

Diversity in Breast Cancer: from Genomics to Racial Disparities

Drs. D. Shon Black and Lyndsay Harris

MOLECULAR PROFILING IN BREAST CANCER

Recent advances in technology have led to our ability to 'profile' breast cancer based upon expression patterns of thousands of genes simultaneously. This technique, known as Microarray Profiling, is being used to better understand why some breast cancers behave very aggressively and others show a more indolent course. In addition, the 'gene profiles' can shed light on mechanisms of resistance to treatment by identifying which genes are expressed in tumors that do not respond to therapy. Investigators at Yale Cancer Center are applying these novel technologies to treat women with breast cancers in Connecticut and to better understand how gene expression patterns vary in our population and how they influence patient outcome.

Initial studies of microarray profiling performed by Perou, Sorlie, and colleagues were the first to identify biologic subtypes of breast cancer using gene expression profiling (Nature 2000, Proc Natl Acad Sci U S A. 2001, American Journal of Pathology 2002). Among the categories emerging from these studies are estrogen receptor (ER) and/or progesterone receptor (PR) positive tumors, HER2 gene amplified tumors, and so-called 'triple negative tumors.' (Figure 1) From a therapeutic perspective, these molecular classifications are important, as it reduces the heterogeneity of patient groups and increases the likelihood of response

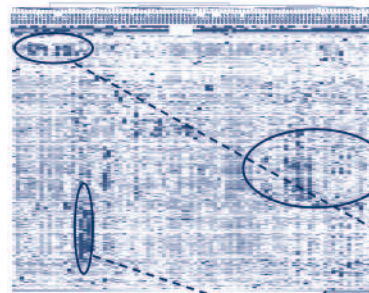
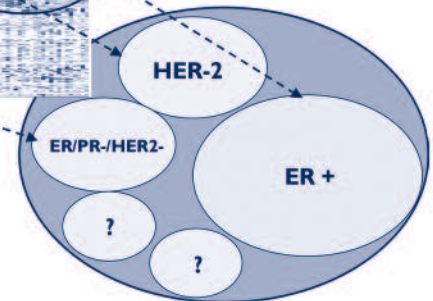


Figure 1 Subclasses of breast cancer, as shown on a DNA microarray slide.



to therapy. There are two clear examples of this in breast cancer.

The first, and perhaps most important, finding in the biology of breast cancer was the class distinction between ER positive and negative tumors. ER positive tumors respond to anti-estrogenic therapy (Lancet 2004), while ER negative tumors do not (JCO 2001). A second example is that of HER2 gene amplified tumors, which have been shown to respond preferentially to the anti-HER2 monoclonal antibody, trastuzumab (Herceptin[®]) (NEJM 2005). It is gratifying, then, that expression profiling is able to identify these subgroups across platforms, and has further pointed out sets of genes that define these tumor types.

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Improving Cancer Detection with Breast Tomosynthesis

Dr. Liane Philpotts

There is a new technology on the horizon for the detection and diagnosis of breast cancer. It is called breast tomosynthesis.

Mammography is one of the best studied and also most criticized of medical tests. It has been shown to detect many breast cancers at a stage that has a favorable prognosis, ultimately reducing the mortality from the disease by more than 30%. At the same time, it is not a perfect test, as all cancers are not detected and many false positives

are generated that require additional imaging and biopsy. The anxiety produced and costs incurred are not insignificant.

Breast Tomosynthesis is similar to mammography in that it involves x-rays passing through a breast that is immobilized in compression. However, rather than a 2-D, "compressed" mammographic image, it generates a series of images of the breast as a result of the x-ray tube moving in an arc. Tomosynthesis

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Editor's Letter

Dr. Joanne Weidhaas
(203) 737-2165
joanne.weidhaas@yale.edu

Three years ago the leadership of Yale School of Medicine, Yale-New Haven Hospital, and Yale Cancer Center made the decision to rejuvenate their cancer programs. This has led to the recruitment of nationally recognized breast cancer experts in surgery, medical oncology, radiation therapy, pathology, and diagnostic imaging and an investment in new state-of-the-art technology.

These efforts have resulted in two multidisciplinary coordinated programs that address all aspects of breast cancer diagnosis and treatment through the Yale-New Haven Breast Center and the Yale Cancer Center Breast Cancer Program. The goal of both of these programs is to provide the finest care to patients with breast diseases, to conduct cutting edge research to advance knowledge and practice in breast disease, and to educate health care providers, patients, and the public about breast cancer.

This newsletter is the first in a series of newsletters that will describe the progress we have made by highlighting new developments in breast cancer diagnosis, screening, prevention, and treatment. We would especially like to thank Dr. Joanne Weidhaas for agreeing to be the editor for these newsletters. Dr. Weidhaas is not only one of the finest young breast radiation oncologists in the country, but she is also one of our brightest physician scientists. She is particularly suited to provide perspective and balance when evaluating emerging new technologies in breast disease. Please feel free to contact her with comments or suggestions at any time.

Sincerely,
Donald Lannin, MD
Lyndsay Harris, MD
Liane Philpotts, MD
Co-Medical Directors

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TRIPLE NEGATIVE BREAST CANCER: A BAD ACTOR WITH UNIQUE BIOLOGIC FEATURES

While successful application of targeted therapy for ER positive and HER2 positive breast cancer has been achieved, the 'triple negative' or ER/PR/HER2 negative phenotype represents an aggressive and poorly understood subclass of breast cancer with a much worse outcome (Journal of Clinical Pathology 2006). In fact, Dr. Bruce Haffty and colleagues recently showed that breast cancer patients treated at Yale University with lumpectomy and radiation were much more likely to have a distant relapse if their tumors were 'triple negative' (in press; JCO October 2006). (Figure 2). Fortunately, breast conserving therapy appears to be equally effective in patients with triple negative tumors in this study, suggesting that these patients remain sensitive to radiation.

To better understand the reasons for this worse prognosis, Drs. Joanne Weidhaas, Frank Slack, and collaborators are currently studying the molecular features of the triple negative breast tumors using the Yale Breast Cancer database. In addition to 'traditional' gene expression profiling, they will evaluate these tumors for the expression of a novel set of molecules known as 'microRNAs', which have been shown to be misregulated in cancer and associated with resistance to particular therapies.

In addition to this molecular characterization, Dr. Fattaneh Tavassoli, a world renowned breast pathologist and Director of Breast Pathology at Yale University, is studying the histologic features and protein expression patterns of triple negative breast cancer. Recent studies have equated the triple negative phenotype as 'basal-like' due to the expression of basal keratins (CK5, CK14, CK15, and CK17) (Modern Pathology 2006). In addition, these tumors characteristically express myoepithelial genes, wnt-pathway genes, anti-apoptotic genes and other genes of unclear

significance. These tumors are also characterized by low expression of BRCA1 (breast cancer associated 1), and this phenotype is common among BRCA1 carriers and sporadic tumors that resemble tumors in BRCA1 carriers. Dr. Tavassoli has further characterized these basal tumors into different groups depending on their histopathologic features, expression of cytokeratins, and growth factor receptors, including the epidermal growth factor receptor (EGFR) (International Journal of Surgical Pathology 2005). These variants may behave very differently and may account for the observation that some triple negative tumors do very poorly while others do not.

TRIPLE NEGATIVE BREAST CANCER: NEW OPTIONS FOR TARGETED THERAPY

It is particularly striking that while triple negative tumors generally have a poor prognosis, at least some of these tumors respond more favorably to chemotherapy and those tumors which achieve a pathologic complete response after preoperative therapy have an excellent prognosis (personal communication with L. Carey). Hence, it is critical to understand the variability in this subtype of breast cancer, which patients will benefit from chemotherapy, and what is the optimal chemotherapy regimen. For example, for those patients who do not benefit from chemotherapy, there may be alternative targets in these tumors which would allow the design of a novel therapy approach. Potential targets include EGFR, c-met, and PDGF. In addition, these tumors may be particularly sensitive to agents which prevent DNA single strand break repair. Preclinical studies by Ashworth and colleagues (Cancer Research 2006) suggest that PARP inhibitors, which prevent the repair of single strand breaks, may be particularly active in BRCA null tumors as these tumors already lack the ability to repair double strand breaks and need to use alter-

CLINICAL TRIALS Breast Cancer Program

BREAST CANCER:

HIC 27735	A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer	Joanne Weidhaas, MD, PhD	(203) 737-2165
HIC 0601000957	Phase II Trial of Mammosite Breast Brachytherapy Optimization in the Treatment of Stage 0, I, and II Breast Carcinoma	Joanne Weidhaas, MD, PhD	(203) 737-2165
HIC 0511000860	A Phase I Study of the mTOR Inhibitor Rapamycin (Rapamune, Sirolimus) in Combination with Abraxane (Paclitaxel protein-bound particles) in Advanced Solid Cancers	Maysa Abu-Khalaf, MD	(203) 785-7564
HIC 0602001073	A Randomized, Phase II Trial of Preoperative Herceptin/Navelbine versus Taxotere/Carboplatin/Herceptin in Early Stage, HER-2 Positive Breast Cancer	Lyndsay Harris, MD	(203) 785-7836
HSRRC 06-26	The Symptom Experience, Cosmetic Outcome, and Quality of Life in Women with Early Stage Breast Cancer Undergoing Partial Breast Irradiation	Tish Knobf, RN, PhD	(203) 737-2357
HIC 0508000436	A Phase IA, Multicenter, Dose-Escalation Study of Oral AEE788 on a Continuous Daily Dosing Schedule in Adult Patients with Advanced Cancer	James Lee, MD, PhD and Lyndsay Harris, MD	(203) 785-7836
HIC 0602001154	A Multicenter, Controlled Clinical Trial to Evaluate the Hologic 3-D Tomosynthesis Mammography System used in Conjunction with Conventional 2-D Digital Mammography	Liane Philpotts, MD	(203) 785-5590

Breast Cancer Program: The Multidisciplinary Team

MEDICAL ONCOLOGY:

(203) 785-4191

Maysa Abu-Khalaf, MD
Gina Chung, MD
Michael DiGiovanna, MD, PhD
Lyndsay Harris, MD,
Program Co-Director
Harriet Kluger, MD
Kenneth Miller, MD

RADIATION ONCOLOGY:

(203) 688-1861

Susan Higgins, MD
Joanne Weidhaas, MD, PhD

PATHOLOGY

Maritza Martel, MD
Idris Tolgay Ocal, MD
David Rimm, MD
Fattaneh Tavassoli, MD

BREAST IMAGING:

(203) 688-6800

Liva Andrejeva, MD
Jennifer Fan, MD
Regina J. Hooley, MD
Laura J. Horvath, MD
Carol H. Lee, MD
Liane Philpotts, MD
Irena Tocino, MD

SURGERY:

(203) 785-2328

Dahlia Black, MD
Baiba Grube, MD
Donald Lannin, MD,
Program Co-Director

native pathways to repair DNA damage. This ‘achilles heel’ may be explored in the clinic using a PARP inhibitor in combination with certain chemotherapy agents and has led to a clinical trial designed by Yale investigators, Drs. James Lee and Lyndsay Harris, to focus treatment on triple negative tumors.

DIFFERENCES IN BREAST CANCER BY RACE

Another striking feature about triple negative tumors is that they occur more frequently in premenopausal African-American women. Recent studies from our group and others have investigated the association of triple negative phenotype, African-American race, and outcome from breast cancer. A recent paper from Carey et al shows that African-American women under 50 have a frequency of 39% triple negative tumors as compared with 16% in white women (JAMA 2006). Results from the national SEER database (SEER cancer statistics review, 1973-2002, NCI: 2006) showed that African-American women with breast cancer have a 37% higher death rate than White women and that in young women less than 35 years of age African-Americans have a higher incidence of breast cancer. In addition, we recently observed in a cohort of patients with metastatic breast cancer that African-American women are more likely to have triple negative disease and have a worse prognosis, even after the diagnosis of metastases.

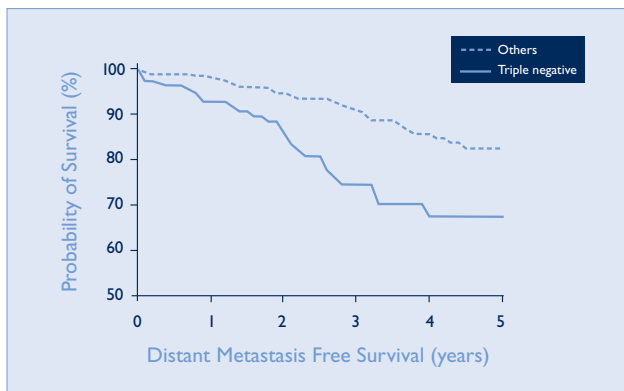


Figure 2 Distant metastasis free survival as a function of subtype of breast cancer in the Yale Breast Cancer Database (Haffty et al, Journal of Clinical Oncology, Oct 2006.)

Several factors may contribute to the worse outcomes in these African-American women including limitations to access healthcare and screening programs, aggressive tumor biology, increased tumor genetic alterations, and inadequate oncologic treatment. In an effort to understand the lower rates of diagnosis and survival in minority breast cancer patients, Dr. Beth Jones in the Yale School of Medicine

Department of Epidemiology and Public Health has studied breast cancer in African-American women in Connecticut and was one of the first to show a biologic difference in breast cancer in these women. Dr. Jones has shown that mammography screening patterns differ between white and non-white women (Cancer 2003). Her group found that 28% of women requiring follow-up of an abnormal mammogram did not receive further workup in 3 months. African-American women and women without a primary care provider were independent predictors of inadequate follow-up, possibly delaying a breast cancer diagnosis and treatment (Cancer Causes Control 2005).

Racial differences in breast cancer subtypes and survival outcomes remain after adjusting for access to healthcare and socioeconomic status, suggesting a biologic difference in breast cancers across ethnicities especially in younger women. Molecular studies by Beth Jones’ group (Cancer 2004) showed that African-American women more often have breast cancers with a higher grade (41% versus 21%), negative receptor status (54% versus 39%), and alterations in the tumor suppressor gene p53 (age adjusted odds ratio 4.00) compared to white women. Identifying the genetic alterations in these more aggressive breast cancers may explain the worse outcomes in this patient population.

RESEARCH ON RACIAL DISPARITIES IN BREAST CANCER: NATURE VS NURTURE?

Through combined research between the Yale-New Haven Breast Center and the Office for Elimination of Cancer Disparities, future studies will examine how to prevent the worse outcomes in African-American women. Dr. D. Shon Black and Dr. Lyndsay Harris are studying the contributions of genetic alterations in young African-American patients with aggressive basal-like breast cancers compared to inadequate participation in screening programs and limitations in healthcare access. They will examine how the basal-like triple negative receptor tumors initially present in this population and which diagnostic imaging modality is most frequently used and which is most effective. They will also examine the different genetic alterations in breast cancers of young minority patients compared to non-minority patients which could potentially lead to specific therapeutic targets for this high risk population. Prevention programs to increase local community involvement in breast cancer awareness, improvements in the follow-up system of abnormal mammograms, and the characterization and identification of high risk women before a breast cancer diagnosis are part of the goals of the collaborative effort for the breast center and cancer disparities center.

As the clinicians at Yale learn more about the genetic diversity of breast cancers and their affected patient populations, tailored prevention strategies and treatment plans will improve breast cancer outcomes for all patients in all of our communities.

Partial Breast Irradiation Under Study at Yale

Dr. Joanne Weidhaas

The Department of Therapeutic Radiology at Yale-New Haven Hospital has been evaluating the role of accelerated partial breast irradiation (PBI) in the management of early stage breast cancer. Yale has enrolled over thirty patients in a Phase III clinical trial (RTOG 0413/NSABP B-39) investigating the role of standard whole breast radiation therapy vs. PBI in the management of selected patients with early stage breast cancer (Stages 0, I and II) following lumpectomy with negative margins. In this trial, patients are randomly assigned to either standard whole breast irradiation or to PBI. PBI has the primary advantage of offering the patient a shorter course of treatment than traditional whole breast irradiation (1 week versus 6.5 weeks), with less normal tissue radiation exposure. PBI is being investigated with the hope that it may eventually provide a more convenient but equally efficacious method for delivering radiation treatment, thereby allowing a greater number of women to safely choose breast conservation as management for their breast cancer.

This randomized Phase III trial plans to accrue over 3,000 patients nationwide, and within its first year of being opened has successfully randomized over 1,500 of these patients, indicating the nationwide interest in this exciting new treatment approach. Early results indicate that PBI has been safely and successfully delivered with less normal tissue toxicity than whole breast irradiation. Breast cancer outcomes comparing whole breast irradiation and PBI are continuously being collected. In this trial, PBI can be delivered by three possible methods: 1) external beam conformal partial breast irradiation; 2) mammosite balloon catheter technique; and 3) a multi-catheter interstitial technique. Yale offers all three of these techniques, and the choice of which method to use is individualized based upon a joint evaluation between the treating physicians and discussions with the patient.

For those patients where standard whole breast irradiation is not an option because of ineligibility or refusal of the randomized trial, we also have an open phase II study of PBI. These patients receive PBI via the mammosite balloon catheter technique. This trial evaluates the improvement of side effects from PBI through radiation dose modification. In parallel with both of the randomized and phase II PBI trials, the Yale School of Nursing is performing a quality of life study of the different forms of PBI in these patients.

For further information regarding these protocols or for appointments for consultation, please contact the Yale Department of Therapeutic Radiology at (203) 688-1861.

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takes less than 10 seconds per view, not much longer than routine mammography. Similar to leafing through the pages of a book, the breast tissue can be examined in thin slices, or reconstructed in 3-D.

The limiting factor in the development of this technology was achieving a radiation dose to the breast that was low and similar to mammography. Present day mammography generates very small radiation doses to women. Imaging studies such as CT scans utilize much higher doses, which would be unacceptable to use in a healthy screening population. Over the past few years, physicists have perfected the technique of tomosynthesis such that the radiation dose is equivalent to a routine digital mammographic image.

If these early results are reproduced in larger studies, the rewards for women will be significant.

The advantages of tomosynthesis will likely lie in its ability to detect more and smaller sized cancers that might otherwise have been hidden by dense tissues. Preliminary studies have shown an increase in cancer detection of 16%. Mammographic detection of breast cancer is limited by the density of the normal breast tissue. In breasts that are moderately to extremely dense, a cancer can be extremely difficult to find. By removing some of the layers of tissue, which is essentially what tomosynthesis does, cancer detection should be improved. In addition, superimposed or overlapping tissues can have the appearance of a mass on a 2-D mammogram, resulting in the patient being recalled for additional imaging. Again, preliminary studies have shown great promise for tomosynthesis, with a decrease in the recall rates of up to 85%.

If these early results are reproduced in larger studies, the rewards for women will be significant. Yale is embarking on a multi-center study to obtain FDA approval for a tomosynthesis machine, manufactured by Hologic. Approximately 1,400 women will be enrolled in this trial. The results will likely be available in a year. If promising, breast tomosynthesis may be available to women in the very near future.

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These articles share the latest news in clinical trials and illustrate how novel concepts will push the frontier forward, not only for our patients, but for all other breast patients around the world.