A n understanding of normal cellular transformation to malignancy is not defined clearly in the study of breast cancer. Deciphering the breast cancer pathophysiologic pathway is necessary for the design of effective cancer prevention strategies (Miller, Bates, & Nabell, 2002). Recent studies showing a significant association between proliferative breast cells and increased risk of breast cancer development highlight the importance of clarifying precursors to disease development (Fabian & Kimler, 2001; Wrensch et al., 2001). Studzinski and Harrison (2002) wrote that precise breast cancer diagnosis, monitoring, and treatment require understanding the control of cell growth, which may lead to the ultimate goal—prevention. Studying the progression from normal cell growth patterns to malignancy has been difficult because of the populations on whom most research has been performed. These populations typically include patients with advanced or metastatic disease. These studies may be limited in their usefulness because events surrounding carcinogenesis already have taken place (Briand & Lykkesfeldt, 2001). Researchers generally agree that carcinogenesis is a result of a combination of inherited susceptibility (germline mutations) and acquired genetic changes (somatic mutations), possibly involving more than 200 genes (Miller et al.; Studzinski & Harrison). This article will discuss the current theories of breast carcinogenesis, emphasizing the progression of normal cells through malignant transformation. Carcinogenesis theory lends support to the idea of using breast epithelial cells to analyze possible precursors to malignancy, leading to enhanced breast cancer risk-prediction models. Types of intraductal sampling techniques will be reviewed, as well as the correlation between tissue cytology and intraductal cytology.

Kimberly Baltzell, RN, PhD(c), is a doctoral candidate in the Department of Physiologic Nursing at the University of California, San Francisco (UCSF), Suzanne E. Eder, NP, RN, is a nurse practitioner at the UCSF Breast Care Center, and Margaret Wrensch, MPH, PhD, is a professor in the Departments of Neurological Surgery and Epidemiology/Biostatistics at UCSF. (Submitted December 2003. Accepted for publication September 3, 2004.) (Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Oncology Nursing Forum or the Oncology Nursing Society.)
Carcinogenesis Theory Overview

Development of Breast Cells

Breast cells begin to complete their growth during puberty. Prior to that time, the mammary gland consists of a fat pad with a primary duct and several ductal branches (Miller et al., 2002). With the onset of menarche, rapid growth occurs, regulated by estradiol and progesterone. The cyclic nature of estrogen exposure continues to act on the breast tissue, yet ductal development stops after puberty is completed.

Although the formation of ducts is over, the duct end buds continue interchanging rounds of growth and cessation in response to hormonal changes produced by the menstrual cycle (Miller et al., 2002). This balance of proliferation and apoptosis (cell death) keeps the breast epithelium in check, and imbalance in this system is the basis of many carcinogenesis theories. The protective effect of full-term, early pregnancy is linked to its association with ductal differentiation, leaving breast cells less vulnerable to these cyclic events that may lead to cancer development.

Estrogen is thought to play a key role in the development of normal breast cells, as well as the development of breast cancer cells (Allred, Mohsin, & Fuqua, 2001). Estrogen is responsible for the elongation of breast ducts and thickening of the epithelium that occurs in puberty (Rosen, 2001). Differentiation of the lobuloalveolar units occurs during puberty, with insulin, progesterone, and growth hormone contributing to the process (McCarty & Tucker, 1992; Rosen). These changes continue through menstrual cycles, pregnancy, lactation, and menopause.

Carcinogenesis Theories

Carcinogenesis is described as a multistage process whereby normal cell proliferation continues unchecked because of aberrant genetic or chromosomal alterations, leading to invasive and metastatic growth (Briand & Lykkesfeldt, 2001).

Cancer of the breast generally is divided into two etiologic origin groups. The first group is cancer that is deemed to arise from strong hereditary sources, primarily a mutation of either the *BRCA1* or *BRCA2* gene (Miller et al., 2002). These germline mutations are believed to be responsible for about 5%–10% of all breast cancers and 65% of all inherited breast cancers. The second group of breast cancers, the remaining 90%, is defined as sporadic and nonfamilial. The processes for both types of cancers, however, seem to be a combination of genetic susceptibility and epigenetic factors (Briand & Lykkesfeldt, 2001). Epigenetic factors are defined as altered expression of genes, although base pairs remain unchanged (Tannock & Hill, 1998). Epigenetics may hold great promise for future interventions, given that epigenetic alterations are reversible and mutations are not.

What is known about carcinogenic pathways? Five individual steps necessary for malignant transformation have been proposed (Hahn & Weinberg, 2002). The steps are independence from mitogenic stimulation, evasion of apoptosis, immortalization, resistance to exogenous growth-inhibitory signals, and angiogenesis.

Mitogenic stimulation independence may occur as a result of the mutation of an oncogene (e.g., ras, HER2-neu), in essence turning on a cell’s ability to override its own growth control checks. Cancer cells do not depend on external signals to make a commitment to proliferate (Hahn & Weinberg, 2002). A breast cancer oncogene of interest is HER2-neu. Mutations of these genes may occur by base substitutions, translocation, amplification, or viral insertions. Whatever the method of mutation or activation employed, the affected cell takes on an enhanced capacity for growth. HER2-neu is an oncogene that frequently is overexpressed in tumors (Miller et al., 2002). Tumors with an abundance of this oncogene often have poorer responses to chemotherapy; however, this is an exciting area of exploration for new treatment modalities.

The evasion of apoptosis might occur as a result of a mutated tumor suppressor gene (e.g., p53), inhibiting the back-up system in place for both cell outgrowth and damaged cell surveillance and repair. Mutated p53 is present in about 30%–40% of human cancers (Dickson & Lippmann, 2000). It is the most frequently studied tumor suppressor gene, which, under normal circumstances, functions as an apoptosis inducer or inhibitor of cell overgrowth. Mutated p53 interferes with normal p53, and researchers have speculated that restoring normal p53 may inhibit cancer growth (Yin, Tainsky, Bischoff, Strong, & Wahl, 1992).

Immortalization results from damage to telomeres (the chromosomal end caps), allowing cells to maintain their proliferative potential indefinitely. Even in the presence of proper nutrients and space, normal cells stop dividing as the telomeres shorten and no longer can stabilize chromosomes. A malignant cell, in contrast, maintains its proliferative potential indefinitely. Molecular mechanisms that inhibit this cell senescence are unclear (Tannock & Hill, 1998).

Resistance to exogenous growth-inhibitory signals works in tandem with one of the other behaviors of cancer cells, independent mitogenic stimulation, allowing cells to proliferate unchecked. All interrupted pathways lead to the hallmarks of malignancy: an increase in cell proliferation and lack of cell death. Finally, the ability of a cell to create additional blood flow appears to be a trait of cancer cells. Circulatory access is believed to be necessary for a tumor to grow larger than two centimeters.

Hormones play a major role in the development of breast cancer. Henderson, Pike, Bernstein, and Ross (1996) wrote that the role of hormones involves their effects on breast cell proliferation and that this increased cell division is vital for the genesis of human cancer. They also cited the activation of oncogenes and mutation of tumor-suppressor genes as necessary for the development of a malignant phenotype. This progression is illustrated in Figure 1.

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Figure 1. Progression to Malignant Phenotype

*Note.* Based on information from Henderson et al., 1996.
Knudson (1971) inspired many carcinogenesis models based on his theory of a multistep process involving an initial “hit” of one of the tumor-suppressor gene alleles, inactivating it, resulting in homozygosity of the chromosome. In addition, cell division is required for all processes leading to breast cancer development. This theory supports a cellular continuum of normal cell appearance through an abnormal proliferative phase, followed by the progression to a malignancy.

Other studies have debated the hypothesis that cancer arises from mutations. Prehn (1994) wrote that mutations may have limited biologic significance. Cancer is hypothesized to give rise to mutations, rather than mutations giving rise to cancer. This theory is based on the epigenetic events surrounding breast cancer development; however, progression from a normal cellular state through abnormalities into malignancy is supported.

Vineis (2003) proposed a Darwinian approach to carcinogenesis whereby epigenetic events influence a cell’s decision to progress to malignancy. The two phases are genetic change followed by selective advantage. The resistance of cells to events such as apoptosis allows for survival of the fittest, allowing mutated cells to adapt more readily to specific environmental niches better than normal cells. Vineis used this hypothesis to explain the difference in international rates of breast cancer because genetic differences account for only a small portion of the variation. Changes in environment as well as the presence of “selective advantage” combine to create cancer rates for specific populations. Willet, Rockhill, Hankinson, Hunter, and Colditz (2000) attributed the increase in breast cancer incidence in women who migrated from low-risk countries (primarily Asian) to high-risk countries (primarily Northern European) to the length of time spent in the high-risk country and adoption of the destination country’s lifestyle.

Briand and Lykkesfeldt (2001) reviewed a decade of work on a human breast epithelial cell line, HMT-3522, to formulate an epigenetic model for breast carcinogenesis. They cautioned that following breast cancer events in advanced cases does not illuminate events related to how carcinogenesis actually begins. They believed that cell culture is an appropriate medium for exploring the events that lead to malignant transformation. The study’s hypothesis suggested that mutation is a necessary step in the carcinogenesis process; however, epigenetic events influence which cells progress to cancer.

The primary assumption made in the study of breast carcinogenesis is the notion of cells progressing on a continuum. Although which cells will progress to a malignant state from a proliferative state (hyperplasia or atypia) is unknown, recent studies showing an increased risk of breast cancer development in women with proliferative findings have suggested a relationship (Wrensch et al., 2001). The ability to invade surrounding breast tissue and metastasize is present in 20%–50% of breast precancers (O’Shaughnessy, 2000). If hyperplasia and atypical hyperplasia are the result of the first several steps in the process outlined by Hahn and Weinberg (2002), identifying these cellular changes prior to circulatory access and commitment to metastasis is critical. The theory of malignant transformation using cell culture supports the concept of malignant conversion (Martin, 1996). By recognizing the progression of abnormal cell development as a continuum, some borderlines have been created between benign states and malignancies. Page and Rogers (1992) disputed the idea of categorizing cells as either benign or malignant. All tumor cells are believed to have sprung from a single cell, and tumor progression is a phenomenon that concludes that benign tumors often evolve into malignancies (Martin). A malignant phenotype arises from the cell population with the most rapid and favored growth pattern. The earlier discussion supports the idea of benign cells revealing changes that may be indicative of a progression to cancer. Perhaps the analysis of breast epithelial cells will illuminate important precursors to breast cancer. Evidence of intraductal and atypical hyperplasia in epithelial cells may allow for prediction and prevention of breast cancer, whereas advanced progression to invasive cancer requires more aggressive vigilance and treatment (see Figure 2.).

### Evaluating Breast Cancer Risk

The most commonly used models for evaluating breast cancer risk are the Gail model, the Claus model, and BRCA PRO (developed by statisticians at the Duke University Institute for Statistics and Decision Sciences). Each model was designed from a different population, and, because the models are not used uniformly in clinical practice, the accuracy of the results is a function of healthcare providers’ knowledge.

The Gail model uses age, age at menarche, number of prior breast biopsies, age at first live birth, and number of first-degree relatives affected by breast cancer to assess risk. Absolute risk is calculated for five years from the time of assessment and lifetime risk up to age 90 (Gail et al., 1989). The model is most appropriate for evaluating risk in women with limited family history of breast cancer. The Gail model uses limited family history of breast cancer and tends to overestimate risk in young women (Kelly, 2000).

Another breast cancer risk assessment model was developed by Claus, Risch, and Thompson (1993). The model addressed several of the alleged shortcomings of the Gail model by incorporating more extensive family history into the analysis. In addition, the Claus model integrates age at diagnosis of breast cancer into its calculations. This information has become more important since the discovery of BRCA1 and BRCA2 mutations, allowing healthcare professionals to consider the possibility of recommending genetic testing. This model is most helpful in determining risk for women with a strong family history of breast cancer. The nonfamily history information included in the Gail model is not considered in the Claus calculations.

<table>
<thead>
<tr>
<th>Goal: Identify women at highest risk so they can be targeted for a proactive risk management strategy.</th>
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<tbody>
<tr>
<td>Normal duct</td>
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**Figure 2. Cellular Progression From Normal Duct Epithelium to Carcinoma**

*Note.* Image courtesy of Cytyc Corporation and affiliates. Used with permission.
Computer programs also have been designed to assess women’s risk of a BRCA1 or BRCA2 mutation. The BRCAPro program is considered to be the most comprehensive estimate of genetic mutation risk and has been compared favorably against the assessment of experienced risk counselors (Euhus, Smith, et al., 2002).

Although each of the models is useful in specific populations, no tool completely captures the many factors believed to contribute to a woman’s risk of developing breast cancer. Viewing cells directly from the breast duct epithelium would allow the addition of biologic information to models of risk assessment. Cells can be obtained through nipple aspiration, ductal lavage, and periareolar fine-needle aspiration (FNA).

**Obtaining Epithelial Cells to Evaluate the Carcinogenic Process**

The ability to study breast epithelial cells for precancerous changes is necessary to evaluate where in the carcinogenic process intervention is most effective. Studies have found a strong association between the presence of hyperplasia and atypical hyperplasia and future breast cancer development give this exploration credibility (Fabian et al., 2000; Wrensch et al., 2001). Tissue biopsy is an unrealistic screening tool in large populations of women. Other less invasive methods of obtaining breast epithelial cells include nipple aspiration, ductal lavage, and periareolar FNA. Although no specific screening guidelines exist at present, all results obtained from these methods are interpreted in the context of a breast cancer risk assessment. Appropriate candidates for epithelial cell study include women with a family history of breast cancer, a known genetic mutation such as BRCA1 or BRCA2, or a prior history of breast cancer (to assess the contralateral breast). Additionally, these women should be asymptomatic with a normal breast examination and screening mammogram.

**Nipple Aspiration**

Obtaining breast epithelial cells through a simple suction technique is known as nipple aspiration. This technique was pioneered by George Papanicolaou, MD, based on cytologic evaluation of cervical specimens and their relationship to cervical cancer (Papanicolaou, Holmquist, Bader, & Falk, 1958). Studies have shown varying degrees of success in obtaining nipple aspirate fluid (NAF) using aspiration. Sauter et al. (1997) concluded that NAF can be obtained in essentially all eligible subjects. Other studies have reported that nipple aspiration is far inferior to other techniques such as ductal lavage in obtaining an adequate number of cells for evaluation (Dooley et al., 2001). Past studies have obtained NAF from as few as 25% to as many as 95% of study subjects (Rose, Lahti, Laaksjo, Kettunen, & Wynder, 1986). Wrensch et al. (2001) noted that obtaining fluid depends on the quantity of fluid present, duct and nipple characteristics, subject age, and the skill of the technician collecting the fluid. Wrensch et al. (1990) found that four important factors were positively related to the ability to obtain breast fluid: age up to 35–50 years, earlier age at menarche, non-Asian compared to Asian ethnicity, and history of lactation. Of interest is the finding that women who do not yield fluid may be less likely to develop breast cancer than women who do yield fluid (Wrensch et al., 1992).

**Ductal Lavage**

Clinically, ductal lavage is used as a risk assessment tool and in the assessment of suspicious nipple discharge. Ductal lavage has its most important clinical application as a risk assessment tool and is best used in a breast cancer prevention program that addresses the broader issues of breast cancer prevention. Ductal lavage is described as a procedure that uses a microcatheter to cannulate identified ductal orifices for the collection of breast epithelial cells for analysis (Dooley et al., 2001) (see Figure 3). The procedure is performed with only topical anesthesia to facilitate cannula insertion. Dooley et al. found that of 507 women tested, a majority (78%) of subjects’ samples were adequate for analysis. The study used comparison groups, examining specimen adequacy of ductal lavage versus nipple aspiration. Of the subjects who underwent ductal lavage, a median of 13,500 cells were collected per duct, with 24% of the subjects showing cellular abnormalities ranging from mild atypia to malignancy. The procedure was well tolerated, with most subjects rating the pain on par with mammography. In addition, ductal lavage was 3.5 times more likely to result in a cytologic diagnosis than nipple aspiration (p < 0.001). The abundance of cells available from ductal lavage makes it a promising tool to enhance risk assessment. Informed consent is obtained prior to the procedure. When educating a woman about ductal lavage, healthcare providers should discuss the procedure, possible adverse effects, possible results, and their implications.

Ductal lavage has five potential cytologic interpretations: benign, inadequate cellular material for diagnosis, mild atypical cells, marked atypical cells, or malignant. In discussions about the implications of ductal lavage, healthcare providers must explain that ductal lavage is not a screening tool for breast cancer. Ductal lavage is not a substitute for screening tests such as mammography. The false-negative rate of ductal lavage has not been defined. Women should be counseled about the possible results of ductal lavage and their implications. When the result is benign, the woman must be...
counseled that several ducts have not been sampled. A benign result gives information on only the ducts sampled. Follow-up would include ductal lavage performed on a yearly basis for continued risk assessment. The frequency of follow-up ductal lavage remains, however, a study question. It currently is based on the frequency of traditional screening methods used in breast cancer, such as mammography.

Limitations of this method include the possibility of infection, injury to the breast, and technical problems that affect cell collection (e.g., dehydration, cold) (Esserman, Adduci, Chew, & Ljung, 2003). In addition to these limitations, ductal lavage is not yet considered the standard of care in breast cancer prevention. Most insurance companies will not authorize or provide reimbursement for ductal lavage. The current fee for ductal lavage is about $900 per duct. During a ductal lavage, as many as four ducts may be accessed. Patients may receive ductal lavage by participating in study protocols, in which case they are not burdened with providing payment.

**Fine-Needle Aspiration**

FNA often is recommended for clinical diagnosis of suspicious breast lumps (Hughes, Mansel, & Webster, 2000). This procedure provides highly accurate information (99% accuracy rate) when performed by skilled practitioners and read by experienced cytopathologists (Barrows, Anderson, Lamb, & Dixon, 1986). In addition to providing diagnostic information about breast lumps, periareolar FNA is being explored as a potential methodology for assessing cellular characteristics leading to increased breast cancer risk (Fabian et al., 2000). Fabian et al. suggested that limitations of other methods discussed earlier point to the feasibility of using periareolar FNA to obtain specimens for risk assessment. In their study, which updated results from a cohort of 480 high-risk women (defined as having one of the following major risk factors: family history of breast cancer, prior lymph node-negative breast cancer, or a prior biopsy indicating atypical lobular or ductal hyperplasia or carcinoma in situ), cytologic evidence of atypical hyperplasia was predictive of breast cancer development. The authors cautioned that this procedure is best employed with women who are premenopausal or those who are postmenopausal and receiving hormone replacement therapy (HRT) because of the limitations of periareolar FNA in obtaining adequate specimens in fatty or invovled breast tissue. HRT delays the development of fatty breast tissue, maintaining a breast structure similar to premenopausal breast tissue. Other studies have used periareolar FNA to enhance individual risk assessment (Euhus, Cler, et al., 2002). Using loss of heterozygosity in breast epithelium as the marker of interest, Euhus, Cler, et al. were able to demonstrate that periareolar FNA may be a feasible method for molecular analysis to define subsets of high-risk women. Masood (1999) emphasized the importance of standardizing both the practice and interpretation of periareolar FNA to justify its use in breast cancer studies, paying particular attention to well-established cytomorphologic criteria (see Table 1).

**Correlation Between Tissue Cytology and Intraductal Cytology**

If any of the methods of extracting breast epithelial cells are to be useful in assessing risk, a strong correlation must be present between findings in tissue biopsy (the current gold standard for analyzing breast cell changes) and less invasive means of obtaining those cells. Because 90% of breast cancers are believed to be of ductal-lobular origin, analyzing cells from the ducts to determine whether any precancerous changes have taken place is logical. King, Chew, Petrakis, and Ernst (1983) assigned strict criteria for evaluating cytomorphologic changes in breast epithelial cells. The most important finding of their study was the significant association between atypical hyperplasia found in epithelial cells in nipple fluid and atypical hyperplasia found in biopsy tissue. The authors also concluded that the relationship between atypical hyperplasia in the two sources was most significant for women with more marked changes. Using epithelial cells from breast fluid was less reliable for women with benign breast disease. In addition, the study was one of the first to compare cytology between nipple fluid and biopsy using morphologic terms applied to tissue biopsy. One study, which evaluated cells from nipple aspiration only, found cytomorphic and histologic correlation only when ductal carcinoma in situ and extensive nipple involvement were found in the tissue biopsy (Krishnamurthy et al., 2003). This may be a limitation overcome by using one of the other methods outlined earlier, such as ductal lavage or FNA.

**Sensitivity and Specificity Issues**

To provide meaningful information, methods of obtaining epithelial cells must have acceptable levels of sensitivity and specificity. Sensitivity is defined as the ability of the test to truly determine the presence of a real breast cancer precursor, and specificity is the ability of the test to correctly identify cells that would not lead inevitably to breast cancer (Last, 2001). Sensitivity is the rate of true positives; specificity is the rate of true negatives.

Ductal lavage yields abundant epithelial cells for evaluation (Dooley et al., 2001). Cytologic studies are performed easily on these specimens; however, what to do with the information remains unclear. Recent studies have questioned the sensitivity and specificity of this method, suggesting that it remains a breast cancer detection method best used in clinical trials (Domchek, 2002). Dooley et al. found ductal lavage to be 3.2 times more sensitive in detecting abnormalities in breast cells than nipple aspiration (79 versus 32 breasts) in a study of 507 women. Sensitivity is less of a concerning issue than specificity in ductal lavage. Until breast carcinogenesis theory is elucidated further, what actions to take in response to abnormal findings remains unclear.

Nipple aspiration is less invasive than ductal lavage; however, the number of cells available for study from aspiration is limited. Dooley et al. (2001) compared cellular yield between ductal lavage and nipple aspiration and found a significant difference (13,500 cells versus 120 cells, respectively). Additional studies have found that cytologic evaluation of nipple aspiration is not useful given its low predictive value (Krishnamurthy et al., 2003; Shao & Nguyen, 2001). The authors speculated that if breast cancer was present, the ducts probably were obstructed and cancer cells would not be aspirated. Because the precise precursors to carcinogenesis have not been defined clearly, searching for more accurate tumor markers is recommended as a priority.

FNA is associated with a high rate of accuracy under optimal circumstances (Barrows et al., 1986). A study of 1,158 FNAs concluded that the procedure is sensitive and specific...
when used to evaluate clinically suspicious breast masses (Ariga et al., 2002). In groups of women divided by age (40 years and younger versus 41 years and older), sensitivity was 99% and 98% and specificity 99% and 97%, respectively. Having established a cytologic and histologic correlation in FNA, its usefulness as a risk assessment tool is being studied (Fabian et al., 2000).

Sensitivity and specificity traditionally have been used as markers to evaluate the accuracy of a diagnostic tool. These evaluation standards are not applied easily to the use of breast epithelial cells as markers of breast cancer risk versus as markers of actual breast cancer. An important distinction must be made between using breast epithelial cells for the purpose of diagnosis versus the use of the cells as a measure of risk assessment. At the present time, these cells are best used as an enhancement to risk assessment, not as an independent diagnostic tool. Therefore, measures of sensitivity and specificity must be defined in relation to the risk assessment goals of breast epithelial cell evaluation.

### Table 1. Pros and Cons of Breast Epithelial Cell Extraction Methods

<table>
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<tr>
<th>Method</th>
<th>Description</th>
<th>Pros</th>
<th>Cons</th>
</tr>
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| Nipple aspiration           | Use of simple suction technique employing a handheld device; droplets of nipple fluid are collected via capillary tube for analysis. | - Completely noninvasive  
- Inexpensive  
- Can be done by any trained healthcare professional  
- Can be collected outside the clinical setting | - Ability to collect fluid depends on ability of healthcare professional if woman has secreting ducts.  
- Fewer cells are available for cytologic diagnosis compared to ductal lavage. |
| Ductal lavage               | Use of microcatheter to cannulate ductal orifices; saline wash removes cells in collection container for analysis. | - Performed with a topical anesthetic only  
- Yields large number of cells for analysis | - More invasive than nipple aspiration  
- Low risk of infection or injury to the breast  
- Not all ducts are sampled. |
| Periareolar fine-needle aspiration | Use of a small needle to remove cells from the breast tissue for analysis. | - Do not need intact ductal system to obtain cells for analysis | - Invasive procedure  
- Accuracy of readings  
- Depends on experience of healthcare professional performing procedure |

Using Ductal Fluid to Explore Carcinogenesis

The paths to carcinogenesis appear to be varied and numerous. Only by viewing the process as a work in progress will researchers develop interventions that may allow for true cure or prevention. As the majority of breast cancer cases are not the result of known germline mutations, an understanding of the genetic and epigenetic events that lead to malignancy is necessary to further the creation of new treatment modalities. This understanding may be advanced by viewing cells to sort out true precursors from benign changes. Access to breast epithelial cells via the nipple orifices or through periareolar FNA is pivotal for studying women who have developed breast cancer as well as those who have not developed it. Perhaps the study of changes in breast epithelial cells over time will allow researchers to begin to specify when premalignant changes take place and the events related to those changes. The methods outlined in this article for obtaining breast epithelial cells may determine when proliferative cells progress to something more ominous or regress back to normal. The carcinogenic continuum may be illuminated by viewing cytologic or molecular changes over time that are correlated with cancer development.

Reevaluating the use of current breast cancer risk assessment models by incorporating a more biologic component may enable healthcare professionals to more accurately assess risk. Nipple aspiration and ductal lavage are important adjutants to risk assessment that could be performed easily in an outpatient setting. RNs and advanced practice nurses who work in the area of breast cancer risk assessment could perform these procedures safely and competently and inform patients regarding results in the context of individual risk assessment. Currently, nurse practitioners are trained by surgeons to perform ductal lavage and nipple aspiration. Institution-specific protocols are developed jointly by nurse practitioners and surgeons and guide practice. The skill set required is similar to that of placing an IV catheter.

Nipple aspiration, ductal lavage, and periareolar FNA are tools that hold great promise for exploring the breast carcinogenesis process. Through the observation of cellular and molecular abnormalities, opportunities for intervening in carcinogenesis will be revealed.

Author Contact: Kimberly Baltzell, RN, PhD(c), can be reached at kbaltzell@earthlink.net, with copy to editor at rose_mary@earthlink.net.

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cancer risk for women with a first degree family history of ovarian cancer. 

*Breast Cancer Research and Treatment, 28, 115–120.*


