SCREENING FOR BENIGN BREAST DISEASE

A NEW CLINICAL METHOD FOR DETERMINATION OF BREAST CANCER RISK

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INTRODUCTION

Breast cancer is a leading health concern among women in the U.S. Over 200,000 new cases are identified every year, resulting in over 40,000 deaths annually. In spite of the fact that more than $3 billion is spent annually in the U.S for breast cancer screening, only modest progress in reducing the death rate has been achieved. This paper will review the limitations of current practices, and highlight an opportunity to significantly change the death rate for breast cancer by screening for benign breast disease, using a model similar to the Pap test.

The Pap test is arguably the most successful cancer screening technology in history. The effectiveness of the Pap test in reducing the death rate of cervical cancer is directly related to the ability to determine precancerous conditions in the cervix before a cancer forms. Combined with repeated testing, i.e. annual well-woman visits, the Pap test's simplicity and low cost led to widespread adoption. The annual death rate from cervical cancer has decreased over 70% since its introduction.

A noninvasive "Pap Test for the Breast" designed for the primary care setting may yield similar results, if simplicity and low cost lead to widespread adoption of Nipple Aspirate Fluid (NAF) cytological screening for benign breast disease. Most all breast cancers begin in the milk ducts; breast ductal epithelium undergoes pre-neoplastic changes that are recognized histologically and cytologically. This progression of disease is quite similar to that of cervical cancer. Just as an abnormal Pap test is an important tool in identifying cellular changes in a woman's cervix, the same applies to cellular changes within her breast ducts. There is a strong correlation between benign breast disease and the risk of developing breast cancer.

The gynecologist is on the front line of breast health in the U.S. According to the most recent American College of Obstetrics and Gynecology Guidelines for Women's Health Care, Breast Disorders, ACOG Recommendations- "The American College of Obstetricians and Gynecologists recognizes the obstetrician-gynecologist's role in diagnosing and treating breast disease. The College has adopted the goals of assisting and educating obstetrician-gynecologists in the diagnosis and treatment of benign beast disease and in the reduction of mortality from breast cancer." In regular practice, if a woman finds a suspicious lump in her breast, her first call is almost always to her gynecologist, who is then responsible for managing the case.

In the United States, medical treatment for breast cancer exceeds $8 billion per year.[1] The five-year survival rate for localized breast cancer (Stage 0 or 1) is 100% compared to 20% when the cancer has spread to other areas (Stage 4).[2] Finding cancer early saves lives and has financial benefits; finding women at high risk is an important tool in finding breast cancer earlier.

## THE NEED FOR IMPROVED SCREENING FOR BREAST DISEASE

- In the United States, breast cancer is the leading cause of cancer death in women aged 20-59[3]
- 70% of women who develop breast cancer have no identifiable risk factors other than age[5]
- 8 out of 9 women who develop breast cancer do not have an affected mother, sister or daughter.[4]
- A woman diagnosed with breast cancer within 2 years of giving birth has approximately a 50% mortality rate.[6]

Despite the estimated $3 billion spent annually in the United States on breast cancer screening, the death rate from breast cancer has had only modest improvement compared to cervical cancer in the same time period. Much of this decline is due to finding smaller tumors; this trend may not continue given technological limits in detecting smaller lesions.

In contrast, significant progress has been made in reducing deaths from cervical cancer, attributed in large part to the introduction and widespread adoption of the Pap test as a screen for cervical disease, prior to the formation of a cancer.

As Dr. Shala Masood points out, "Primary prevention of breast cancer requires identification and elimination of cancer-causing agents ……. Secondary prevention involves screening individuals who are at increased risk for breast cancer in hopes that early intervention will affect survival."[7]

In the absence of new breast cancer screening technologies, a Stanford University study on future mortality rates recently reported that "even under optimal conditions, it is not likely that the HP2010 (National Center for Health Statistics Healthy People 2010 Initiative) goal for age adjusted breast cancer mortality of 22.3 deaths per 100,000 would be attained. Instead, breast cancer mortality is predicted to level off starting 2005."[8]
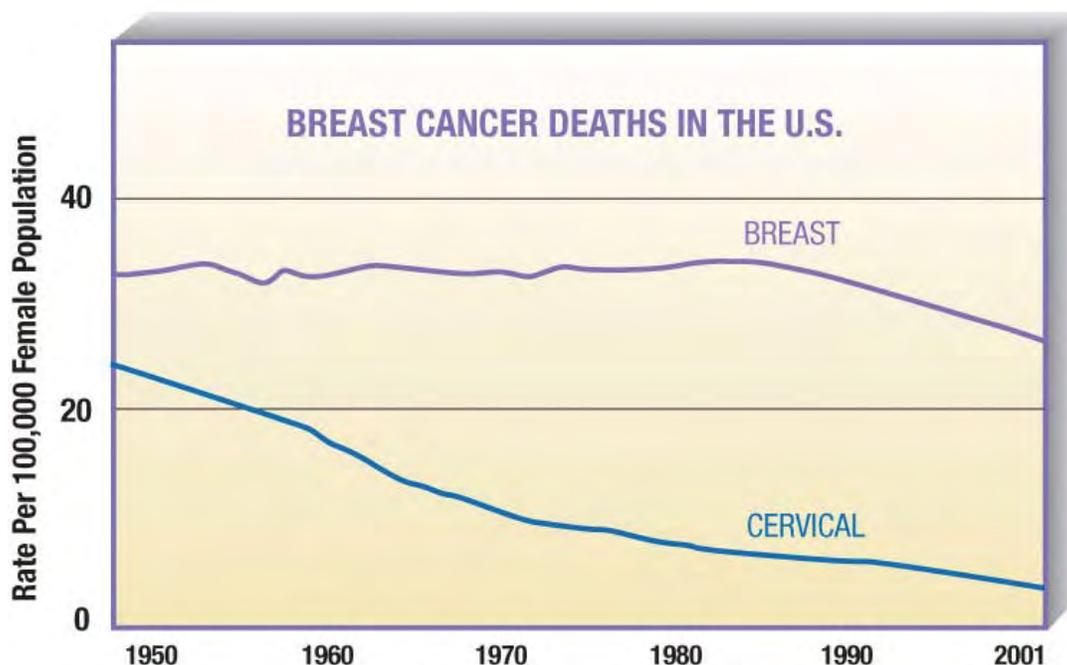
Source: American Cancer Society, Surveillance Research 2005

OVERVIEW OF SCREENING & RISK ASSESSMENT

There are three general categories of disease testing, each having its own uniquely defined purpose.

Diagnostic Testing

A diagnostic test is defined as a specific test used to confirm the presence of disease. In the case of breast cancer, once an abnormality has been identified through screening, diagnostic testing typically includes a biopsy for direct tissue examination and determination of malignancy.

Screening

Screening is generally defined as systematic testing for the early detection of disease in people with no symptoms of the disease. Screening tests are not performed to diagnose a disease, but to identify currently asymptomatic individuals for whom more specific diagnostic testing is warranted.

In developing cancer screening summaries, the National Cancer Institute (NCI) PDQ Screening and Prevention Editorial Board uses the following definitions:

1. Screening is a means of detecting disease early in asymptomatic people.

2. Positive results of examinations, tests, or procedures used in screening are usually not diagnostic but identify persons at increased risk for the presence of cancer who warrant further evaluation.[9]

Numerous attempts have been made to establish clear guidelines for the selection of appropriate patients and tests for screening. A disease should be serious enough to warrant large-scale screening, and treatment before symptoms develop or deteriorate should be of more benefit in reducing morbidity and mortality than treatment later. The estimated prevalence of pre-clinical disease should be high in the population being screened. Breast cancer clearly meets these criteria for screening.

The ideal screening test is inexpensive, easy to administer, and poses little risk and causes minimal discomfort for the patient. In addition, results of the screening test must be valid, reliable, and reproducible.[10] Further, the results should allow clinicians to act upon them.

Risk Assessment

Risk assessment is the process of evaluating whether a person has traits that are known to increase the risk of developing a specific disease- preferably before the disease has developed. Through tailoring an appropriate care-path for these individuals, the ultimate goal is to reduce their risk and prevent the disease from occurring at all.

These goals are consistent regardless of the disease state that is being assessed (heart disease, osteoporosis, cancer, etc.). Various methods to assess risks for a variety of diseases exist and are in general practice today.

The most familiar testing occurs in the cardiovascular areas, as well as for osteoporosis and certain cancers. Examples of risk assessment testing include: family history questionnaires, blood pressure monitoring, cholesterol testing, and bone density testing.

Strategies to manage the high-risk patient exist and are recommended to those found to be at increased risk for disease. These include: enhanced vigilance/ increased screening and surveillance, chemoprevention or other appropriate medical therapies, counseling in lifestyle modification (diet/exercise etc), and surgical intervention, if appropriate.

In managing risk of disease development, patients and physicians are very familiar with medications to treat high blood pressure, high cholesterol, bone density loss, etc. Perhaps not as widely known, there is also a chemopreventive agent (tamoxifen) that is approved by the FDA to reduce the risk of breast cancer in high-risk women. Other drugs are in clinical evaluation and are showing promise.

BREAST CANCER SCREENING OVERVIEW

Every woman is at risk for developing breast cancer. Identified risk factors for breast cancer include several that cannot be changed: gender, age, family history, genetic changes, abnormal breast biopsy, early menarche, late menopause, as well as factors that can be changed including: parity, lactation, alcohol consumption, diet and exercise.

Current Breast Cancer Screening Guidelines

Breast cancer screening continues to generate some of the most intense debates in medicine. Screening recommendations are not standardized, the guidelines are not fully consistent for when to start screening, which tests to use, and how frequently a patient should be screened.

To date, breast cancer screening guidelines include the utilization of a combination of three tests: clinical breast exam, breast self-examination and mammography. Clinical breast examination and the breast self-examination have been long standing fundamentals in breast cancer screening and are recommended by most professional medical organizations, including the American College of Obstetrics and Gynecology as well as the American Cancer Society. The effectiveness of breast self-examination, however, has been challenged in the literature.[11]

The American Cancer Society states: "Women at increased risk should talk with their doctors about the benefits and limitations of starting mammograms when they are younger, having additional tests (such as breast ultrasound or MRI), or having more frequent exams."[12]

The National Cancer Institute specifically states "Women who are at higher than average risk of breast cancer should seek expert medical advice about whether they should begin screening before age 40 and the frequency of screening."[13] Dr. Masood further points out that "with the current availability of tamoxifen as a chemopreventive agent and with the increasing emphasis on early breast cancer detection and prevention, more women seek consultation to determine their risk for breast cancer."[7]

It is clear that the establishment of an individual's risk for breast cancer is important in order for her physician and the patient herself to make informed choices regarding the appropriate approach to screening.

Current Breast Cancer Risk Assessment Methods

Risk assessment does not take the place of routine screening for and diagnosis of breast abnormalities. All women, regardless of their risk assessment, should undergo routine screening as recommended by their healthcare providers.

The determination and differentiation of a "high-risk" woman from a "normal-risk" woman varies. More than 70% of women who develop breast cancer are not defined as high-risk by any definition. This need is further accentuated when contemplating the impact breast cancer has on younger women. Currently, a woman under 40 with no direct family history has only breast exams to help her in assessing her risk. Clearly a method is needed to better identify women at risk of developing breast cancer.

Although four models are currently available to predict the risk of breast cancer, the most commonly used risk assessment tool is the Gail Model. The Gail model was developed by analyzing breast cancer risk factors from a case-controlled subset of participants of the Breast Cancer Detection and Demonstration Project (BCDDP), a 1970's study of women participating in a mammography screening program. This model estimates the likelihood that an individual woman will develop breast cancer over a 5-year period and over her projected lifetime by accounting for 5 significant predictors of a woman's lifetime breast cancer risk: 1) current age 2) age at menarche 3) number of breast biopsies 4) age at first live birth 5) number of first degree relatives with breast cancer.[14]

The Gail model has several limitations – it does not account for risk conferred by the paternal or extended family history and it does not account for well-known pathologic indices of increased breast cancer risk such as lobular carcinoma in situ. Furthermore, the BCDDP patient cohort which was utilized to develop the Gail model, included only women who were undergoing mammogram screening (aged 40 and above).

The American Society of Breast Surgeons states that "The most widely used risk assessment tool, the Gail Model, has been validated as a method of predicting breast cancer incidence in a large population, however, is less accurate at predicting individual risk."[15] Rockhill et al, also determined that the Gail model's discriminatory accuracy at the individual level is particularly suboptimal.[16]

With the identification of specific gene mutations associated with breast cancer development (BRCA1 and BRCA2), there has been consideration of risk assessment using genetic testing. The utilization of genetic testing for screening has been limited by cost, as well as clinical utility. BRCA1 and BRCA2 mutations occur in less than 1% of the general population, and susceptibility from mutations such as BRCA1 and BRCA2 are involved in only 5 to 10% of all breast cancer cases.[17] While a woman with a BRCA1 or BRCA2 genetic alteration is more likely to develop breast cancer than a woman without, most women with BRCA1 or BRCA2 mutation will not develop breast cancer.

Ductal lavage is a minimally invasive ductal cell collection method, which uses a small catheter inserted inside the ducts at the nipple. This procedure is not for routine screening of asymptomatic women, and is limited to use in high risk women. The manufacturer of the FirstCyte™ ductal lavage system claims that their system may yield some benefits over noninvasive NAF cytology.

In contrast to the Cytyc FirstCyte™ claims, The American Society of Breast Surgeons has issued an official statement regarding ductal lavage, which reads in part, "Ductal lavage is a minimally invasive method

of collecting breast epithelial cells for cytologic examination. Because most breast cancer originates from the same layer of epithelial cells that line the milk ducts, it appears that atypical changes in breast epithelial cells will confer similar relative risk increases regardless of the method of collection. There is no reason to believe that the long-term risk associated with atypia diagnosed by ductal lavage will be different from other methods of determining cytologic atypia."[15]
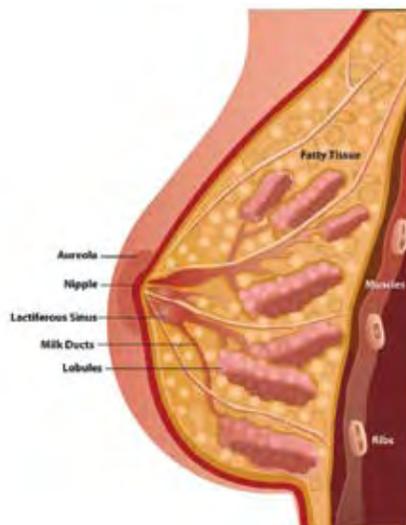
BREAST CANCER DEVELOPMENT

To appreciate the concept of screening for benign breast disease, and the analogy to the Pap test, it is important to understand the disease and it's course of development. Virtually all breast cancer originates in the epithelial cells that line the interior of the milk ducts in the breasts. Like cervical cancer, breast cancer progresses through identifiable stages of development.[18]

BREAST CANCER & CERVICAL CANCER PROGRESS THROUGH SIMILAR STAGES

A major difference between the Pap test and NAF cytology is that most asymptomatic women are nonsecretors, or have acellular samples. These are normal states and confers the lowest risk of developing breast cancer.[18] [19] The major difference in reporting results from a Pap test, and NAF cytology, is that in the Pap test it may be reported that the sample is inadequate for analysis. In NAF cytology this is reported as an acellular sample normal result, which confers the lowest relative risk in patients that are secretors. Further, those patients who do produce NAF and are "acellular" represent the lowest relative risk category of patients producing fluid. In their seminal paper published in 2001, Wrensch, Petrakis et al confirmed that women who do not produce a NAF sample are at a significantly reduced risk of developing breast cancer, compared to women with abnormal cytology.
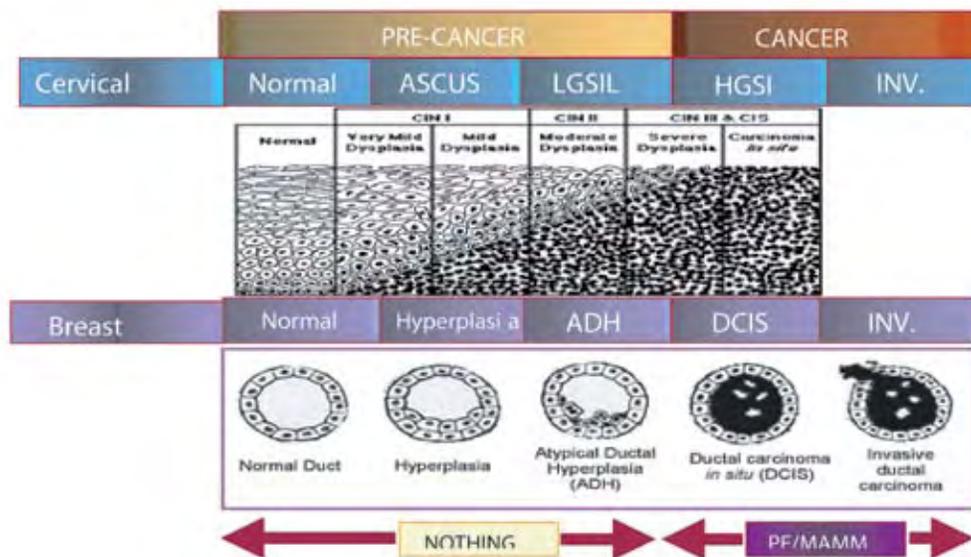
The Wrensch et al findings have been replicated in an independent study reported by University of California Berkley researcher, Dr. Gertrude Buehring. She prospectively reviewed the long-term status of 972 women 25 years after a single NAF collection. She reported that "women with NAF epithelial cells were more likely to develop breast cancer than women with no NAF and this was significant in the age group 18-54.[20] In these studies, a minimum of 10 epithelial cells were required for analysis with no apparent improvement in predictive value based on increased cellular yield.

Like cervical cancer, breast cancer typically grows slowly, taking, on average, 8 years before it can be detected by mammography, or up to 10 years before the lesion is palpable.[21] The inability of current breast screening methods to detect cellular changes at an early stage of development, as the Pap test does for cervical cancer, is one reason for the lack of significant reduction in the death rate of breast cancer.

NAF CYTOLOGY IN SCREENING FOR BENIGN BREAST DISEASE

Screening for benign breast disease is not a diagnostic test for breast cancer. Similar to screening for cervical cancer with the Pap test, NAF screening provides a sampling of the epithelial cells that line the interior of the duct. Like the Pap test, its greatest potential will occur with repeat annual testing and widespread adoption.

Nipple aspiration to collect breast fluid is a simple, acceptable, noninvasive technique that can provide information on the character of the breast epithelium in a significant proportion of women in whom breast biopsy is not clinically or ethically warranted.

This test lends itself to widespread adoption in the primary care setting, since women are used to visiting their gynecologist on a regular basis. The gynecologist is on the front line of breast health, and is the caretaker of the breast. The most recent American College of Obstetrics and Gynecology Guidelines for Women's Health Care, Breast Disorders, states that "Concerns regarding breast disorders are commonly raised at gynecologic or obstetrics visits. Ten percent of women younger than 21 years of age experience complaints related to fibrocystic conditions of the breasts. Such complaints are more common in the premenopausal period. With increasing frequency, women expect their obstetrician-gynecologists to assume responsibility for education, screening, counseling, and treatment concerning benign conditions of the breast."[22] Further, the guidelines of the American College of Gynecology and Obstetrics include a clinical breast exam as part of the annual well-woman visit. If a woman finds a suspicious lump in her breast, she almost always visits her gynecologist prior to any other clinician.

As with the Pap test, the majority of tests will be normal. In the small percentage where atypia is found, risk management strategies are available to help reduce patient anxiety and mitigate the risk of developing breast cancer. [23] An accurate assessment of breast cancer risk can guide clinical decisions about postmenopausal hormone therapy (HRT), when to start mammography and other screening tests, preventive tamoxifen therapy and prophylactic surgery.

Recently, Jeffrey Tice et al, investigated the impact of the addition of NAF assessment to the Gail Model. This study calculated Gail model scores for the Wrensch/Petrakis cohort of 6904 women and compared it to a model that included the Gail variables and NAF cytology results.

The conclusion of this work states "NAF cytology has the potential to improve prediction models of breast cancer incidence, particularly for high-risk women.[24] This supports the premise that population-derived models can be improved through the inclusion of patient-specific information; specifically, the Gail model can be improved with NAF.

Because of the usual slow-growing nature of breast cancer, like the Pap test, repeat screening at regular intervals would be expected to increase the sensitivity of the NAF cytology.

NAF Cytology Enables Early Detection of Cellular Changes Before a Lesion Forms

NAF testing meets all standardized criteria for an appropriate screening technology - there is a significant incidence of breast cancer in the general population, diagnostic and care-path guidelines exist to evaluate women who have benign breast disease. NAF collection is simple, inexpensive, acceptable to patients, and easily accomplished in the primary care setting.
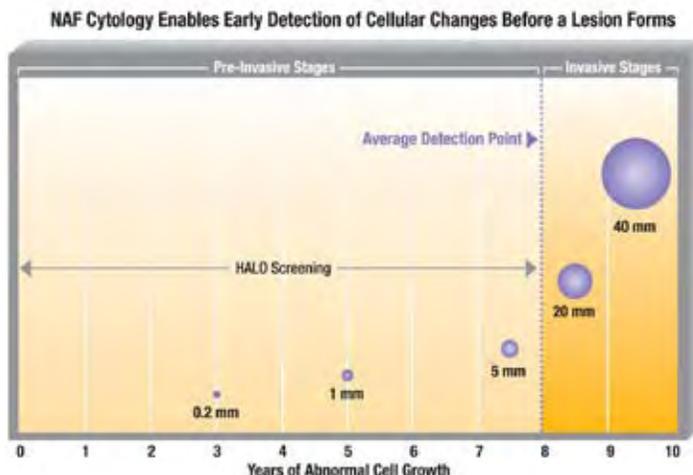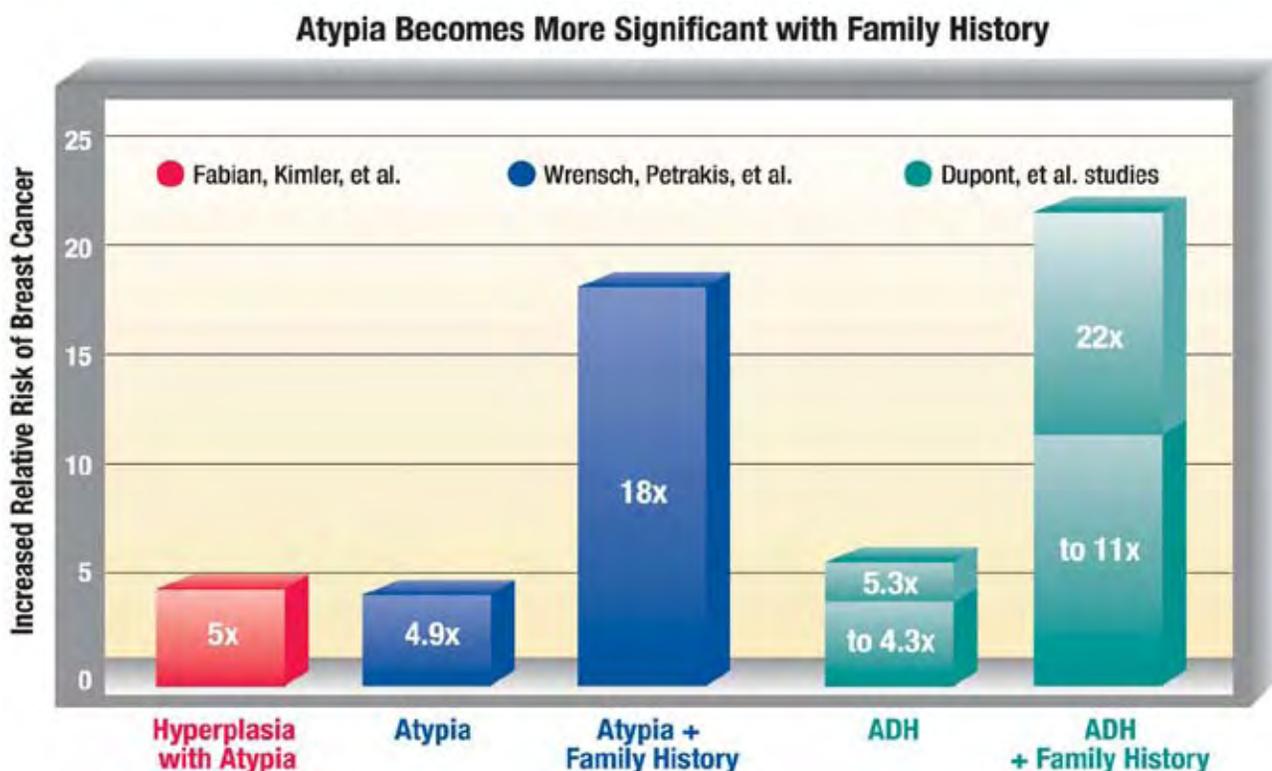
CLINICAL UTILITY OF SCREENING FOR BENIGN BREAST DISEASE

"Benign breast disease is an important risk factor for breast cancer." [25]

With the understanding that virtually all breast cancers begin in the milk ducts, Nipple Aspirate Fluid (NAF) examination allows the determination of benign breast disease, and the attendant increase in relative risk, years before an abnormality becomes visible by imaging or becomes a palpable lesion.

The study of NAF to determine benign breast disease is not new. In 1958, Dr. George Papanicolaou et al described obtaining fluid

Cytologic Assessment-Clinically Validated

Cytologic atypia and hystologically identified atypical hyperplasia (ADH) found through random FNA or biopsy confer similar increase in breast cancer relative risk.

from the breast milk ducts by suction to analyze cell samples. Just like his procedure for detecting normal versus abnormal cells in the cervix (the "Pap test"), this technique demonstrated the ability to find abnormal cells in nipple aspirate fluid (NAF) from within the breast duct. Dr. Papanicolaou concluded that "cytology of breast secretions was valuable in differential diagnosis of mammary diseases and carcinoma" and that "a cytological diagnosis of malignancy was highly reliable."[26] More recently, Hollingsworth stated, "If there were some way to sample cells of the breast, as the Pap smear does for cervical cancer then things would be different." [27]
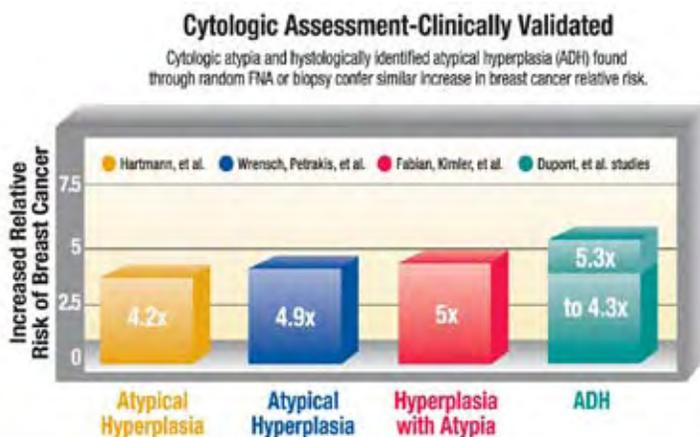
Multiple clinical studies involving over 30,000 patients all reach the same conclusion: benign breast disease, specifically atypia, confers a significantly higher risk of breast cancer. On average, these clinical studies demonstrate the presence of atypia to mean a woman has a greater than 4X (i.e., 400%) relative risk of developing breast cancer than women who do not produce fluid.

Atypia Becomes More Significant with Family History

Increased Relative Risk of Breast Cancer

- ● Fabian, Kimler, et al.
- ● Wrensch, Petrakis, et al.
- ● Dupont, et al. studies

Category	Value
Hyperplasia with Atypia	5x
Atypia	4.9x
Atypia + Family History	18x
ADH	5.3x to 4.3x
ADH + Family History	22x to 11x

The findings of Wrensch, Petrakis et al and the clinical significance of atypical hyperplasia have been validated through independent studies of samples collected from NAF, fine needle aspiration biopsy, or surgical excision.

An official statement from the American Society of Breast Surgeons reads in part "A variety of techniques exist to obtain cells for examination, including open surgical biopsy, fine needle aspiration (FNA), nipple aspirate fluid (NAF), and ductal lavage. In current studies of surgical biopsy, FNA and NAF report a 5-fold increase in the relative risk of developing breast cancer when cellular atypia is found. There is conflicting data on the increased risk of breast cancer when atypia is coupled with a first degree family history of breast cancer. In some studies, this combination confers an 11 to 22-fold increase in relative risk of developing breast cancer."[15]

As stated in the Hollingsworth, Singletary et al. review, "Current comprehensive assessment and management of women at increased risk for breast cancer" in the American Journal of Surgery; "Attempting to gauge a woman's risk for the development of breast cancer was largely speculative at the clinical level for many years, while the epidemiologists and statisticians worked toward objectivity. When the Gail model of breast cancer

risk assessment was chosen for use in the Breast Cancer Prevention Trial (NSABP P-1), the era of quantitative risk assessment in clinical breast care was launched. The success of that trial in achieving a 49% risk reduction in the development of breast cancer reinforced the utility of objective measures of risk."[23]

The current American College of Obstetricians and Gynecologist Guidelines for Women's Health Care, ACOG Recommendations, states "The obstetrician-gynecologist is in a favorable position to diagnose breast disease and should have a good understanding of the natural history as well as the diagnosis and treatment of these conditions. Established screening guidelines should be followed to allow early detection of breast cancer. The final diagnosis of breast mass rests on histological examination, physical examination, imaging, and cytological evaluations which all contribute information but are not definitive.
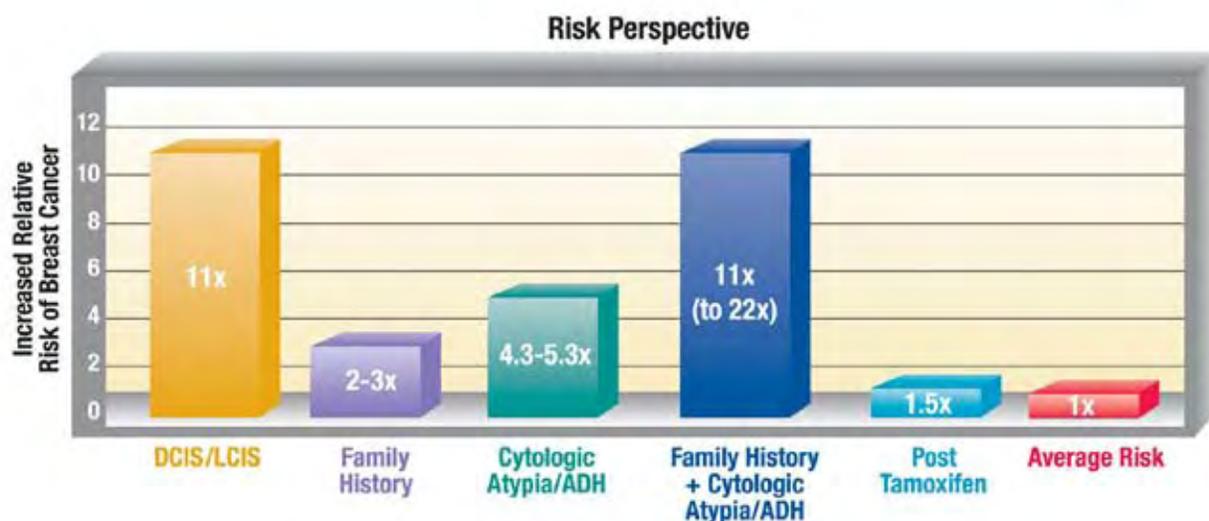
Risk Perspective

The American College of Obstetricians and Gynecologists recognizes the obstetrician-gynecologist's role in diagnosing and treating breast disease. The College has adopted the goals of assisting in educating obstetrician-gynecologists in the diagnosis and treatment of benign breast disease and in the reduction of mortality from breast cancer."[22]

Combined, the clinical record is clear:

- The presence of benign breast disease is an important risk factor
- Family history included with benign breast disease increases relative risk
- The current standard, the Gail Model, can be improved with the addition of NAF cytology
- It is possible to achieve risk reduction in the development of breast cancer
- The obstetrician-gynecologist has a leading role in the screening and diagnosis of benign breast disease in the primary care setting

FUTURE DEVELOPMENTS

Cervical cancer is the second leading cause of cancer death among women worldwide.[28] Introducing cervical screening programs to underserved populations results in a 60% to 90% reduction in cervical cancer rates within three years.[29] This remarkable development can be credited to the multiple treatment technologies which were developed after widespread adoption of the Pap test in identifying women at high risk, such as colposcopy in the 1970's, the Loop electrosurgical excision procedure (LEEP), Cone Biopsy and Cryosurgery. We would expect to see similar treatment technologies developed once screening for benign breast disease becomes more widely accepted.

Cytological examination of NAF is the standard method of analysis today. A large research effort is underway for new methods of NAF analysis, such as Proteomics, RNA, DNA and fluid biomarkers. Work in proteomics and related fields may find the biomarkers in NAF that will further improve the efforts to detect benign breast disease and identify high risk women that will most benefit from pre-cancerous clinical efforts. In searching for benign breast disease today, or finding biomarkers for breast cancer at some point in the future, analyzing NAF significantly changes how the gynecologist can fight the battle against breast cancer.

CONCLUSION

It is clearly established that early detection and treatment of cancer saves lives.   The best example of this is the reduction in mortality attributed to the widespread use of the cervical Pap test as a screen for atypical cervical epithelial cells. Cervical cancer has gone from being the most common cause of cancer death for U.S. women in the 1940's, to not even one of the top ten causes of cancer mortality today. Unfortunately, even with the widespread utilization of breast cancer screening modalities, a similar reduction in breast cancer mortality has not yet been achieved.

The National Cancer Institute states that "More accurate methods for predicting who is at high risk for developing cancer and which treatment option(s) would be most effective on a patient-by-patient basis will contribute significantly to reducing the cancer burden."[30]

While there is a lack of a general consensus regarding breast cancer screening guidelines due to the limitations of existing technologies, there is clear and convincing evidence that NAF assessment has clinical utility for the identification of asymptomatic women who are at increased risk for developing breast cancer.

NAF and the evaluation of the cells found within NAF samples are well studied, validated, objective measures of the intraductal environment, where most breast cancers originate.   Screening for benign breast disease using NAF can be easily incorporated into standard breast health assessment protocols. The obstetrician-gynecologist's role in the primary care setting can facilitate routine screening for benign breast disease at the well women visit, which would address the American College of Obstetricians and Gynecologists guidelines for diagnosing and treating breast disease.

Just as routine Pap test testing has been credited with the reduction in invasive cervical cancer incidence and mortality, incorporating NAF assessment into the routine well-woman examination may ultimately have a similar impact on breast cancer.

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