Image Based Biomarkers of Breast Cancer Risk: Analysis of Risk Disparity Among Minority Populations

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ABSTRACT

Advances in understanding breast cancer risk factors, coupled with advances in screening methodologies and prevention strategies, are critical to the development of personalized breast cancer surveillance and prevention. This HBCU/MI Partnership Training Award has built upon a collaboration between DSU and Penn, with the objectives to: (1) extend the skills of DSU faculty to become competitive breast cancer researchers; (2) establish an independent research program at DSU by performing a joint research project focused on breast cancer risk disparity in minority populations; and (3) produce high quality publications and funded grants at DSU to sustain breast cancer research.

DSU Faculty Training Related to Breast Cancer Research

The training program developed for DSU, which combines didactic instruction covering breast cancer fundamentals with ongoing research training, is designed to inculcated the DSU faculty with the culture and language of breast cancer research.

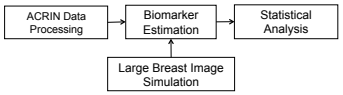
Each DSU faculty member attended up to 3 courses at Penn to augment their knowledge of breast cancer. The courses also provided exemplary didactic methods, so that DSU could create new curricula for DSU students relevant to breast cancer. Courses included:

- GCB535: Intro to Bioinformatics
- CAMB512 Cancer Biology and Genetics
- BE545/CIS537 Biomedical Image Analysis
- GCB / CAMB 752: Seminar in Genomics
- BE483 Molecular Imaging
- EP801 Fundamentals of Epidemiologic Study Designs.

In addition, a seminar course on the *Basics of Breast Cancer* was taught by Penn faculty at DSU, covering epidemiology, anatomy, pathology, imaging, and clinical oncology.

The research training component of the grant is focused on the assessment of the racial dependence of image-based risk biomarkers (IBRB) of breast cancer. Our long-term goal is to develop an accurate method for breast cancer risk estimation in minority populations by including IBRB and genetic risk factors. Despite evidence of racial disparities in breast cancer statistics, reported results to date have not established a racial dependence on IBRB.

The first aim of our project is to assess IBRB racial dependence in a large clinical trial using images from the ACRIN DMIST study.[1] During preliminary work, a large number of women were identified for whom multiple images were taken to capture the whole breast. As a result, the IBRB cannot be estimated for these women using existing methods. Thus, we have additionally undertaken efforts to develop a method to combine IBRB data from multiple images. To validate these methods, we have used synthetic mammograms generated from software breast phantoms.[2]

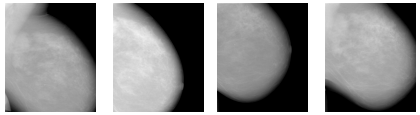


The flow-chart of research steps aimed at exploring IBRB racial dependence

Preparing Clinical Data from ACRIN DMIST Study

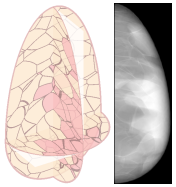
After IRB approval, we created a database of 11,106 (5,553 minority and corresponding Caucasian controls) cancer-free women gathered as part of the ACRIN DMIST study. The anonymized database consisted of both study images and selected study forms. The images have been stored in a CTP/MIRC database, facilitating queries and convenient interface with other processing steps. Scripts have been developed for querying MIRC XML files to perform quality control and to prepare the data for IBRB estimation.

Previously, we demonstrated that in a database of 657 women with mammography exams, 85 (i.e., 13%) cases has only partial breast visualization in a single image due to breast size. To date, we have observed a similar percentage in an initial assessment of 990 ACRIN cases. This high prevalence has required that we develop a strategy to measure IBRB in breasts spanning multiple images.



Partial breast visualization, with 4 images to capture the whole breast

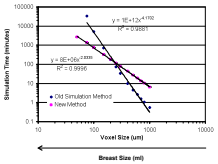
Simulation of Large Breasts



Sections (left) and a synthetic mammogram (right) of a sample software breast phantom

We are currently developing a method to combine images with partial breast visualization, to be validated using synthetic mammograms of an anthropomorphic software breast phantom developed at Penn. The simulation of large breasts required that we improve the software phantom design in terms of simulation time, memory requirements, and scalability.[2]

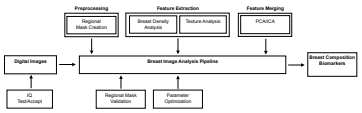
Jointly, we have added two specific features to simulate large breasts, including simulating the partial volume of tissues in a voxel and improving the efficiency of the software through parallelization of the phantom generation procedure. The method developed is octree-based. This algorithm has been shown to almost achieve the theoretical lower bound in computational complexity of such simulations.



Simulation time vs. voxel size (or breast size) for the original Penn method and the new Penn/DSU method

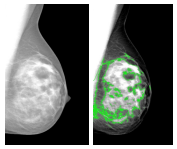
Estimate Image-Based Risk Biomarkers

We have been developing an interface between the MIRC study database and IBRB image analysis pipeline, which are physically located in two different labs at Penn. The proposed interface will allow remote access to both the MIRC and pipeline servers. The analysis protocol is designed so that any incoming image is automatically analyzed. From the MIRC server it will be possible to start an automatic sequence pushing images to the pipeline. After each image has been processed, the resulting breast density data and texture images are automatically pushed to MIRC and stored as associated record series. This organization would allow running additional image analyses remotely from DSU, after the migration of the study database from Penn to DSU.

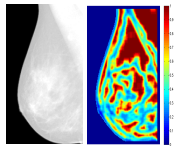


The flow-chart of the breast image analysis pipeline

The IBRB image analysis pipeline employs a fully-automated breast percent density (PD%) estimation technique based on an adaptive multi-class fuzzy-c-means algorithm. The segmented dense tissue regions are also used to create a regional tissue mask from which the imaging parenchymal descriptors are extracted. Parenchymal texture analysis is performed by extracting multiple descriptors, offering a range of optimization and image processing parameters, as well as the first-order statistics of the original breast image and the stochastic fractal dimension image, and second-order statistics extracted from the co-occurrence and run-length matrices. Statistical information for any desired feature (e.g., mean, median, skewness, and central-moments) can be calculated for any image set. A two-level feature merging approach combining principal component analysis (PCA) with independent component analysis (ICA) is used to compute a breast composition imaging biomarker vector.



An original mammogram (left) with the segmented dense tissue region (right)



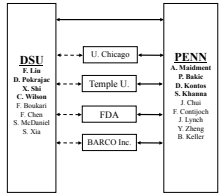
An original mammogram (left) with the corresponding entropy image (right)

Perform Statistical Analysis of Risk Biomarkers

The extracted breast density and parenchymal texture descriptors will be used to test racial dependence of image-based biomarkers of breast cancer risk. We plan to publish our results and compare them with reports in the literature (e.g. [4]). In addition, the results of the pipeline analysis of ACRIN data will be used in our long term research goal of developing a an accurate method for breast cancer risk estimation in minority populations by including IBRB and genetic risk factors.

Conclusion and Impact

Our ultimate hope is that this DoD BCRP HBCU/MI award will provide an excellent environment at DSU for their faculty to conduct state of the art breast cancer research. Our success is evident by the expanding number of faculty and staff involved in breast cancer research at DSU, and the high-quality of the presentations and publications resulting from this project. Moreover, DSU is becoming an integral part of a network of established breast cancer investigators at Penn and beyond. For the rest of the award time we will focus on completing the research aims and preparing strong grant applications to sustain breast cancer research at DSU.



The expanding network of DSU research collaborators resulting from this DoD HBCU/MI Partnership Training Award

List of journal papers, conference and invited presentations, and patent applications:

- Pokrajac, D., Maidment, A.D.A., Bakic, P.R.: "Optimized Generation of High Resolution Breast Anthropomorphic Software Phantoms," submitted for publication in Medical Physics, 2011.
- Xia, S., Liu, F., Maidment, A.D.A., Bakic, P.R.: "Refinements to the Deformation Model of An Anthropomorphic Computer Generated Breast Phantom," Med Phys 37: 3131, 2010. (Presented at the 2010 AAPM Meeting.)
- Pokrajac, D., Maidment, A.D.A., Bakic, P.R.: "A Method for Fast Generation of High Resolution Software Breast Phantom," Med Phys 38: 3431, 2011. (Presented at the 2011 AAPM Meeting.)
- Chui, J., Pokrajac, D., Maidment, A.D.A., Bakic, P.R.: "Roadmap for Efficient Parallelization of Breast Anatomy Simulation," Submitted for the 2012 SPIE Medical Imaging Conference.
- Chen, F., Pokrajac, D., Shi, X., Liu, F., Maidment, A.D.A., Bakic, P.R.: "Partial Volume Effect Simulation in Software Breast Phantoms," Submitted for the 2012 SPIE Medical Imaging Conference.
- Contijoch, F., Lynch, J., Pokrajac, D., Maidment, A.D.A., Bakic, P.R.: "Shape Analysis of Simulated Breast Anatomical Structures," Submitted for the 2012 SPIE Medical Imaging Conference.
- Bakic P. and Pokrajac D. (2010) Advanced Design of Anthropomorphic Software Breast Phantoms: Work in Progress", Invited talk at the DSU/Penn Breast Cancer Basics Seminar.
- Pokrajac D. and Bakic P (2011) Computer Science Issues in Modeling Breast Tissue ", Invited talk at the DSU Computer Science Club.
- Pokrajac, D.D., Bakic, P.R., Maidment, A.D.A., "Techniques for Simulation of Multi-dimensional Spatial Regions," Provisional Patent Application, University of Delaware/Delaware State University. (DSU No. 12-01), 2011.

References

1. Pisano ED, Gatsonis C, Hendrick E, et al. (2005) Diagnostic performance of digital versus film mammography for breast-cancer screening. N Engl J Med 353(17),1773-83.
2. Pokrajac D, Maidment A, Bakic P. (2011) A method for fast generation of high resolution software breast phantoms. Med Phys 38: 3431. (Presented at the 2011 Joint AAPM/COMP Meeting, Vancouver, Canada.)
3. Zheng Y, Keller B., Wang Y. et al. (2011) A Fully-Automated Software Pipeline for Parenchymal Pattern Analysis in Digital Breast Images: Towards the Translation of Imaging Biomarkers in Routine Breast Cancer Risk Assessment. Accepted for presentation at the 2011 RSNA Scientific Assembly and Annual Meeting.
4. del Carmen MG, Halpern EF, Kopans DB, et al. (2007) Mammographic Breast Density and Race. Am J Radiol 188:1147-1150.

Acknowledgements

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