

**WOMEN'S HEALTH INTERDISCIPLINARY
RESEARCH CENTER
[WHIRC]**



BREAST CANCER GROUP
May 2009

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INTRODUCTION

The Program in Research on Women's Health at Boston Medical Center was launched in 1993 by Drs. Marianne N. Prout and Gail E. Sonenshein. The goal was to promote interdisciplinary research on women's health at the medical campus by bringing bench scientists, clinical investigators and public health researchers together to determine collaborative research directions and helping to obtain funds for the research. Some of the key achievements were:

- The development of a monthly interdisciplinary seminar series. The concept was to focus on a particular disease each month and have speakers from each of the three different disciplines. Various members of the campus came together and sometimes met there for the first time. Seminars were held in the areas of breast cancer, obesity and diabetes, cardiovascular disease, arthritis and autoimmunity, bone health, etc. The seminar series, which is still ongoing, has helped lead to the development of the obesity center here, spawned many interdisciplinary grants, and provided CME credits for continuing education.
- The development of working groups in areas of substantial interest, including the Breast Cancer Working Group, which has expanded and includes members from the School of Public Health, the Goldman School of Dental Medicine, and from the Departments of Biochemistry, Geriatrics, Medicine, Otolaryngology, Pathology & Laboratory Medicine, Surgical Oncology, and the Cancer Center in the School of Medicine. Members of the Breast Cancer Working Group have received research and training grants from the Susan Komen Foundation, the Department of Defense (DOD) breast cancer initiative, NIH (RO1s and a Program Project grant on Signaling in Breast Carcinogenesis) and funding from the Avon Foundation, American Institute for Cancer Research and the LaPann Foundation.
- Awarding of a National Center of Excellence on Women's Health to Boston University by the DHHS in 1997. The CoE was headed by Dr. Karen Freund with Drs. Prout and Sonenshein served as Co-Associate Directors. The goals of the CoE included expanding the research base in women's health, providing training at all levels, and addressing community needs through outreach, research and clinical care. The CoE funding supported faculty in 3 schools, 9 departments in the School of Medicine and the VA.
- Selection for one of twenty K12 junior faculty training awards entitled "BIRCWH" (Building Interdisciplinary Research Careers in Women's Health) to promote careers in women's health. Young investigators from the Schools of Medicine and Public Health and the Sargent School of Rehabilitation have been provided with mentored support to foster their development. Now in its 6th year of funding with Dr. Karen Freund as PI, it has supported 14 investigators, all of who have successfully competed for external grant funding.

As a culmination of 10 years of these and other efforts, the Women's Health Interdisciplinary Research Center (WHIRC) was created at the Boston Medical Campus in February 2005. The Center replaces the Program, while maintaining and extending its goals. The mission of WHIRC is to promote women's health through research and training. **A major goal of WHIRC remains the eradication of breast cancer in our lifetime.**

Dr. Sonenshein is the Director and Dr. Karen Freund is the Executive Associate Director; Drs. Marianne Prout and Ann Rothstein are Associate Directors. (Dr. Rothstein heads the group on autoimmunity.)

Breast Cancer Research and Treatment

Breast cancer is the most common non-skin cancer among women in the Western world, and is the second most frequent cause of death due to cancer among women in the United States. Over the past 50 years, there has been a profound increase in the incidence of breast cancer worldwide, in both industrialized and developing countries, and the life-time risk of developing breast cancer for American women has increased from 1 in 20 in 1960, to 1 in 8 today. Research devoted to understanding why breast cancer develops has been successful in identifying risk factors, including genetic abnormalities in BRCA-1 and 2. Mutations in the genes identified to date seem to play a more significant role in familial breast cancer syndromes than in the much more common sporadic cases of breast cancer. Overall, it has been estimated that these inherited breast cancer susceptibility genes account for 5% of human breast cancers. Of note, changes in genetic predispositions cannot explain the rising incidence of disease over a relatively short time frame. The fact that populations that migrate from nations with a low incidence of breast cancer to those with a high incidence manifest a high incidence of this disease within 1 or 2 generations suggests that environmental or dietary factors contribute significantly to the development of breast cancer. Studies have shown that sporadic breast cancer incidence varies with environmental influences, including exposure to carcinogens, as well as diet. Work under the aegis of the Boston University WHIRC, which is described in this brochure, has used an interdisciplinary, multi-pronged approach to attack the problem of breast cancer.

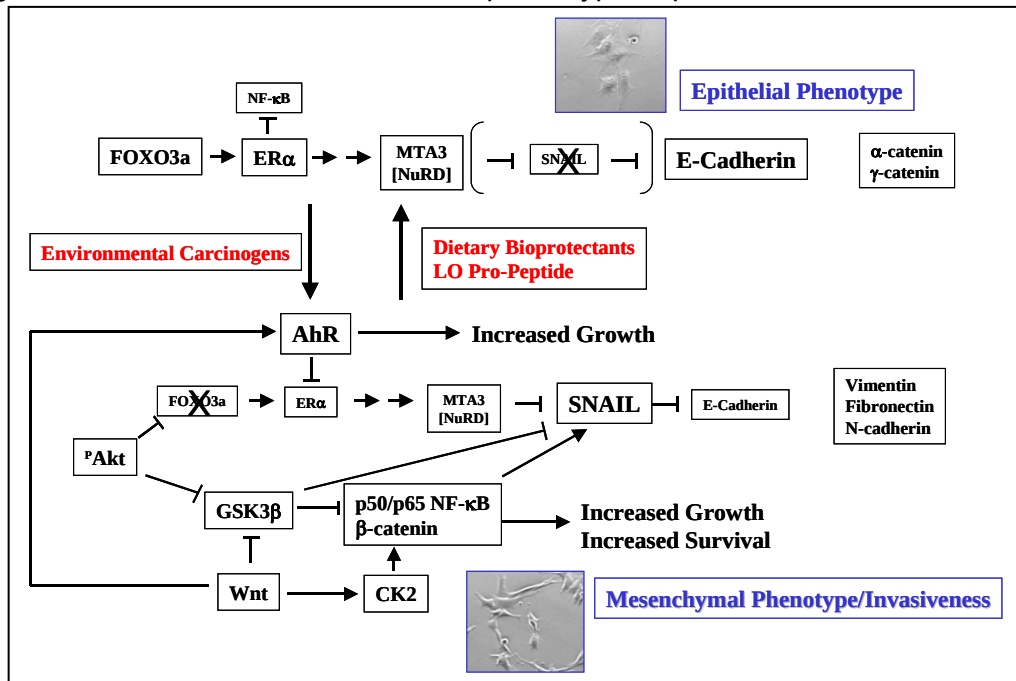
This brochure begins with a description of the studies funded by a program project grant (Dr. G. Sonenshein, P.I.) that are designed to elucidate signaling changes that are induced by carcinogen exposure that promotes the transformation process (pp 5-11). Following this initial section, research is described in the order of disease progression, first “Genetic Dysregulation” (pp 12-14) and then “Cancer Progression and Metastasis” (pp 15-21). A section on the use of *Xenopus* Models (pp 22-24) concludes the Basic/Translational Research section. The Clinical Studies section follows, including health disparities, prevention and clinical trials (pp 25-29). This is followed by work on the effects of aging on breast cancer care (p 30). It ends with a discussion of efforts by the Slone Epidemiology Center (including the Black Women’s Health Study) (pp 31-33), and the School of Public Health on Environmental Risk Factors (p 34). For each section, we have indicated the source(s) of funding.

Boston Medical Center is the predominant provider of health care to traditionally underserved minorities and other vulnerable communities in our region. Our Clinical Trials Office is a national leader in recruitment of minorities to clinical trials. A significant amount of research ongoing at BUSM/BMC seeks to uncover or examine causes of racial and ethnic disparities in health care access and outcomes. Many of the researchers involved in the WHIRC have made long-standing contributions to scholarship in this area. The recent creation of the WHIRC provides focus to these ongoing efforts and provides momentum for increasing breast cancer research with a focus on disparity populations and the effects of the environment.

BASIC/TRANSLATIONAL RESEARCH

Carcinogenesis and Signaling Group¹

Epidemiologic studies on patterns of the disease, animal studies, and *in vitro* evidence all indicate that environmental factors contribute to breast cancer pathogenesis. These studies have led to the hypothesis that environmental contributions, including diet, drugs, hormones, and environmental chemicals and carcinogens, are critical to the disease process. Thus, environmental carcinogens, in particular aromatic hydrocarbons, have been shown to cause genetic mutations. However, the possible effects of environmental carcinogens on cell growth control pathways were poorly understood. A group of investigators including Drs. D. Seldin, D. Sherr, A. Rogers, and G. Sonenshein hypothesized that the induction of signaling cascades upon exposure to environmental carcinogens plays a pivotal role in promoting mammary gland tumorigenesis. In particular, it was hypothesized that oxidative stress resulting from induction of the activation of P-450 enzyme cascade would lead to activation of the NF- κ B family of transcription factors, implicated in control of proliferation, cell survival, and neoplastic transformation. This paradigm-shifting hypothesis was confirmed. A relatively new paradigm, which is the central focus of the work funded by a program project grant to the group is that **environmental exposures throughout a woman's lifetime have an impact upon signaling events that promote the development of breast cancer, and these represent targets for treatment and prevention.** The overall scheme is given in the figure below. It is proposed that the normal epithelial phenotype of cells can be altered by exposure to environmental carcinogens inducing activation of signaling cascades that convert cells to a mesenchymal (migratory or invasive) more transformed phenotype. These pathways include those regulated by aromatic hydrocarbon receptor (AhR), CK2, Wnt and NF- κ B. Importantly, the group is identifying dietary compounds and gene products that revert this EMT conversion, causing the cell to return to a more normal phenotype of potential use in the clinic.



¹Supported by NIH Program Project Grant PO1 ES11624 and RO1 CA129129.

Serine-Threonine Kinases in Wnt Signaling and Mammary Tumorigenesis



**David C. Seldin, M.D., Ph.D.,
Medicine**

Esther Landesman-Bollag, Ph.D.
Patrick Hogan
Nicolas Currier
Anna Belkina

A major focus of our laboratory is on the role of regulatory serine-threonine kinases in mammary gland development and transformation. We have been studying two kinases that regulate the Wnt signaling pathway, a growth and differentiation pathway that is reactivated in many cancers. Wnt signaling is negatively regulated by GSK3 (glycogen synthase kinase 3), which acts on the N-terminus of the critical transcriptional co-factor β -catenin to signal its degradation. GSK3 action is opposed by protein kinase CK2, which phosphorylates the central armadillo repeat region of β -catenin, stabilizing it. Elevated CK2 expression was found in human breast cancer specimens and cell lines. In work funded by NIEHS, transgenic expression of a kinase inactive GSK3 β or a functional CK2 α was found to promote mammary tumorigenesis in mouse model systems (see upper figures on page 11). We are studying the interactions of these pathways and enzymes with NF- κ B and other regulatory pathways in breast cancer, and with chemical carcinogens and AhR activation. We are also developing novel inhibitors for CK2 that may be useful for cancer therapeutics.

Aromatic Hydrocarbon Receptor (AhR) Signaling in Breast Cancer



**David H. Sherr, Ph.D.
Pathology & Laboratory Medicine and the School of Public
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Zhi-Xiong (Jim) Xiao (Co-Investigator)
Supraja Narasimhan
Sandy Solomon, Ph.D.

It has been suggested that exposure to and bio-accumulation of ubiquitous environmental chemicals, such as polycyclic aromatic hydrocarbons (PAH), have played a role in the dramatic rise in human breast cancer incidence observed in the U.S. over the last 25 years. In animal models, malignant transformation (cancer formation) induced by PAH and related pollutants (dioxins) is mediated through the aryl hydrocarbon receptor (AhR)/transcription factor. AhR activation by environmental pollutants induces enzymes, which metabolize environmental chemicals into mutagenic intermediates. The AhR also has been implicated in the induction of proto-oncogenes,

which contribute to human cancer cell growth and metastasis. Our laboratory has demonstrated that the AhR is constitutively active in human mammary tumors as if cells were constantly exposed to environmental chemicals like hydrocarbons and dioxins. Furthermore, inhibition of AhR activity with naturally occurring bioflavonoids or through molecular techniques (e.g. inhibitory siRNA) blocks human mammary tumor cell growth and invasion in culture. These studies suggest that the AhR may represent a biomarker of malignant transformation and that molecular studies of AhR signaling will lead to rational therapeutic strategies that target the AhR as a regulator of aberrant cell growth and metastasis. In one such approach, the laboratory is screening hundreds of naturally occurring plant- and animal-derived compounds for their ability to inhibit the AhR, thereby either preventing or ameliorating breast cancer. In a second approach, the laboratory has developed candidate cancer vaccines, which induce human lymphocytes to specifically kill human mammary tumor cell lines in tissue culture.

NF- κ B Family of Transcription Factors in Breast Cancer



Gail E. Sonenshein, Ph.D
Biochemistry and Director, WHIRC

Nora Mineva, Ph.D.
Mathilde Romagnoli, Ph.D.

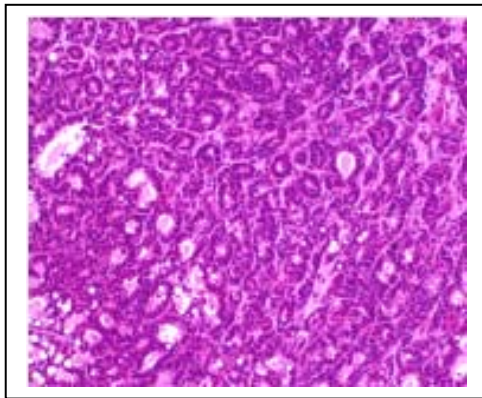
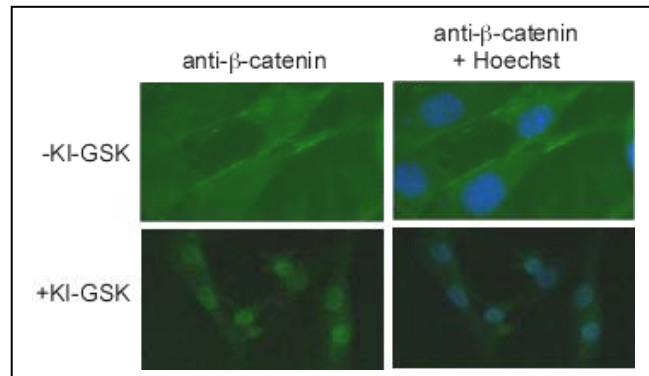
NF- κ B transcription factors normally exist in non-B cells, such as epithelial cells, in inactive forms sequestered in the cytoplasm. However, members of the signaling group hypothesized that carcinogen exposure could activate NF- κ B. We confirmed that most human breast cancers display aberrant constitutive expression of NF- κ B factors. Moreover we showed that the induction of NF- κ B by environmental carcinogens precedes neoplastic transformation. A causal role of the c-Rel NF- κ B factor in mammary tumor formation has been shown in rodents (see lower figure on page 11), and related to activation of genes critical for neoplastic transformation, cell proliferation and survival, such as *c-Myc*, *Cyclin D1* and *Bcl-xl*. More recently, we have implicated NF- κ B in promoting an invasive phenotype of human breast disease. We are currently investigating the roles of NF- κ B in transformation of mammary cells from an epithelial to a mesenchymal phenotype, interaction with Wnt and AhR signaling pathways, and estrogen receptor activity, as well as the mechanisms of NF- κ B activation. We have also demonstrated that green tea polyphenols can reverse the transformed phenotype, and are in the process of elucidating its mechanism of action and performing pre-clinical testing of its efficacy in combinatorial therapy approaches. Lastly, we have demonstrated the ability of 1,25-Dihydroxyvitamin D₃ to decrease the levels of NF- κ B subunits that promote survival of breast cancer cells. These studies continue to identify new targets for treatment of breast cancer.

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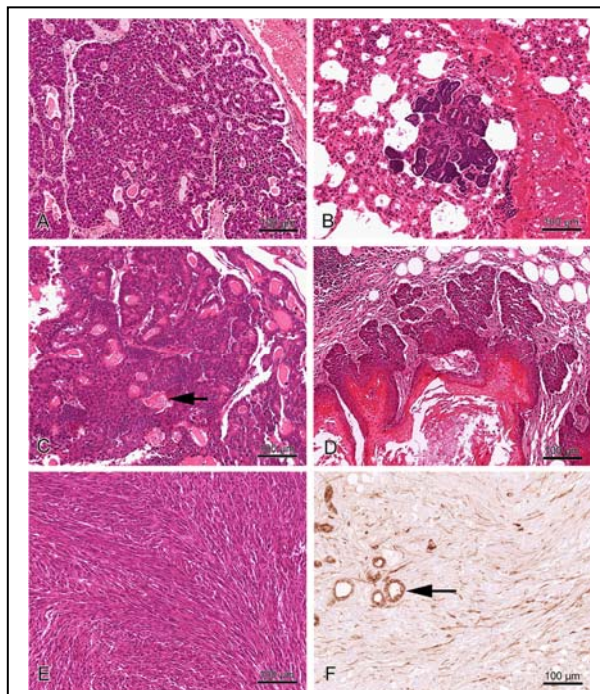
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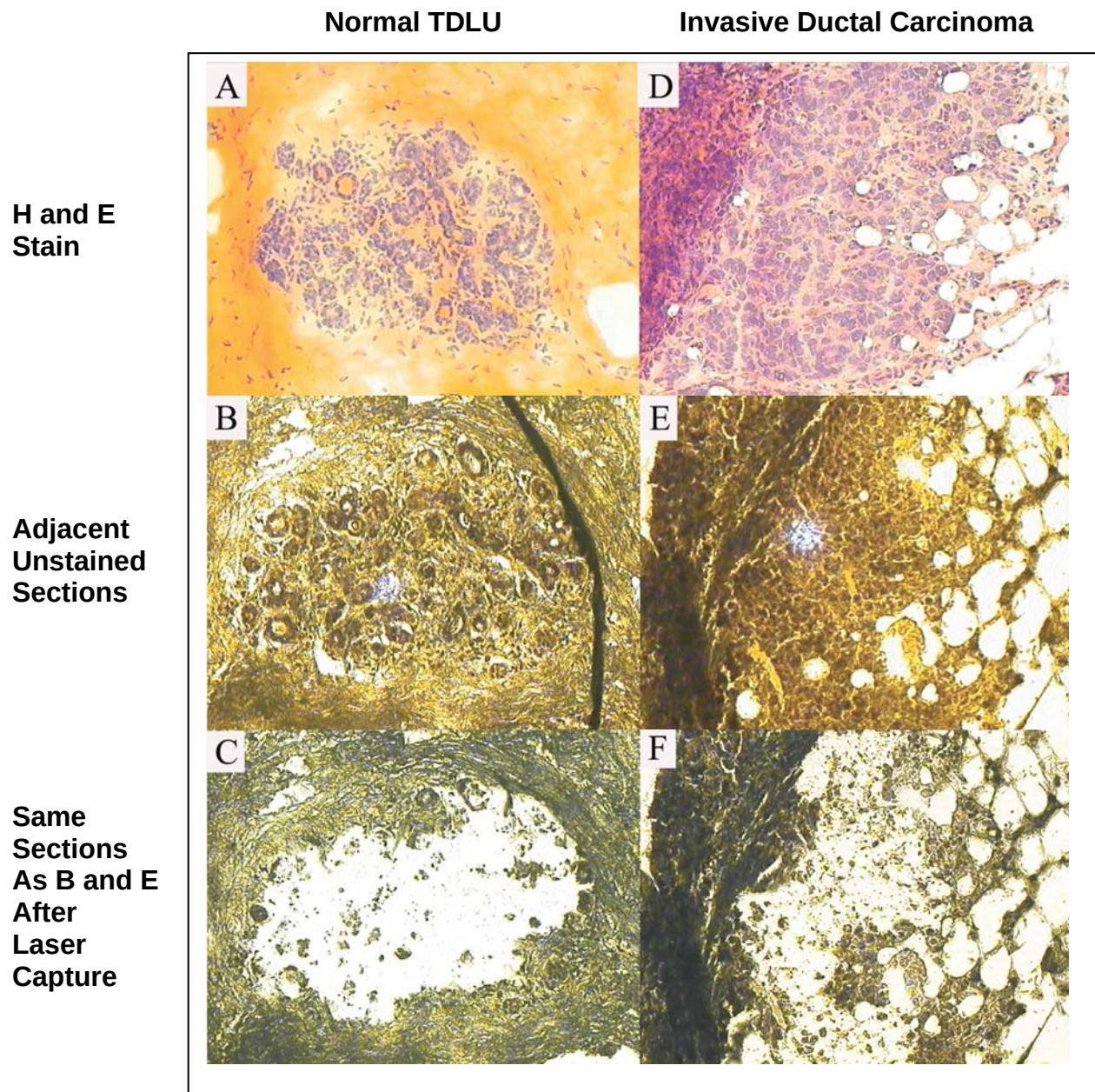
Wnt signaling and mammary tumorigenesis. (Left panel), an example of an adenocarcinoma caused by transgenic overexpression of protein kinase CK2 α in the mammary gland [From Landesman-Bollag et al. Protein kinase CK2 is upregulated in mammary gland development and transformation, *Oncogene*, 20:3247-3257 (2001)]. (Right panel), kinase inactive (KI) GSK3 β drives β -catenin into the nucleus of C57MG mammary epithelial cells, and promotes mammary tumorigenesis (Farago et al., *Cancer Research* 65: 5792-5801 (2005)).



In vivo demonstration of a causal role of the aberrant NF- κ B c-Rel activation in mammary tumorigenesis.

Representative histopathologies of mammary tumors that developed in MMTV-*c-rel* transgenic mice after multiple cycles of pregnancy and regression. A) Adenocarcinoma; B) Pulmonary metastasis in a mouse with mammary adenocarcinomas; C) Adenosquamous carcinoma showing areas with extracellular squamous differentiation (arrow); D) Squamous cell carcinoma; E) Spindle cell carcinoma; F) Immunohistochemistry for cytokeratin 8 expression in the spindle cell carcinoma shown in 2E; Note the staining of many of the spindle cells and staining of luminal epithelium in the glands (arrow). [From Romieu-Mourez et al., MMTV-*c-rel* transgenic mice develop mammary tumors. *Mol. Cell. Biol.* 23: 5738-5754 (2003).

Genetic Dysregulation



Laser Capture Microdissection

Genetic Abnormalities Early in Breast Carcinogenesis²



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Medicine

Pamela S Larson, Ph.D.

Lyndsey Emery

Bethany Hannafon

Kelly Graham

V Kristina Perry

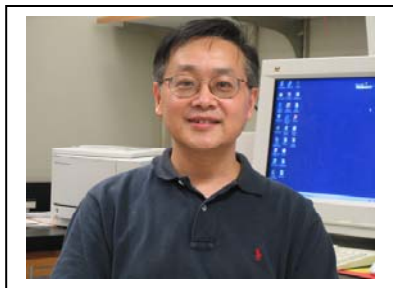
This lab investigates the molecular and genetic alterations that are important early in human breast carcinogenesis. Our overall goal is to identify the abnormalities characterizing early cancer development. We are particularly interested in abnormalities that are present even before the tissue is histologically fully malignant. We hypothesize that these genetic abnormalities are biologically meaningful and clinically relevant. In testing this hypothesis, we (and others) have shown that cancer-related abnormalities can be present in hyperplastic lesions and even in histologically normal epithelium. We study primary human tissues, and we ask questions and employ techniques suitable to that material, including laser capture microdissection, loss of heterozygosity and DNA copy number alteration, gene and miRNA expression measured by microarray and quantitative PCR, and immunohistochemistry. By definition, the work is multidisciplinary, and collaborations with pathologists, geneticists, surgeons and bioinformaticians and biostatisticians are crucial. In addition, we have projects ongoing with organizations both inside and out side BUMC, including the Framingham Heart Study and the Nurses' Health Study-Benign Breast Disease Substudy. Identifying and understanding the landscape of molecular and genetic abnormalities in premalignant and histologically normal tissue should generate novel markers of breast cancer risk, uncover mechanisms implicated early in tumorigenesis, and identify new targets for cancer prevention and treatment.

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Tumor Suppressor Proteins p53 and Rb in Breast Cancer³



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Inactivation of the tumor suppressor proteins p53 and retinoblastoma protein (Rb) plays a key role in human cancer development. We are interested in signaling cascade that regulates p53 and Rb network in response to growth or stress signals. We have discovered that DNA damage induces p53 protein conformation change via protein isomerization that lead to p53 activation, cell growth arrest and apoptosis. Additionally, we have identified a crosstalk between the IGF survival signaling and the p53 pathway. We have documented that the oncoprotein MDM2 binds to and promotes Rb protein degradation via 20S proteasome. We are currently studying the growth factor signaling (Her2, AKT, mTOR and GSK3b) that regulates p53 and Rb pathways during cell proliferation, apoptosis and cellular senescence. We are also investigating p53-related p63 in epithelial stem cell biology.

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Cancer Progression and Metastasis

Restoring Sensitivity to Hormonal Therapy in Breast Cancer⁴



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Our laboratory is interested in the mechanism by which estrogen receptor-positive breast tumors that are responsive to hormonal therapies acquire resistance to such treatment and how this process might be reversed. In breast cancer cell lines, over-expression of two proteins, AND-34/BCAR3 and p130Cas, reproducibly induce resistance to anti-estrogens. AND-34 is expressed in half of human breast tumors but not in normal breast tissue. We have determined that these proteins bind to one another, and that over-expression of AND-34 induces anti-estrogen resistance as a result of activation of PI3K, Akt, Rac and the *cyclin D1* promoter. Currently we are examining the correlation of AND-34 expression and anti-estrogen resistance in patients with breast cancer.

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⁴ Supported by grants from the NCI R01 CA114094, and the Logica Foundation.

Role of Adapter-Type Proteins in Mammary Gland Development and Breast Cancer⁵



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My laboratory is working on delineating molecular mechanisms that are important for tumor initiation and progression, with a specific focus on the expanding family of cytoplasmic adapter proteins. Adapter proteins are integrally involved in the intracellular regulation of diverse signaling events. Variations in their distinct domains, and complex interactions with other molecules, endow the members of the adapter protein family with important roles in the control of cellular proliferation, differentiation, adhesion, and motility. Currently, we are investigating the participation of p130Cas/BCAR1 (Cas/Breast Cancer Antiestrogen Resistant 1) in pathways of growth regulation in cancers of the mammary gland, and attempting to identify additional signaling molecules that associate with Cas. In our NIH-funded work, we have developed a transgenic animal model expressing a dominant-interfering Cas to investigate the role(s) of this molecule in normal mammary development and in breast cancer in vivo induced by aberrant expression of ErbB family and Src family tyrosine kinases. Moreover, we have utilized this approach to restore responsiveness to tamoxifen in resistant cells. Our long-term goal is to develop novel inhibitors that block Cas signaling.

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Role of Prohibitin in Breast Cancer Development⁶



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My lab studies the molecular mechanism involved in estrogen antagonist induced growth suppression. Tamoxifen, the current endocrine therapy and chemo-prevention of choice in early and advanced breast cancer, leads to highly-significant decreases in the rates of both disease recurrence and death. However, tamoxifen therapy is limited by the inevitable development of cellular resistance. Recent studies have shown that the E2F pathway is involved in estrogen antagonist-induced growth arrest in breast cancer cells. We reported that a potential tumor suppressor, prohibitin, represses the transcriptional activity of E2F, and this repression correlates with the ability of prohibitin to induce growth arrest. The highly evolutionally-conserved prohibitin gene was originally identified based on its ability to induce growth arrest at G₁/S. A role for prohibitin in breast cancer was suggested by the finding of prohibitin mutations in certain breast cancers. We hypothesized that prohibitin plays a role in the cell cycle regulation of breast cancer cells. Our recent study shown that prohibitin pathway indeed plays critical role in estrogen antagonist-induced growth suppression. Prohibitin interacts with the estrogen receptor and regulates its function. We have recently initiated an interdisciplinary translational investigation to translate the bench-level results clinically. Our future studies are aimed at understanding the detailed molecular mechanism of growth suppression mediated by estrogen antagonist, which may lead to identification of novel target for the designing of improved breast cancer therapy.

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Roles of the Pus1p-SRA-Estrogen Receptor Signaling Axis, and the EI24-Bcl-2 Complex in Breast Cancer Development⁷



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My laboratory has two major projects that study different aspects of breast carcinogenesis. In the first we are analyzing the role of a recently-discovered coactivator of estrogen receptor (ER) signaling in breast cancer cells. This coactivator is an enzyme named Pus1p that chemically alters, and thereby activates yet another coactivator or ER-signaling, an RNA molecule named steroid receptor RNA activator (SRA). SRA is overexpressed in human breast cancers and has been shown to cause hyperproliferation of breast epithelial cells, presumably through overstimulation of ER-activity. Thus, the Pus1p-SRA-ER-signaling axis plays an important but largely unexplored role in breast tumors when they are dependent on estrogen for their growth. We are currently analyzing the relationship between Pus1p and SRA and its effect on ER-activity in breast cancer to better understand this new mechanism of gene regulation. We are also trying to develop a new RNA inhibitor of Pus1p activity, and thereby SRA-ER-signaling which may present a novel strategy to treat ER-dependent tumors.

The second project studies the action of a suspected breast cancer tumor suppressor EI24/PIG8. EI24/PIG8 is induced by p53 in response to DNA-damaging agents, and may play a specific role in suppression of tumor spreading. We have now also obtained evidence that shows that loss of EI24/PIG8, a common event in invasive breast cancer, contributes to chemotherapy resistance in breast cancer cells. We are planning to further study the effects of EI24/PIG8 on resistance to different chemotherapy regimens to test the hypothesis that the EI24/PIG8 status in breast tumors can serve as a novel marker for resistance to certain types of chemotherapy.

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Lysyl Oxidase Inhibition of Ras-Mediated Signaling and Transformation⁸



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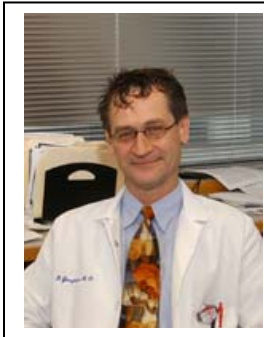
The *lysyl oxidase* (LOX) gene was identified as the *ras* recision gene (*rrg*), with ability to suppress Ha-Ras-induced transformed phenotype. We showed that the LOX gene suppresses Ras-mediated activation of NF- κ B factors in NIH 3T3 cells, via inhibition of the PI3K/Akt and Raf/MEK pathways. LOX is synthesized as a 50 kDa pro-enzyme, secreted into the extracellular environment where it is processed to a functional 32 kDa enzyme and an 18 kDa pro-peptide (LOX-PP). We recently showed that the LOX-PP, and not the LOX enzyme, inhibits *ras*-dependent transformation of NIH 3T3, and thus, has the *rrg* activity. We have now extended our studies showing that the LOX-PP inhibits breast cancers driven by Ras- and Her-2/neu, which signals via Ras. This inhibition correlates with a reversion to invasive cell status to a more normal phenotype, inhibition of NF- κ B and kinase cascades. LOX-PP was shown to function as a tumor suppressor of breast cancer in a xenograft model in nude mice. Experiments are continuing to elucidate the mechanism of its action. A non-synonymous single nucleotide polymorphism (SNP) was reported within the LOX gene in human gastric cancers. We noted that it maps to highly conserved regions within the LOX-PP, and showed that the SNP dramatically impairs LOX-PP ability to revert invasive phenotype *in vitro* and in nude mice. The SNP was detected in 6 of 9 human breast cancer cell lines analyzed. Collaborative work with Drs. Rosenberg and Palmer of the Slone Epidemiology has suggested that the SNP is associated increased risk of ER α negative breast cancer in African-American women. The overall goals of this work are to determine the potential use of the LOX-PP or its derivatives in treatment of patients with Her-2/neu or Ras-mediated breast disease, and of the mutations as biomarkers.

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T-Cell Gene Therapy to Eradicate Disseminated Breast Cancers⁹



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Whereas progress has been made reducing recurrence in adjuvant settings with hormone, chemical and biological therapies, there is still no agent for breast cancer that offers any hope of “eradicating” (i.e., “curing”) breast cancer once it has spread to the bones or other organs (“metastatic”). Our aim is to devise a therapy with *intent to cure* metastatic, widely disseminated tumors in patients. T cells have the capacity to hunt down and eliminate infected host cells, or, when properly directed, tumorous host cells, anywhere in the body. Our group has specialized in creating modified patient T cells to express chimeric immune receptors (CIRs) that when introduced into patient T cells create so-called “designer T cells”, “re-educating” those cells to “think” that the tumor has a virus infection, attacking and destroying it. In their simplest form, these CIRs are immunoglobulin-T cell receptors (IgTCR), i.e., molecular fusion products of antibody (Ab) binding domains with the ζ signaling chain of the TCR that provides Signal 1. When expressed by gene therapy techniques in recipient T cells, the “designer T cells” combine the specificity of Ab with the cytotoxic potency of T cells in a new type of immune therapy against breast cancers. A prior clinical trial by our group showed that breast tumors could be attacked, but that the attack was short-lived. Efforts are underway to extend the activity of these designer T cells in vivo, via new signals engineered in the designer T cells and also via adjunctive manipulations outside and inside the body to conquer major subsets of breast cancer.

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New Molecular and Therapeutic Approaches to Breast Cancer¹⁰



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There are multiple areas of breast cancer-related research ongoing in our laboratory. Two directions involve breast cancer treatment. The first is directed towards the finding that a significant fraction of breast cancers contain the Epstein-Barr virus genome. Basic and translational work has resulted in the development of a therapeutic, now in clinical trials, which selectively induces genes in the viral genome, which is integrated in the breast cancer cell, rendering it susceptible to anti-viral agents, which destroy the tumor cell. A second treatment strategy is based on analysis of aberrant cell cycle checkpoint control in transformed cells, and the development of small molecules, which take advantage of this dysregulation to induce apoptosis. An avenue of translational research investigation studies the molecular mechanisms required for the anti-tumor actions of hormone antagonists. Finally, a new adhesion molecule, which regulates breast cancer cell invasion and adhesion, has been discovered and is being analyzed.

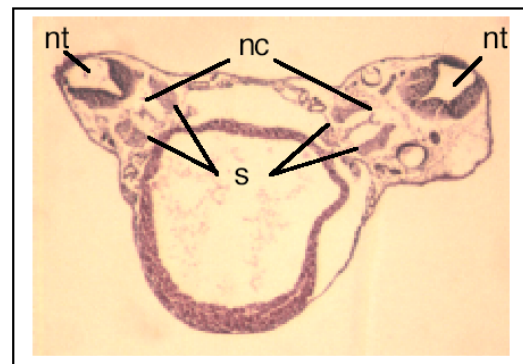
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XENOPUS MODELS OF REGULATION OF DEVELOPMENT AND CANCER

In order to develop strategies for preventative and therapeutic treatment of cancer growth, progression and metastasis, it is important to understand how these processes are controlled. The processes of tumorigenesis and embryogenesis share many cellular mechanisms such as rapid cell growth and division, epithelial-mesenchymal transition, apoptosis, and cell migration, and many of the signaling pathways that control them are conserved. For example, metastasis occurs when cells break away from the primary growth, invade adjacent tissues, and implant into unaffected areas to seed new tumors. This process depends on the cells' ability to move across and through different tissues. Similar cell motility is observed in developing embryos and platelet-derived growth factor stimulated signaling pathways appear to be involved in both processes. Importantly, during cancer initiation and progression, developmental signaling pathways are often reawakened, however, their normal regulation is lost. Embryos of the frog *Xenopus laevis* provide a powerful model for studies of development as they are readily amenable to manipulation yet share the cellular and molecular mechanisms that are the basis of cancer. It is hoped that by understanding the molecular basis of normal cellular processes in a tissue environment, targets for drug design to combat aberrant cell behavior such as during cancer development and progression will be identified.



Axis duplication in *Xenopus* embryos. (*Left panel*), when injected into *Xenopus* embryos, CK2 causes duplication of the embryonic body axis, which is a characteristic of Wnt signaling in development. Embryos with two sets of eyes and cement glands (in the position of the chin) can be seen. (*Right panel*), histologically, this embryos show duplicated axial structures including neural tube (nt), notocord (nc) and somites (s) that can be seen in this transverse section of an stage 38 embryo. [From Dominguez *et al.* Protein kinase CK2 is required for dorsal axis formation In *Xenopus* embryos, Dev Biol. 274:110-24 (2004)].

Platelet-Derived Growth Factor Signaling in Cell Survival and Motility¹¹



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Platelet-derived growth factors and their receptors (PDGFRs) play a critical role in cell motility in a variety of cultured cells, whole organisms and tumors however, the precise molecular mechanisms underlying this role are not fully understood. We use embryos of the frog, *Xenopus laevis*, as a model system to analyze the molecular basis of cell motility *in vivo*. These embryos normally undergo a series of well-defined cell movements across and through different tissues during their early development. We discovered that when signaling through PDGFR is blocked in these embryos, directed cell migration is disrupted and the cells die by apoptosis. Cell survival is restored by expression of chimera receptors that lack the PDGFR extracellular domain but directed cell migration is not. Directed migration can be restored however, by overexpression of wild-type PDGFR, and the receptor must be tyrosine phosphorylated for this to occur. These findings strongly suggest that, in addition to inducing receptor dimerization and tyrosine kinase activation, the interaction of PDGF with the extracellular portion of PDGFR also plays critical roles in the full range of normal cell responses such as directed cell migration. We are currently investigating these roles as well as the downstream signaling pathways necessary for directed cell motility.

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The Wnt Pathway in Embryonic Development and Cancer¹²



***M. Isabel Dominguez, Ph.D.
Medicine***

*Kathleen Chea
Mirka Hlavacova*

One of the signaling pathways that is upregulated in many human cancers is the Wnt pathway, that normally regulates embryonic development. Much effort is devoted to the search for specific inhibitors of Wnt signaling. However, the gaps in our knowledge of how Wnt signaling happens impair our ability to design inhibitors. The goal of our laboratory is to understand how the Wnt signaling pathway functions in order to find appropriate therapeutic targets. Our strategy is to use frog embryos as a model organism. In frog embryos, canonical Wnt signaling components are easily, rapidly and efficiently assayed where ventral overexpression leads to embryos with duplicated dorsal structures ("ectopic axis induction assay") Using this specific developmental assay, we have shown that an enzyme called protein kinase CK2 is required for Wnt signaling. Interestingly, CK2 is highly expressed in human cancers including breast, lymphoma and head and neck. In addition, mice engineered to overexpress CK2 in breast tissue and lymphocytes develop breast and lymphoid tumors. These results identify CK2 as a component of Wnt signaling essential for embryonic development that is overactive in tumors. We are currently studying the mechanism that CK2 uses to activate Wnt signaling since understanding how molecules are activated and work upon growth factor signaling is essential for developing new specific treatment strategies. We are also designing novel CK2 inhibitor molecules and analyzing their effects in blocking Wnt-dependent embryonic processes and aberrant Wnt signaling in breast cancer cells.

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BREAST CANCER CONTROL STUDIES

Understanding and Addressing Racial Disparities in Breast Cancer Care¹³

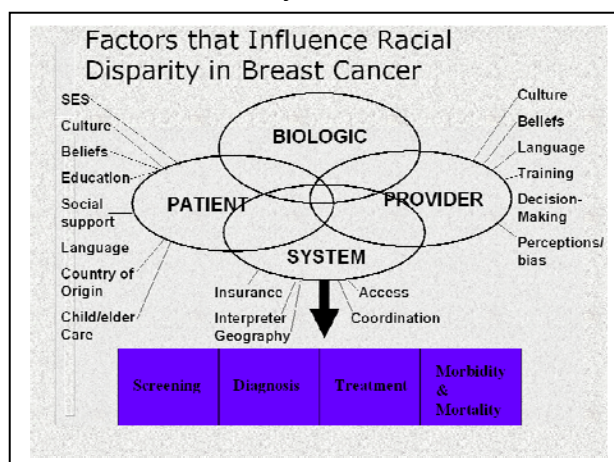


Karen M. Freund, M.D., M.P.H.
Chief, Women's Health Unit, Medicine
Director, Center of Excellence in Women's Health
Executive Associate Director, WHIRC

Tracy Battaglia M.D., Co-Investigator
 Michele David, M.D., Co-Investigator
 Arlene Ash, Ph.D., Co-Investigator

Arpita Aggarwal, M.D.
 Michael Posner MA
 Bonnie Sherman, Ph.D.

The focus of research in the Women's Health Unit in the past 10 years has been on addressing the psychosocial factors which influence racial disparities in the receipt of health care services, which in turn lead to disparities in breast cancer mortality. This focus has addressed a broad number of issues in screening, diagnosis and treatment phases of care. It has looked at the role of patient beliefs and behaviors, physician attitudes and decision making, and the role of systems barriers, especially navigating the increasing complex health care system. We have documented disparities in screening that account for some but not all of the mortality gap in breast cancer, and that recent trends towards parity in screening have not eliminated racial disparities. Ongoing work is now addressing models of intervention into beliefs and barriers, including patient navigator and advocacy training. Our most recent work, funded through the Avon Foundation, has documented disparities in diagnostic service delivery. We have then developed a novel patient navigator intervention, and demonstrated through this pilot intervention, significant improvements in timeliness of diagnostic services. Our future plans are to evaluate this model in a control clinical study in a broader and more generalizable multi-site study in collaboration with our community health centers.



¹³ This work is supported by grants from the Susan G. Komen Foundation, the Avon Foundation, the Department of Defense Breast Cancer Program, and the NCI.

Cancer Prevention and Control Among Minority Women



Tracy A. Battaglia, M.D., M.P.H.
General Internal Medicine

My research interests focus on understanding and addressing the psychosocial determinants of cancer care among minority women as they relate to disparities in cancer outcomes. Using survey methodology I have investigated both provider and patient level barriers to receipt of primary and secondary prevention for breast cancer. An ongoing survey of urban minority women seeks to identify how risk perceptions affect breast and colorectal cancer screening practices. Also, as Co-Director of the Avon Initiative at Boston Medical Center I am leading the management and development of a rich database of all women referred to our diagnostic breast health practice in the Women's Health Group. We are investigating determinants of follow up care as well as the effectiveness of a patient navigation program aimed to improve adherence to breast health care among the underserved minority women we serve.

Communication, Cultural Models of Breast Cancer Beliefs and Screening



Michele David, M.D., M.P.H., M.B.A.
Women's Health Unit, Medicine
Co-Director, Haitian Health Institute

My research has worked to identify cultural beliefs, and factors that contribute to delays in cancer screening and/or impede cancer evaluation and treatment, especially in the Haitian community. Many Haitians adhere to a traditional system of attitudes and beliefs about health and illness, which may result in delays in presentation for breast cancer and other serious illnesses. We have conducted an in-person, randomized, cross-sectional survey in low income neighborhoods in the Boston area to understand these belief systems and their impact on screening in immigrant subpopulations. To address access to care issues among immigrants, we are collaborating with community agencies in a consumer advocacy and a community participatory model. Through a

collaboration with Health Care For All and the Haitian Health Institute, we have designed and are implementing a community advocacy project, that will allow consumers to better navigate the health care system and become more effective advocates for their needs.

Breast Cancer Care and Well-Being Among Sexual Minority Women



Ulrike Boehmer, Ph.D.¹⁴
School of Public Health

My research focuses on understanding disparities in breast cancer due to sexual orientation. I have investigated the health care experiences of sexual minority women with breast cancer, their coping and adjustment to this disease, as well as their support environment, consisting of female partners, family members or going through treatment alone. I am now expanding on these findings in two ways. One, I am leading a new population-based study of Massachusetts' breast cancer survivors of different sexual orientations. In this American Cancer Society-funded study, we will collect data on women with breast cancer of different sexual orientations to assess quality of life and the factors thought to impact it. The results of this assessment will inform the intervention phase of the study. For the intervention development we will use the information learned about the health needs of sexual minority women to adapt a standardized intervention program to sexual minority women with breast cancer. Second, I am investigating the sexual well-being of sexual minority women with breast cancer. This study, funded by the Susan G. Komen Breast Cancer Foundation, will provide clinicians with information about critical areas that impact the sexual health of sexual minority women with breast cancer. The findings of this study will inform the development of interventions geared toward improving sexual health in sexual minority breast cancer survivors.

¹⁴ Supported by funds from the SG Komen Foundation and the American Cancer Society

Clinical Trials of Breast Cancer Prevention¹⁵



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School of Public Health

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Karen Freund, M.D., Co-Investigator
Rita Blanchard, M.D., Co-Investigator
Elizabeth Pottier, Prevention Trials Program Manager
Feleshia Battles, Community Outreach Coordinator

There are several breast cancer prevention trials currently ongoing. Dr. Prout heads the National Surgical Adjuvant Breast and Bowel Project (NSABP) at the Boston Medical Campus. "A Clinical Trial to Determine the Worth of Tamoxifen for Preventing Breast Cancer" began in summer, 1992 and completed accrual in September, 1997 with 13388 women in the U.S. and Canada, including 180 women through Boston Medical Center and its 7 affiliates. Therapy was unblinded on March 31, 1998 showing a 49% reduction in breast cancer risk in the women receiving tamoxifen compared to placebo. Long-term follow-up of the participants who received tamoxifen continues. NSABP's second breast cancer prevention trial, "Study of Tamoxifen and Raloxifene (STAR) for the prevention of Breast Cancer", opened in July, 1999 and closed to accrual in November, 2004 with the enrollment of 19,747 women in the U.S. and Canada, 210 at BMC and its 15 collaborating sites (ranking BMC in the top 10% of centers for accrual). Participants in STAR continue on therapy.

Dr. Prout developed and has led the STAR Community Outreach Program for Education (SCOPE), a collaboration among Boston Medical Center, Beth Israel Deaconess, and Dana Farber Cancer Institute. This program, 1 of 16 nationally, has provided education, information, and risk assessments in the diverse communities in Boston since 2000. Boston Medical Center is the only Boston location and 1 of 2 in New England for Co-STAR, a sub-study of STAR designed to compare the effects of tamoxifen and raloxifene on age-associated declines in memory and other cognitive abilities in women over age 65 within the context of a randomized clinical trial. The cognitive outcomes in Co-STAR participants will also be compared with those from participants in a parallel study of the effects of HRT on cognitive outcomes, WHISCA.

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Aging and Breast Cancer¹⁶



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Soe Soe Thwin, M.S.P.H.
Jaclyn Bosco, M.P.H.
Thomas Ahern, M.P.H

Our group conducts research on breast cancer etiology, disparities in breast cancer therapy in relation to age and race/ethnicity, and the consequences of those disparities. We are particularly focused on the determinants and consequences of less than definitive therapy among older women with newly diagnosed early stage breast cancer. Ongoing studies include: 1) a longitudinal follow-up study of over 800 women 65 years of age with stage I-IIIa breast cancer treated in Greater Los Angeles, Minnesota, Rhode Island, and North Carolina; and 2) a 10-year study of breast cancer treatment effectiveness among 1859 women with early stage breast cancer cared for in six integrated health care systems participating in the Cancer Research Network.

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SLONE EPIDEMIOLOGY CENTER¹⁷

A primary research interest of the Slone Epidemiology Center is the assessment of risk factors for breast cancer. Ongoing studies include the Black Women's Health Study, the Case-Control Surveillance Study, and the DES Follow-Up Study.



Lynn Rosenberg, Sc.D.
Slone Epidemiology Center

Begun in 1995, the Black Women's Health Study is the largest follow-up study of the health of African-American women yet conducted, with 59,000 participants. The primary aim of this ongoing nationwide study is to elucidate risk factors for breast cancer in African-American women. Every two years, the study collects data on potential risk factors and on the occurrence of illness through postal questionnaires. Potential breast cancer risk factors of particular interest are physical activity, diet, oral contraceptive use, postmenopausal female hormone use, reproductive factors, body mass, cigarette smoking, alcohol consumption, and genetic polymorphisms. Findings from the study concerning parity and breast cancer have helped to elucidate the black-white crossover in breast cancer incidence at around age 45, and findings on obesity have helped to elucidate why there is not an epidemic of breast cancer among postmenopausal black women despite the high prevalence of obesity among them. A case-control study in progress since 1976, termed the Case-Control Surveillance Study, assesses the influence of medications and other factors on the risk of cancer; breast cancer is a primary focus. Data are collected via in-person interviews of hospital patients. The study raised the hypothesis that alcohol increases breast cancer risk; that association has been confirmed in many subsequent studies. DNA is collected through buccal swabs, making it possible to assess the influence on breast cancer risk of genetic polymorphisms that may be related to the metabolism of drugs or carcinogens. The database currently includes information collected from more than 7,000 patients with breast cancer and 75,000 other patients.

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***Julie Palmer, Sc.D.
Slone Epidemiology Center***

As part of the Black Women's Health Study, we have just completed collecting DNA samples (through the mouthwash-swish method) from 27,000 participants in the study. Our repository of DNA from these 27,000 African-American women who have also provided questionnaire data on health outcomes and behavioral factors is the largest of its kind. We have begun genotyping of samples from 1000 women with breast cancer and 1000 matched controls to assess a number of putative low-penetrance causal variants in relation to breast cancer risk. These data, in conjunction with questionnaire information, will be used to examine interactions of genetic and environmental factors to influence breast cancer risk. We are about to begin similar genetic analyses of colon cancer in African-American women. We are currently seeking funding to conduct a genome-wide association study of breast cancer among our study participants; it would have the potential to identify previously undiscovered genes that increase the risk of breast cancer in black women. In a separate project, we have been studying cancer-related health effects of exposure to diethylstilbestrol (DES), in collaboration with four other data collection sites. We recently published a new finding regarding the health effects of DES -- an increased risk of breast cancer in women who were exposed prenatally to Diethylstilbestrol. We are now investigating potential mechanisms for the association.

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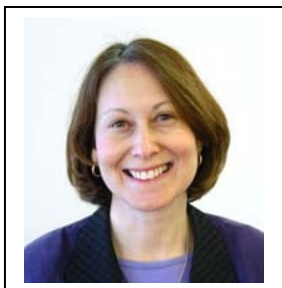
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Environmental Risk Factors for Breast Cancer¹⁸



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My research focuses on the environmental determinants of disease, particularly breast cancer. Specific topics that I have investigated include the risk of breast cancer associated with exposure to pesticides, solvent-contaminated drinking water, magnetic fields, and cigarette smoke; and the use of mapping and spatial statistics to identify breast cancer hot spots. Most of these hypotheses have been investigated in a case-control study of environmental determinants of breast cancer in the Cape Cod region of Massachusetts, a fragile ecosystem that has been impacted by many different sources of environmental pollution. I have also had the pleasure of serving as a faculty member of Project LEAD, an innovative science program sponsored by the National Breast Cancer Coalition that trains breast cancer activists to serve as consumer advocates at all levels of the research and policy process.

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