



The 2nd International Symposium on the Intraductal Approach to Breast Cancer

More than 80 physicians, scientists, and researchers gathered in Santa Barbara, California, May 31-June 3 for the Susan Love MD Breast Cancer Foundation's 2nd International Symposium on the Intraductal Approach to Breast Cancer. The Symposium provided a unique opportunity for researchers throughout the world to meet others who share their interest in this exciting field, which includes techniques such as nipple aspiration, ductal lavage, ductoscopy, and endoscopy. These techniques are used provide access through the nipple to the milk ducts inside of the breasts. Since at least 95% of all breast cancers begin in the lining of the milk duct, these scientists study the fluid and cells inside the breast ducts to find information that will provide the answers to the early diagnosis, treatment, and eradication of breast cancer

Since its inception, the Foundation (formerly the Santa Barbara Breast Cancer Institute, founded in 1983) has played a leading role in promoting research on the intraductal approach to breast cancer. "The Foundation supports the intraductal approach because of the potential this research area has to advance breast cancer detection, prevention, and treatment," said Dr. Love, the Foundation's medical director. "This approach is not new. It took years of research to get where we are. The purpose of this Symposium is to exchange ideas and work to advance the field even further."

History of the Intraductal Approach

The Symposium began by introducing conference participants to the history of the intraductal approach. This history includes the groundbreaking work of Otto W. Sartorius, MD, the founder of the Santa Barbara Breast Cancer Institute and the man who is often referred to as the "father" of the intraductal approach to the breast. In the 1970s, Dr. Sartorius was one of a handful of researchers focusing on the intraductal approach. He made the important discovery that malignant cells could be found in fluid that was suctioned from the nipple (nipple aspirate fluid; NAF) when palpation or mammography could not detect cancer. Then he developed a tiny catheter that he could insert through the nipple into the duct so that he could explore the anatomy inside of the breast to gain insight into where and how cancer develops.

Using this tiny catheter, Dr. Sartorius established that there were six to nine ducts emptying on each nipple's surface, that each duct drained only one lobule, and that each ductal tree/lobular unit was independent and not interconnected. Further, in the normal duct there was no transfer of fluid across the epithelial layer—no leakage into the interstitial space. "These findings," said Adeline Hackett, PhD, who worked with Dr. Sartorius and discussed his work at the Symposium, "had important implications for future research on the early treatment of breast disease."

Only a handful of researchers had begun to explore the intraductal approach prior to Dr. Sartorius. Nicholas Petrakis, MD, professor emeritus in the Department of Epidemiology and Biostatistics at the University of California, San Francisco, another pioneer in the intraductal approach to the breast, told conference participants about the work of two of these researchers: Geoffrey Keynes, MD, and George Papanicolaou, MD. Dr. Petrakis discussed why these men's work was critical to today's focus on the breast ducts and ductal fluid, and described how it laid the groundwork for the research that he, Dr. Sartorius, and others at the Symposium have already conducted and will be conducting in the future.

One of the first discoveries made using the intraductal approach was that not all women produce NAF. Dr. Petrakis told Symposium participants that in his research he found that the ability to extract breast fluid (NAF) was related to many different factors. These factors include age, onset of menarche, the number of children a woman has had, whether she has breast fed, and if she has had an oophorectomy (removal of the ovaries). He also found that breast fluid could contain products such as progesterone, estradiol, testosterone, protein, growth hormone, cholesterol, nicotine, and caffeine.



Dr. Petrakis also discussed his prospective study of 2701 women who underwent nipple aspiration between 1973 and 1980. In that study, after a median of 14 years at follow-up, women who originally had atypical cells in their ductal fluid had a nearly five times greater risk of developing breast cancer at follow-up than did women who did not yield any fluid. Margaret Wrensch, PhD, an adjunct professor at the University of California, San Francisco, collaborated with Dr. Petrakis on this study and presented additional findings at the Symposium.

Dr. Wrensch noted that women with atypical cells in their ductal fluid and a first-degree family history of breast cancer were six times more likely to develop breast cancer than were women with atypical cells who did not have a family history of breast cancer. The results from this study, Dr. Wrensch explained, illustrate a relationship between atypical cells in the duct and breast cancer risk and "they support the hypothesis that NAF that contains atypical cells is associated with an increased risk of breast cancer." She continues to follow women in this study and expects to publish a 20-year follow-up summary on the relationship between abnormal cells in NAF and breast cancer risk.

Current Research using the Intraductal Approach

After an update on the history of the intraductal approach, conference participants learned about and discussed research studies now underway that are using intraductal techniques. Gertrude Case Buehring, PhD, an associate professor in the School of Public Health at the University of California, Berkeley, has been studying the relationship between NAF and breast cancer risk since the 1970s. In 1979, she published results from a study of 1,744 women who volunteered to give NAF for research purposes. In that study, premenopausal women were more likely to produce NAF than were postmenopausal women; women who had lactated were more likely to produce NAF than women who had never lactated; and, women who were not using oral contraceptives were more likely to produce NAF than those who were using them. Dr. Buehring is currently trying to find these volunteers so that she can conduct a 25-year follow-up study on the relationship between the ability to obtain NAF and breast cancer risk. "If our hypothesis is correct," she said, "then not being able to get NAF from a women would not be a serious flaw since those most at risk would be those from whom we could get fluid that contained epithelial cells... It would also support the usefulness of this method for routine screening."

Conference participants also had the opportunity to learn about the most recent research on ductal lavage by Susan Love, MD. She described the grant she received from the Department of Defense to develop ductal lavage and establish its utility. "At least 95% if not all breast cancer begins in the lining of the milk duct," explained Dr. Love. "This is why the intraductal approach is so important. By permitting easy and reproducible access to the cells lining the milk duct, ductal lavage can help us to understand how cancer develops and whether and how prevention or treatment works."

Dr. Love explained the ductal lavage procedure, which entails inserting a catheter into a breast duct identified by NAF, instilling saline into the duct, and then rinsing out the duct to obtain epithelial cells. Her research showed that this technique was very effective at detecting abnormal cells in the duct. She also described some of the research she conducted to explore the anatomy of the breast ducts and the ductal orifices. "What we found," said Dr. Love, "was that each breast had two to four central ducts with four to eight peripheral ones. We also found that the ducts did not exist in the quadrants of the breast in the way that had been previously believed. Instead, we found that the ductal systems project backward to the chest wall in a consistent pattern. Each ductal system matches a duct, and breast cancer arises in one ductal system. This is why we don't get clean margins when we remove a tumor. We are taking out a wedge, because that's how we've thought of the breast, but the ducts are not in wedges at all."

Dr. Love told the Symposium participants that this research on the anatomy of the breast had important implications for how breast cancer is treated. She also noted that ductal lavage has already begun to be used as a decision-making tool for high-risk women. "We don't think ductal lavage is a way to detect cancer," Dr. Love said, "but rather a way to detect precancerous cells. Studies have shown that when



atypical cells are present in ductal fluid a woman has a five times greater risk of developing breast cancer. This doesn't mean it will develop into breast cancer, but it is a risk factor."

After learning from Dr. Love about ductal lavage and the anatomy of the breast, conference participants had the opportunity to see inside the breast duct. The work of William Dooley, MD, chair of Surgical Breast Oncology and director of the Institute for Breast Health at the University of Oklahoma made this possible. In January 2000, Dr. Dooley began using a small endoscope to look inside the breast duct during routine surgical procedures. Through these endoscopic procedures, Dr. Dooley has learned to tell the differences between normal ducts, atypical ductal hyperplasia, DCIS, and invasive ductal carcinoma based on color and appearance. Conference participants were able to see this for themselves when they watched a video presentation of a series of endoscopic procedures performed by Dr. Dooley that showed these different diagnoses. [click here to see video and/or video grabs]

The intraductal approach provides direct access to the inside of the breast where breast cancer begins, and that access has been the catalyst for a number of research studies. For example, it has led Robert Chatterton, Jr., PhD, a professor in the departments of obstetrics and gynecology and physiology at Northwestern University Medical School, to explore whether a relationship exists between estrogen levels in the breast duct, estrogen levels in blood serum, and breast cancer risk.

Dr. Chatterton has already uncovered distinct differences in estrogen levels during the menstrual cycle as well as differences between premenopausal and postmenopausal women. Now he is conducting research on "the relationships between the cellular properties and the ductal fluid in postmenopausal women... with a goal of helping women at high risk for breast cancer determine whether they should use hormone replacement therapy."

In an effort to identify cancer early, Ella Evron, MD, a fellow in oncology at the Johns Hopkins Oncology Center, is using ductal lavage along with the latest research tools and techniques to look for genetic changes in breast tumors. Although Dr. Evron's research is still very preliminary, she told conference participants that she believes that these genetic studies might one day "be a useful tool for early detection of breast cancer."

The availability of the intraductal approach led Sanford Barsky, MD, a professor of pathology at the University of California Los Angeles, School of Medicine, to focus his attention not on the epithelial cells that become cancerous but on the myoepithelial cells that line the duct. "Epithelial cells are those that think about becoming cancer," explained Dr. Barsky. "But if myoepithelial cells change, they do so in benign ways. Even in cases of DCIS, the myoepithelial layer remains untransformed." Because the myoepithelial cells work to keep cancer inside the duct, they are, he said, "the best defense against invasive cancer." Based on his research findings, Dr. Barsky now is trying to develop a breast cancer treatment method that "would wipe out the epithelial cells while preserving and sustaining the myoepithelial cells against invasion."

Future Research using the Intraductal Approach

Conference participants also heard presentations from researchers interested in starting new, or pursuing further, breast cancer research utilizing the intraductal approach. These researchers had applied for grants to help start their work from the Susan Love MD Breast Cancer Foundation; the Symposium gave them an opportunity to describe their work to the grant committee. Then, modeling a unique funding procedure specifically designed to jumpstart intraductal research, the grant committee announced and awarded the grants the following day at the close of the Symposium. As a result of the conference, the Foundation provided a total of \$110,000 to support the pilot work of 13 researchers in a wide scope of different projects related to using the intraductal approach. Their work and awards are described below.

Recipients of the Susan Love MD Foundation Grants to Pursue the Intraductal Approach to Breast Cancer



DR. SUSAN LOVE
RESEARCH FOUNDATION

www.drsusanloveresearchfoundation.org
E-mail: info@dslrf.org

***Rachel Brem, MD**, an associate professor in the department of radiology and director of breast imaging and intervention at George Washington University Medical Center in Washington, DC, for “Efficacy of Ductal Lavage for the Diagnosis of Breast Cancer.” **\$10,000 Research Grant**

***Robert Chatterton, PhD**, a professor in the department of Ob/Gyn and Physiology and director of the immunoassay core facility at Northwestern University School of Medicine, for “Nipple Aspirate Fluid Hormone and Response Parameters.” **\$15,000 Research Grant**

***Laurie Delmolino, PhD**, an instructor at the New England Medical Center, for “The Feasibility of Gene and Protein Profiling of Normal Breast, Atypical, and Breast Cancer Cells from Ductal Lavage.” **\$5,000 Research Grant**

***Christine Erdmann, PhD**, and **Georgianna Farren, MD**, an epidemiologist and a scientist at the Lawrence Berkeley National Laboratory, for “Female Breast Cancer and Environmental Risk Factors for Marin County - Pilot Study, Plus NAF Collection Component.” **\$5,000 Research Grant**

***Laura Esserman, MD, MBA**, an associate professor surgery at the University of California, San Francisco, and program leader for breast oncology at the UCSF Cancer Centers, for “Detection of Telomerase Activity in Ductal Lavage and Ductoscopy Samples.” **\$5,000 Research Grant**

***Julian Kim, MD**, a researcher at the Cleveland Clinic Breast Center, for “Genetic Analysis of Ductal Lavage Cells Using Fluorescence In-Situ Hybridization (FISH) and Molecular Fingerprinting Using Gene Chip Microarrays.” **\$10,000 Research Grant**

***Bonnie King, PhD**, an associate research scientist in the Department of Therapeutic Radiology at Yale University, for “Cytogenetic Analysis of Breast Touch Prep/Ductal Lavage Paired Cases.” **\$10,000 Research Grant**

***Gillian Mitchell, MD**, a clinical research fellow in cancer genetics at the Institute of Cancer Research in London, for “Developing Nipple Aspirate Fluid as a Method for Early Breast Cancer Detection in BRCA1/2 Germline Mutation Carriers.” **\$10,000 Research Grant**

***Jian Yu Rao, MD**, an assistant professor in the Department of Pathology and Laboratory Medicine at the University of California, Los Angeles, for “Molecular Mapping Analysis on Mastectomy Specimens.” **\$10,000 Research Grant**

***Susan Troyan, MD**, surgical director of the BreastCare Center at Beth Israel Deaconess Medical Center in Boston, for “Pilot Study of Ductal Lavage in Women with Microcalcifications on Mammogram.” **\$15,000 Research Grant**

***Shawna Willey, MD**, chief of breast surgery at the George Washington University Medical Center in Washington, DC, for “Expanded Use of Ductal Lavage to Patients with Previous Breast Cancer Treated with Breast-Conserving Surgery and Radiation.” **\$10,000 Research Grant**

***Debrah Wirtzfield, MD**, an assistant professor of surgery at the Roswell Park Cancer Institute, in Buffalo, New York, for “Assessment of Cells Harvested by Breast Ductal Lavage: Flow Cytometry and Microarray Analysis.” **\$5,000 Research Grant**