry while ER-negative breast cancer was associated with high African ancestry. However, ER status could not be mapped to any particular genomic region.
- Admixed populations can be used to test hypotheses generated by epidemiologists. Genes that contribute to diseases such as end-stage renal disease and prostate cancer have been identified through admixture mapping.
- Genome-wide association studies are being done to examine the genetic bases of disease among different populations. Many studies have been done on European populations but few studies have been done on nonwhite populations.

DR. BETH A. JONES:

THE CHANGING U.S. POPULATION AND BREAST CANCER DISPARITIES: LESSONS LEARNED FROM THE STUDY OF AFRICAN-AMERICAN WOMEN

Background

Dr. Beth Jones is a Research Scientist in the School of Public Health, Yale University School of Medicine. The focus of Dr. Jones's teaching and research is health disparities, primarily the study of racial/ethnic disparities in cancer. Dr. Jones has conducted a number of studies that have systematically evaluated factors that contribute to the relatively poor cancer outcomes in African Americans. Using a multidisciplinary approach, she has incorporated the role(s) of tumor characteristics and selected genetic factors, as well as social class, medical care, and psychosocial factors in explaining the lower survival from cancer in African Americans compared with whites. Although most of the work to date has focused on breast cancer, her work has been extended to other cancer sites as well (e.g., prostate, colorectal).

Key Points

- Unlike many other cancers, breast cancer incidence rates are generally lower in African Americans and other racial groups compared with white women. However, breast cancer mortality rates are higher in African-American women. Recent analyses of NCI SEER data for years 1990-2004 indicate that despite significant improvement in breast cancer mortality rates for all women, the gap between African-American and white women is actually widening.
- Racial disparities in mortality are due in part to the later stage at diagnosis generally observed among African Americans—51 percent of breast cancers in African Americans versus 62 percent in whites are diagnosed with localized disease. About 54 percent of breast cancers in Latinas are diagnosed when they are still localized to the breast. However, even when matched for stage, African Americans and Hispanics/Latinas have lower survival rates than whites.

- In order to understand the factors that drive racial/ethnic differences in mortality rates, it is helpful to work from a conceptual framework that focuses on the problem. The underlying question is: How does a variable such as race/ethnicity (top of the framework) impact breast cancer mortality (bottom of the framework)? The framework is a useful tool for identifying factors that contribute to the poorer breast cancer outcomes for African-American women.
- Social determinants contribute to observed differences in breast cancer mortality. These determinants include socioeconomic, sociodemographic, and sociocultural factors, as well as racism and other forms of discrimination. These factors can influence access to care, interactions in the health care setting, screening behavior, and delay in diagnosis, which, in turn, may affect stage at diagnosis.
- For Hispanics/Latinos, and some other racial/ethnic groups, health is further complicated by varying levels of assimilation and acculturation following immigration. First-generation immigrants are likely to be at a disadvantage with respect to cancer prevention due to less familiarity with the health care system, poor access related to lack of insurance, and language barriers. Interestingly, newly arrived immigrants tend to be healthier than the general population, but often lose this advantage over time and in subsequent generations, due to the socioeconomic marginalization associated with minority status.
- Although the triple-negative phenotype and other tumor characteristics associated with poor prognosis, such as p53 mutations, are more common in African Americans, a pattern of larger and higher grade tumors, including triple negatives, is emerging in Hispanic/Latina breast cancer patients. These markers are also more commonly found in women with *BRCA1* and *BRCA2* mutations. However, this tumor profile extends across ethnic groups and appears to be more common among lower socioeconomic populations, indicating that many of the acquired mutations that affect gene expression may be tied to factors linked to potentially modifiable environmental influences.
- Studies have indicated that minorities experience delays in diagnosis; however, the clinical importance (i.e., effect on stage at diagnosis, survival) of these delays has not been convincingly demonstrated. With increased immigration, especially from Central and South America, clinically meaningful delays in diagnosis may increase. Thus, targeted public health efforts related to symptom awareness and the importance of early detection will be needed.
- Obesity has consistently been associated with breast cancer incidence, as well as poor outcomes among those diagnosed. Obesity is more common in some racial/ethnic groups: 59.6% of white women are obese, compared with 69.9% of African-American women and 62.1% of Hispanics/Latinas. Almost one-third of the later stage at diagnosis observed in African Americans can be explained by the higher prevalence of obesity in that population. There is little information available on the association between obesity and breast cancer in Hispanics.
- Although self-reported mammography screening rates are high in the U.S., survey data indicate that screening rates are lower for Hispanic/Latina women than for African-American and white women. High self-reported history of screening is one measure of success of breast cancer control and prevention.
- Adherence to screening guidelines is relatively low among all women; however, African Americans are significantly less likely to be adherent than white women. Additionally, inadequate communication of mammography results (i.e., not receiving results or reporting results different from medical records) is more common for African Americans than for whites. For African-American women, communication is more likely to be inadequate for abnormal results than for normal results; the reverse is true for white women. Furthermore, African-American women are significantly less likely than white women to receive adequate follow-up.
- Strikingly, with as much progress as has been made in terms of new treatments and screening, the current five-year survival rate from breast cancer is about 78 percent for African-American women—the same as it was for white women 25 years ago.

DR. UPENDER MANNE:

RACE/ETHNICITY-SPECIFIC MOLECULAR DETERMINANTS: COLORECTAL CANCER

Background

Upender Manne, Ph.D., is an Associate Professor of Pathology, Associate Scientist of the Comprehensive Cancer Center, and Associate Scientist of the Minority Health and Health Disparity Research Center at the University of Alabama at Birmingham (UAB), Birmingham, Alabama. Dr. Manne received his B.Sc. in biology and chemistry; his M.Sc. in zoology with parasitology, histology and zoonotic diseases; and his Ph.D. in biochemistry of pathogens from Osmania University in Hyderabad, India. For the last 15 years, Dr. Manne's research at UAB has centered on the areas of tumor molecular biology, cancer genetics, discovery and validation of cancer biomarkers, and racial disparities in the biology, epidemiology and pathology of cancer. His studies, which relate to the heterogeneity of cancer, address how admixtures of patient populations for different race/ethnic backgrounds, treatment modalities, cancer stages, anatomic locations of tumors (e.g., proximal vs. distal colon or colon vs. rectum), and epidemiological and socioeconomic factors influence cancer outcomes. The findings from his studies show that consideration of these factors is clinically relevant in that they aid in personalizing cancer therapies. Dr. Manne also serves as a mentor to several basic and clinical translational researchers at UAB; the Morehouse School of Medicine/Grady Memorial Hospital, Atlanta, Georgia; and Tuskegee University, Tuskegee, Alabama. He recently received the coveted Charles Barkley Mentoring Excellence Award for the year 2009.

Key Points

- No single molecular test will provide answers to key clinical questions for all patients, even those with the same cancer type or tumor stage.
- Many factors contribute to disparities in colorectal cancer incidence and outcomes, including late stage of disease at diagnosis, differential opportunity for adjuvant treatment, socioeconomic factors, surgeon variation, and biological/genetic differences.
- A retrospective study was done on African-American and non-Hispanic white patients diagnosed with first sporadic colorectal adenocarcinoma who underwent surgery between 1981 and 1993 at the UAB hospital. Among these patients, African Americans had significantly lower survival rates for colon cancer but not for rectal cancer. A closer look at the data revealed that the largest disparity was observed among patients with early-stage disease; for patients with stage II (localized) disease, African Americans exhibited a 2.5-fold elevated risk of colon cancer mortality.
- Pathologic analysis showed that tumors from African Americans were less differentiated (i.e., more advanced grade) than those from non-Hispanic whites. Furthermore, compared to grade-matched whites, African Americans exhibited increased risk of colon cancer mortality.
- Colorectal tumors develop as a result of multiple sequential molecular changes. One molecule that plays an important role is p53.
- p53 mutations can be identified via DNA sequencing. Abnormalities in p53 signaling can also be inferred by detection of p53 nuclear accumulation using immunohistochemistry; however, immunohistochemical analysis of p53 has been conducted using a variety of techniques and there is some question about which technique(s) best indicate the p53 mutation status of a tumor. It is important to resolve this question because many developing nations do not have the resources to carry out DNA sequencing but can do immunohistochemistry. An assessment was done using cDNA and frozen tissues from 110 colon cancer patients to develop an immunohistochemical protocol that predicts whether a tumor harbors mutant p53. The results indicated that detection of p53 in at least 10

percent of tumor cells was predictive of p53 mutations but only when the tissue was not subjected to antigen retrieval techniques (i.e., boiling in citric acid).

- Studies done in different geographic regions have yielded different answers regarding the prognostic value of identifying p53 mutations for colorectal cancer. Studies published in Europe consistently demonstrate that abnormal p53 is an indicator of poor prognosis. Studies from New England have had similar results, but studies carried out on populations in other regions of the United States have consistently found no prognostic value for p53. The conflicting results from these studies may be due to differences in tumor stage or anatomic location or because of differences in admixture among the different study populations.
- A study of 204 African-American and 300 non-Hispanic white colorectal cancer patients revealed that abnormal p53 (measured by immunohistochemistry) was an indicator of poor prognosis in Caucasians, but not in African Americans, despite the fact that the rate of tumors with nuclear accumulation of p53 was similar among both groups. Further analysis found that the prognostic value of p53 in white patients depends on tumor location—abnormal p53 is associated with poor prognosis when the tumor is located in the proximal but not the distal region of the colon.
- Based on the findings of this study, it was hypothesized that p53 gene mutation patterns are different in Caucasian and African-American patients (i.e., these populations develop different p53 mutations). Sequence analysis revealed that Caucasian patients were more likely than African-American patients to have p53 mutations; in particular, Caucasians had higher rates of mutation in the L3 DNA-binding domain, which are associated with poor outcomes. However, a higher proportion of African-American patients had a particular polymorphism in codon 72 of the p53 gene that results in substitution of an arginine for a proline; this polymorphism is associated with poor prognosis among African Americans but not Caucasians with colon cancer. Experiments in cell culture indicate that cells with two copies of the polymorphism are resistant to oxaliplatin, a drug commonly used to treat colon cancer.
- microRNAs (miRNAs) are small, noncoding RNAs that regulate gene expression at the posttranscriptional level (e.g., influencing translation or mRNA degradation) or by silencing gene transcription. The therapeutic prognostic value of these molecules has been evaluated in several cancers. One study of colorectal cancer demonstrated that high expression of miRNA 21 is an indicator of poor prognosis.
- Expression levels of several miRNAs were assessed in colorectal cancers and benign tissues from African-American and non-Hispanic white colorectal cancer patients; tumors were characterized as high or low expressors. The analysis revealed that some of the miRNAs were informative for both ethnic groups while others were only informative for one or the other. These results illustrate that patient race/ethnicity should be considered in evaluation of the prognostic or predictive value of miRNAs.
- In summary, when the clinical usefulness of molecular markers for colorectal cancer and other cancers is being considered, potential confounding variables must be taken into account; these include tumor stage and location as well as patient race/ethnicity. The colorectum is often considered to be a single organ, but its various regions should be considered as separate organs.

DISCUSSION AND CONCLUDING COMMENTS:

PANEL II

Key Points

- A commonly espoused model of personalized medicine is that treatment decisions will be made based on the genotype of an individual's tumor. However, Dr. Manne's presentation indicates that there

may sometimes be ethnic differences in the value of particular markers. Before a marker is used to dictate treatment, it should be determined whether the marker is informative for a particular patient.

- As biomarkers are identified, it is sometimes possible to determine which patients are likely to have better or worse outcomes, but this information may or may not be clinically useful.
- The extent to which racial differences in stage at diagnosis of breast cancer are due to the lack of follow-up after abnormal mammograms and poor patient-doctor communication observed among African-American women receiving mammograms is unknown.
- There are different guidelines regarding breast cancer screening. ACS recommends that women begin annual screening at age 40, while NCI and other professional groups recommend screening every 1 to 2 years after age 40. Despite the fact that some women, particularly African Americans, are diagnosed with cancer before age 40, reducing the recommended age to begin screening is not advisable, in part because of the risks and consequences of false-positive mammograms. However, the more rigorous ACS guidelines should be promoted.
- In the study presented by Dr. Ziv, European ancestry was associated with increased risk of breast cancer while indigenous American ancestry was protective against breast cancer.
- The autopsy study discussed by Dr. Sakr revealed that cancers and precancerous lesions are present in the prostates of very young men. It is likely that only a small portion of these will become clinically significant; the bulk of the lesions are likely benign or will not be clinically manifested within the man's lifetime. Many laboratories are studying the genetic changes that contribute to prostate cancer progression, but this research has not yet influenced clinical management of patients.
- Many of the genes upregulated in prostate tumors from African Americans compared with Caucasians are involved in immune pathways. Research is being done to determine the cause of this difference and whether the observed upregulation of these genes influences prognosis.
- It may be desirable to achieve individualized (or personalized) medicine, but it is unclear whether this will be feasible or affordable in the short term. It may be more effective to focus, first, on subpopulations instead of individuals to identify high-risk groups that will benefit from different interventions. Subpopulation studies can be used to identify factors that directly relate to risk or response to therapy and this information can be applied to all individuals who have that factor (i.e., going from subpopulation research to individualized medicine). This is how *BRCA1* and *BRCA2* were identified—the results of research conducted on high-risk women and families allow for *BRCA* screening for the general population. Also, a high-risk germ-line sequence variant identified in African-American men with prostate cancer has been subsequently found in other ethnic groups.
- It is important to include all subpopulations in research, although it is recognized that it may be difficult in some cases to find enough participants to generate meaningful data for all subpopulations. Early results should be taken into the community to promote primary prevention activities, if possible.
- Advances in technology are facilitating exciting genetic studies. Resources should be invested to ensure that these technologies are applied to study all populations so that the knowledge gained will benefit as many people as possible.
- Many health disparities are likely due to gene-environment interactions and/or are rooted in exposures. Socially and economically marginalized populations are more likely to be affected by environmental exposures that negatively contribute to health outcomes.
- It is hoped that individualized medicine will result in decreased health care costs. It will likely result in increased diagnostic costs but reduced treatment costs because fewer patients will undergo unnecessary treatment.

PUBLIC COMMENT

Key Points

- Aggregation of cancer incidence and mortality rates may make important trends less evident. For example, reporting aggregate data for Asians/Pacific Islanders—which comprise over 60 groups—may mask the high rates of breast and colorectal cancer among Native Hawaiian, Samoan, and Tongan groups. This is important because perceived risk fuels funding for cancer control programs and research. The Panel should recommend that cancer data be disaggregated. One way to begin to disaggregate these data is to do the detailed studies of genetics like those described in the presentations at the current meeting.
- Haplotype mapping has been done to characterize the genetic profiles of several tribes and groups in Mexico in order to gain insight into their ancestry. These types of efforts should be integrated with similar U.S.-funded studies.
- The region of Veracruz in Mexico was a stopping point for slave trade during the colonial period, resulting in a higher population of blacks in this region than in other areas of Mexico. This has implications for studies done on populations in or from Veracruz. The San Francisco Bay Area Study did not likely include a significant Latina population from Veracruz; however, researchers in Mexico are recruiting participants from Veracruz for similar studies.
- Currently available ancestry informative markers provide some insight, but it is hoped that these markers will be refined and expanded in the future so that they will be even more useful.
- The community needs to hear about the type of research being discussed at the current meeting. Research is important, but it is also important to act on what is known in order to prevent excess suffering and death. Improving community understanding of research will help speed its translation.

CLOSING REMARKS—DR. LEFFALL

- Dr. Leffall thanked the panelists for their informative presentations.

CERTIFICATION OF MEETING SUMMARY

I certify that this summary of the President’s Cancer Panel meeting, *America’s Demographic and Cultural Transformation: Implications for the Cancer Enterprise*, held October 27, 2009, is accurate and complete.

Certified by:

Date: February 2, 2010

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