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Review Article

Breast cancer disparities: Frontline strategies, proceedings of the 7th annual texas conference on health disparities

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Abstract

There are striking disparities in health status, access to health care, and risk factors among racial and ethnic minorities and the general population in Texas. The disparities are multifactorial comprising genetic, sociocultural, and environmental variables. The Texas Center for Health Disparities (TCHD), a NIMHD Center of Excellence (COE), aims to prevent, reduce, and eliminate health disparities in the communities through research, education, and community-based programs. As part of the center's outreach activities, an annual conference is organized to build awareness and knowledge on health disparities. The overall theme for the 2012 conference was "Battling Breast Cancer Disparities: Frontline Strategies". The scientific program consisted of three sessions: "Breakthroughs in Breast Cancer", "Triple Negative Breast Cancer," and "Hormone Resistant Breast Cancer" featuring different aspects of bench-research from molecular biology, proteomics, and genetics to the clinical aspects such as detection, diagnosis, and finally to community-based approaches. This article summarizes the proceedings of the meeting providing salient strategies and best practices presented by the speakers.

Keywords: Breast cancer, conference, disparities, proceedings, triple negative breast cancer

INTRODUCTION

Hispanics and African-Americans, who constitute a high percentage of the minority population in Texas, have nearly a 2-fold higher death rate from cancer. Socioeconomic factors such as education, occupation, lack of health insurance, low maternal age, lifestyle, and genetic differences may account for the disparities in breast cancer. On July 12–13, 2012, the Texas Center for Health Disparities (TCHD) in conjunction with the Institute of Cancer Research (ICR), the National Institute on Minority Health and Health Disparities (NIMHD), National Institutes of Drug Abuse (NIDA), and Health and Human Services Office on Women's Health organized the 7th Annual Texas Conference on Health Disparities entitled "Battling Breast Cancer Disparities: Frontline Strategies". The conference brought close to 500 participants including students, scientists, clinicians, public health policy leaders, and patient's advocates. The conference chaired by Jamboor Vishwanatha (UNT Health Science Center, Fort Worth, TX), highlighted the ongoing research, challenges, and efforts (including community engagement programs) directed at understanding the underlying causes of such disparities and devising innovative strategies to ultimately eliminate them.

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Keynote addresses by Amelie G Ramirez (UT Health Science Center, San Antonio, TX) and Mark Clanton (American Cancer Society) provided a framework for the conference. Each session included presentations by scientists followed by a panel discussion involving patients, patient navigators, and nurse practitioners who provided real life experiences that addressed breast cancer health disparities.

Breakthroughs in breast cancer

The first session featured lectures on the current status of breast cancer research. Saraswati Sukumar (Johns Hopkins University, Baltimore, MD) in her talk entitled "Methylated Genes: Potential for Prediction, Prognosis and Therapeutic Targets" discussed the role of epigenetics in breast cancer. Deoxyribonucleic acid (DNA) methylation is one of many epigenetic events that regulate gene expression. Through cell division cycles, DNA methylation contributes to epigenetic inheritance by leading to changes in the chromosome without altering the DNA sequence. Repetitive regions, transposons and imprinted gene promoters are heavily methylated along with repressive histone modifications to form a silent or inaccessible chromatin in normal cells; whereas the accessible chromatin consists of unmethylated genes accompanied by active histones. During tumorigenesis, control of gene expression by DNA methylation and histone modifications become overturned; tumor suppressor genes become methylated and silenced allowing cell growth and proliferation. In addition, inaccessible regions become transcriptionally active. The discovery that multiples genes in breast cancer cell genome are methylated and changes in gene expression contribute to an invasive phenotype led to a large body of work to address whether methylated genes hold a promise for early detection, prediction, prognosis? Furthermore, can epigenetic therapy translate from the bench to the bedside? The ductal lavage fluid technique was performed to determine if methylation markers typifying a tumor will be more sensitive and precede the appearance of morphological abnormalities, compared with the current cytological procedure. Following the ductal lavage fluid technique, the percent methylation was quantified in multiple genes using Quantitative Multiplex-MSP (QM-MSP) and a clear distinction between tumor and normal tissues was accessed. A pilot study employing primary breast tumors and cell lines showed that epigenetically silenced genes can provide robust relevant prognostic and predictive markers to improve current measures used for clinical decision-making. Translational research implies the successful translation of scientific discoveries from the laboratory into practical applications. Hence, can therapy aimed at reversing gene-silencing of critical molecules that promotes cancer-cell growth benefit patients? RARβ signaling is silenced in breast tumors as a result of histone deacetylation and DNA methylation. Reactivation of silenced RARβ signaling using histone deacetylase inhibitor combined with standard chemotherapies revealed a potential for the use of epigenetic therapy. Current diagnostic markers aided in the detection of breast cancer. However, due to poor specificity, ancillary tests are needed for early detection of breast cancer. Epigenetic therapy holds promise for the future, but challenges remain.

In his presentation "A Health System Approach to Resolve Health Disparities in the Community", Roberto Villarreal (University Health System, San Antonio, TX) spoke about community-based approaches to reduce disparities. Cancer health disparities arise from differences in the incidence, prevalence, mortality, burden of cancer diseases, and other health conditions that exist among specific population groups. Characteristics of these population groups show a lower level of education and income, as well as diversity in geographic location, leaving them often medically underserved (with limited or no access to effective health care). They often tend to fall in the minority group and bear a greater burden of disease than the general population. In the US, disparities are well documented in minority populations, as African-Americans and Hispanics are more likely than Caucasians to lack a usual source of care. Implementation of programs in the community to give access to care is an essential step to improve public health. Using this approach, University Health Systems has committed to reduce disparities in San Antonio through running Community Prevention Clinics, UHS Cancer Committee, UHS Cancer Registry, UHS Women's Health Division (breast and cervical services, family planning, and patient navigation services). With partnerships and grants from Susan G. Komen for the Cure, Cancer Prevention and Research Institute of Texas, UHS navigates minorities through screening and diagnosis in the hope to eliminate disparities.

Chemotherapy is used to treat all stages of breast cancer, from early-invasive to metastatic disease as an adjuvant or neo-adjuvant treatment. Survival prolongation and symptom palliation made chemotherapy a suitable choice of prophylactic treatment for a number of patients. For metastatic breast cancer patients, the toxicities associated with the current therapeutic options (Tamoxifen, Bevacizumab, Trastuzumab, Anthracyclines, Paclitaxel, Eribulin to Capecitabine) make the treatment less suitable and beneficial. Targeted therapies represent the answer in avoiding unnecessary chemo regimens for those patients. Identification of key molecules like ER and HER-2 and their targeted therapies has provided advances in treatments of solid tumors. Due to disease resistance and relapse, these therapies show limited efficacy. The complexity of signaling pathways suggests a combinatorial

targeting of multiple key proteins involved in tumor progression is required for a successful treatment. Stefan Gluck (University of Miami Miller School of Medicine, Miami, FL) stressed the need for novel targeting agents and the importance of combinatorial therapies to overcome the plasticity and resolvability of signaling pathways. Clinical trials showed that while Trastuzumab increases time to disease progression for HER-2+ metastatic patients, a combination of Trastuzumab and Lapatinib improved patients' overall survival. A cross-talk between EGFR and ER pathways is suspected to be the underlying cause of endocrine therapy resistance. An evaluation of the additive effects of combining Lapatinib, a tyrosine kinase inhibitor blocking HER-2 and Letrozole, an aromatase inhibitor demonstrated that dual targeting enhances progression-free survival. Other examples of combined therapies included Trastuzumab and Bevacizumab, Lapatinib and Pazopanib and IGF-R, FGF-R, MET inhibitors. Hence, combinatorial therapies aimed at inhibiting more than one key target leave the malignant cells with fewer escape mechanisms. Novel agents targeting HER-2 awaiting approval include Ertumaxomab, Perifosine, Vorinostat, mTOR, Tanespimycin.

Triple negative breast cancer

The "Triple Negative Breast Cancer" session consisted of two lectures, one given by David Euhus (UT Southwestern Medical Center, Dallas, TX) and the other by Robyn Young (Center for Cancer and Blood Disorders, Ft. Worth TX).

David Euhus provided an overview of Triple Negative Breast Cancer and the described clinical data from his studies. Breast tumors classified as ER-, PR- and HER-2- form a subclass of breast cancer called Triple Negative Breast Cancer (TNBC). A highly diverse group, TNBC is composed of several biologic subtypes. Some TNBC (not all) tend to be enriched for stem cell markers, EMT markers, androgen receptors and increased stroma/tumor ratio enhancing their have poor prognosis. At present there is no proven effective agent targeting a defining vulnerability in TNBC. Chemotherapy agents offer the best hope as palliative treatment or to extend survival, even if by few months. Sub-typing TNBC is necessary to identify molecular-based therapies and to determine appropriate therapeutic regimens to obtain encouraging responses. TNBC presents the lower incidence rate; consisting approximately 10–20% of all breast cancers. More prevalent in African-American women, TNBC is also observed in premenopausal young women. A women's health initiative study assessing breast cancer incidence among minority groups pointed to educational level, income, physical activity, alcohol intake, and diet to be underlying factors responsible to the disparities encountered among African-American and Caucasian women. Factors that were not considered to be risks were age at first live native birth, age at menarche and increasing age. Previously linked to increased risk of ER+ breast cancer in premenopausal women, obesity has now been implicated in TNBC; in addition to BRCA1 mutations. Identification of key molecular drivers making up subtypes of TNBC is of the essence in order to provide clinical platforms for the development of effective treatments.

Robyn Young presented a clinical perspective of TNBC through outcomes from different patients. Case 1 was a 54-year-old, Caucasian female who presented with palpable mass. Tumor diagnosis revealed Invasive Ductal Carcinoma (IDC) of 3.0 cm, grade 3 with extensive Ductal Carcinoma *In Situ* (DCIS) and Lymphovascular Invasion (LVI) and 26/27+ nodes. After feeling a small lump during a self-breast exam, she underwent a mammogram a month after. The results showed very dense tissues in the breast, but no real discrete mass. After surgery, an assessment of risks and benefits using Adjuvant Online revealed patient chances of survival without chemotherapy is 1 out of 100 and with chemotherapy 22 out of 100. Hence the question, "will patient be one of these 22 women or will she be one of the patient experiencing treatment failure?"Case 2 was a 70-year-old, Caucasian female with nonpalpable mass who had ER+ breast cancer in her right breast. This patient was administered Tamoxifen, followed by a mammocyte XRT as adjuvant therapy, with the assumption that the presented tumor is ER+. The new tumor diagnosis revealed TNBC, 1.5 cm, grade 3 and node negative. The patient was then administered Docetaxel/Cytoxan leading to a severe radiation recall reaction resulting from radiation/chemotherapy toxicities. Completely cured, this patient is an unusual case of TNBC. Case 3 was a 41-year-old African American female with palpable "hardness" in her breast. A positron emission tomography (PET) scan in breast, axillary and subclavian nodes showed no evidence of metastatic disease. Given antibiotics for enlarged axillary nodes, a diagnosis 8 months later revealed IDC 10 cm, +LVI and 30/40 nodes. The patient had a family history of breast cancer, two live births, one at the age of 16. The classical TNBC case, this patient's time to disease progression was 3 months. For such patients, IXEMPRA, the first epothilone, would have been the trial option when nothing remains. An FDA-approved drug for metastatic breast cancer, IXEMPRA is active in taxane-resistant disease and is in phase III clinical trial. In triple-negative patients, IXEMPRA (ixabepilone) plus Capecitabine resulted in an objective tumor response rate of 35% compared to 11% with Capecitabine alone. For TNBC patients, a long-term disease free survival is the best to hope for. While our knowledge on the nature of TNBC increases with time, there is still a lot to learn. From the perspective of ER and HER-2, TNBC is clearly a distinct clinical subtype

but further sub-classification is needed. At present, there is a critical need to identify markers to sub-classify TNBC patients. Identification of reliable markers can give lead to effective targeted therapies that will be suited for different subtypes of TNBC.

Hormone resistant breast cancer

Robert Clarke (Georgetown University Medical Center, Washington, DC) addressed the concept of systems biology and their complexity and the components of these systems of biology under the stress of endocrine therapy. A total of 70% of all breast cancer cases are known to express the estrogen receptor alpha (ER-α) and/or progesterone (PR). These breast cancers are generally administered antiestrogens such as Tamoxifen, Fulvestran, or Aromatase inhibitors such as Letrozole. A look at the 10 years recurrence and mortality rates by ER status indicate that while recent advances have been made in endocrine therapies, there is room for improvement. Data comparisons between patients treated with Tamoxifen who had early recurrence (≤3 years) and those with distant recurrence (≥6 years) suggest that not all Tamoxifen failures are driven by the same biology. To understand the biology behind failed Tamoxifen therapies, a systems biology approach is applied to cancer research. This approach consists of integrating high-throughput multi-omics data (proteomics, metabolomics, genomics, and bioinformatics) to model a network of dynamic interactions between biological components. A predictive model of ER-α signaling network constructed on breast tumor microarray data revealed a number of molecules interconnected, relatively different from the ordered signaling pathways. Molecules like NFκB and BCL-2 were shown to be key modulators in endocrine resistance by regulating processes like apoptosis, autophagy and necrosis. An emerging concept from Clarke's presentation is that "resistance may not require using many new genes but changing the usage of existing ones to adapt to the stress of endocrine therapies". In summary, to obtain a global sense of the acquired or *de novo* resistance in ER+ Tamoxifen treated patients, one would be inclined to consider the cell as a network that is modular with both redundancy and degeneracy and coordinates a number of molecules involved in multiple functions.

Changing trends in presentation from cancer systems biology to a single gene alteration, Khandan Keyomarsi (M.D. Anderson Cancer Center, Houston, TX) described the deregulation of the cell cycle in breast cancer and the regulators as relevant markers for prognosis and novel targets for therapy. Cell cycle progression is monitored by a set of checkpoints, controlled by cell cycle regulators. Of the cell cycle regulators, cyclin E has gained increasing interest as several studies showed that its alterations are relevant to breast cancer. The cyclin E gene is amplified in some breast cancer cell lines and this amplification results in mRNA overexpression; allowing its constitutive expression across all phases of the cell cycle. Posttranslationally modified by elastase, cyclin E is cleaved at the N-terminus to generate low molecular weights forms. Western blotting analysis showed the presence of low molecular weight forms of cyclin E (LMW-E) in tumor cells vs normal cells. An accumulation of LMW-E correlate with advanced stage of disease. Translating these findings to animal models, the prognostic and oncogenic relevance of LMW-E overexpression were assessed. Results showed that LMW-E cooperate with mutated p53 pathway to induce metastatic mammary tumors. Complex formation experiments and kinase assays demonstrated that LMW-E in breast cancer are resistant to inhibition of p21 and p27, allowing a bypass of antiestrogen induced G1 arrest. The presence of LMW-E in breast tumors causes a genomic instability correlating with polyploidy and lack of response to antiestrogen therapy. Immunohistochemistry analyses of LMW-E in breast tumors tissues revealed a cytoplasmic localization and association with phosphorylated CDK2 compared to a nuclear localization of the full length protein. For Keyomarsi *et al.*, the next step is to translate clinically this finding by routinely screening cytoplasmic cyclin E/CDK2 to identify patients at high risk of resistance/recurrence and combine inhibitors of CDK2 with hormonal/clinical therapy.

CONCLUSION

The "Breakthroughs in Breast Cancer" session integrated clinical, basic science, and public health perspectives to convey the relevance of translational medicine. The concepts of using systems of biology and single gene alteration to target resistance and recurrence in ER+ tumors were addressed in the "Hormone Resistant Breast Cancer" session which provided new insights into aspects of cancer biology. While ER, PR, HER-2 tumors metastases are frightening, targeted therapies like Tamoxifen and Herceptin bring a cautious optimism. TNBC metastases however tend to be associated with aggressiveness and shorter time to relapse and recurrence. The "Triple Negative Breast Cancer" session recalled the critical need for biomarkers and targeted therapies. The conference highlighted the importance of the complexity and heterogeneity of breast cancer and pointed to the challenges ahead. The 7th Annual Texas Conference on Health Disparities provided a forum for discussion between attendees, clinicians, scientists and patients.

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