

The role of nipple-aspirate fluid cytology in breast-cancer risk screening

By Joel Bentz, MD

The current standard for screening women to assess their breast health and risk of developing breast cancer is review of family history, physical breast exam, plus regular mammography for women over 40. Clinical experience has shown, however, that none of these methods is very effective in identifying cancers at their earliest stages. By the time the cancer is detected by either physical examination or mammography, the woman may have had the disease for years, with significant risk of serious consequences — including death. There is a growing need to identify those women who are at increased risk for developing breast cancer and focusing resources on prevention strategies and earlier detection for these women.

It is generally recognized that benign intraepithelial lesions of the breast ductal system is a biomarker with the closest biologic association to increased risk of developing breast cancer. Previous studies of open breast biopsies have demonstrated that the presence of atypical epithelial cells is associated with a four- to fivefold risk of developing future breast cancer.¹ Multiple long-term studies show that the identification of atypical epithelial cells found in cytology specimens, such as nipple aspirate fluid (NAF) or fine-needle aspiration (FNA), is also associated with an elevated risk of developing breast cancer, as was observed with open biopsies.^{2,3} Today, cytologic examination could be used to identify a subgroup of asymptomatic women who are at increased risk for breast cancer.^{4,5} The majority of these women have no established risk factors for the development of breast cancer. The finding of atypia can alert the treating physician that further surveillance and, in selected cases, preventive efforts may be indicated.

The advent of new acquisition techniques over the past decade makes breast sampling more accessible for healthcare providers and more acceptable for patients. The emergence of these new methods to collect breast samples has meant that laboratories and cytology professionals need to be knowledgeable in the

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LEARNING OBJECTIVES

Upon completion of this article, the reader will be able to:

1. Understand the traditional means of assessing breast-cancer risk, and explain their shortcomings in identifying patients who could benefit from preventive approaches.
2. Describe the longstanding cytomorphology of breast specimens (breast epithelial atypia biomarker) as it relates to the Papanicolaou or “Pap” technique.
3. Discuss the state of technology for breast-fluid collection.
4. Discuss best practice for nipple aspirate fluid (NAF) specimen acquisition, transport, and labeling, as well as slide preparation and staining, and slide screening and interpretation.
5. Describe the recommended classification system for reporting NAF results.

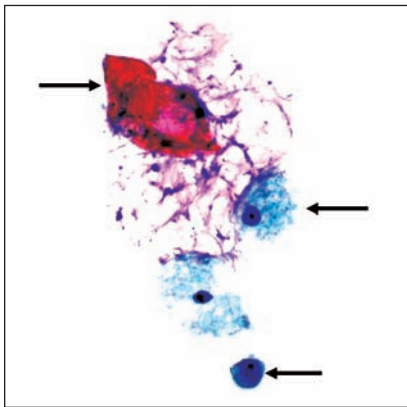


Figure 1. NAF Category 0. Negative for atypical or malignant cells. Rare benign (non-hyperplastic) ductal epithelial cell (arrow). Foam cells and proteinaceous debris noted in the background (arrow). The squamous epithelial cell (arrow) is a contaminate from the breast or nipple surface. ThinPrep-Pap stain.

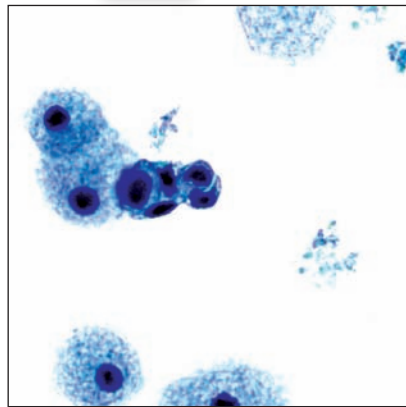


Figure 2. NAF Category I. Benign — normal ductal epithelial cells identified. Foam cells with small cluster of ductal epithelial cells. ThinPrep-Pap stain.

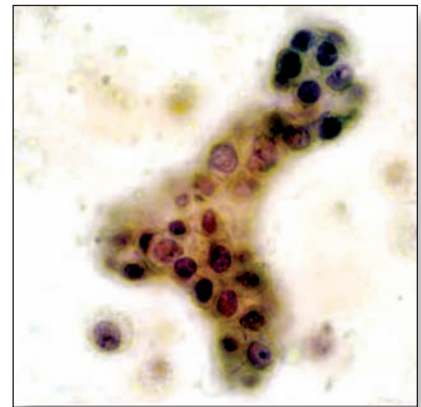


Figure 3. NAF Category II. Benign — hyperplastic ductal epithelial cells identified. Note the slight nuclear enlargement and fine, smooth chromatin, which is evenly distributed. Nucleoli are sometimes present. Millipore Filter-Pap stain.

examination of exfoliative cytology specimens of the breast. The rationale for breast-health screening using cytology is explored here, along with a review of collection methods and guidelines for interpretation and reporting of such specimens.

The need for an effective risk screen

While progress has been made in detecting and treating breast cancer, the disease remains, other than skin cancer, the most common cancer for women in the United States. It accounts for about 26% of all cancers found in U.S. women. An estimated 182,460 cases of invasive breast cancer were expected to be found in 2008, with 40,480 women dying from it.⁶

Despite the high total number of deaths, breast-cancer death rates have been moving downwards in recent years. Improved detection methods (e.g., regular mammograms) are credited with much of the decline in mortality rates, because they help find tumors before those can be felt during a manual breast exam by a physician or a woman herself. Earlier detection means the tumor may be smaller and more treatable, with fewer consequences. But mammograms are not very effective in women with dense breasts, and they are not very helpful if the goal is breast-cancer prevention. Mammograms are not useful for identifying patients who have a significant risk of developing the disease in the future and who might, thus, benefit from preventive care or more frequent observation.

Few women younger than 40 get regular mammograms, yet they are at much greater risk of dying from the disease should they contract it. This is a cohort that would especially benefit from risk screening. Women in the 40 to 50 age range are also prime candidates for risk screening. Although mammograms are widely recommended for women 40 and older, they are not as effective in women under 50, because high breast density interferes with the detection of abnormalities.

In recent decades, more effective means of preventing breast cancer have been developed for women known to be at high risk for the disease. The less aggressive options include increased surveillance (e.g., more frequent clinical breast exams and breast self-exams); lifestyle changes regarding diet and exercise; and

use of enhanced imaging modalities. In some cases, more aggressive means such as chemoprevention (e.g., Tamoxifen) may be used. The National Surgical Adjuvant Breast and Bowel Project (Breast Cancer Prevention Trial) showed that administration of tamoxifen reduced the risk for invasive and non-invasive breast cancer by almost 50% in all age groups. In the subset of patients with ductal atypia, prophylactic tamoxifen reduced breast-cancer incidence by 86%.⁷ Established algorithms also exist for guiding case management of women identified with higher breast-cancer risk.⁸

Despite the availability of these preventive approaches, traditional means of assessing breast-cancer risk are not very useful in identifying patients who could benefit from them. Between 50% and 70% of women who develop breast cancer have no identifiable risk factors, other than age, using today's standard risk-assessment tools. Statistical risk-assessment methods — such as the Gail model, which uses a woman's personal and family medical history to estimate risk — have utility more as an epidemiological tool than for identifying personalized risk.⁹ For example, the Gail model is known to underestimate risk in some patient populations and often overestimates risk in others.¹⁰ Because these traditional methods have proved inadequate, there has been an ongoing interest in developing readily accessible biomarkers that can identify breast-cancer risk with an acceptable degree of individual predictive accuracy. These biomarkers should ideally be present in a reasonable number of at-risk individuals, minimally invasive, and reversible with prevention interventions. A number of risk biomarkers have been identified (e.g., mammographic breast density, serum insulin-like growth factor-I and its binding protein, insulin-like growth-factor-binding protein, serum levels of estradiol and testosterone in postmenopausal women, and breast-tissue markers).

Among those potential tissue biomarkers, findings of epithelial atypia have long held tremendous promise. Numerous prospective studies involving more than 20,000 women have shown ductal atypia, either cytologic or histologic, to be an effective predictor of breast-cancer risk in individuals.^{1,2,11-13} Until recently, a clinical model in which benign breast tissue

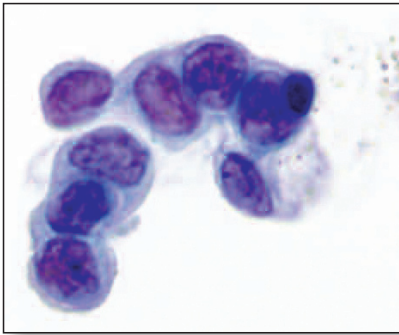


Figure 4. NAF Category III. Atypical ductal epithelial cells. The nuclear/cytoplasmic ratio is increased. The ductal cell nuclei are enlarged, with hyperchromatic nuclei. The chromatin is more coarse, but remains evenly distributed. The nuclear contours are slightly irregular. ThinPrep-Pap stain.

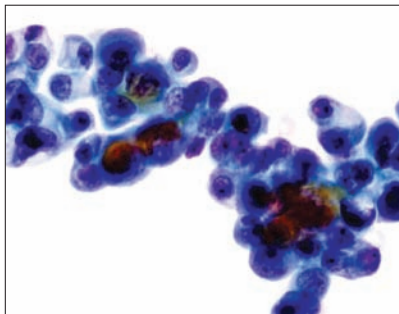


Figure 5. NAF Category III. Atypical hyperplasia. Atypical ductal epithelial cells in large cohesive fragment. Nuclear crowding and overlap, with atypical ductal cells. ThinPrep-Pap stain.

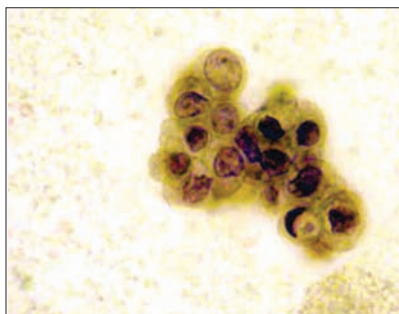


Figure 6. NAF Category IV. Suspicious for malignancy. Group of highly atypical ductal epithelial cells with dark, hyperchromatic chromatin. The chromatin is more irregular in its distribution, and coarsened. Note the nuclear contour pleomorphism is greater. There are prominent nucleoli. Millipore Filter-Pap stain.

can be easily obtained and repeated over time for risk assessment has remained elusive. Open biopsies of palpable masses or mammographic abnormalities over time is impractical because the lesion of

interest is removed on the first biopsy sample. Repeated random open biopsies for risk surveillance are more logical, but few women would subject themselves to such a procedure, especially over many years, and such biopsies may contain little of the terminal ductal-lobular units unless they were specifically directed. Random periareolar FNA is simple and inexpensive, and may be repeated with minimum morbidity. The majority of FNA samples have been noted to be cellular in previously identified high-risk women. The cytologic identification of proliferative breast disease with atypia in these specimens has been associated with future cancer development. Finally, atypia in NAF has been shown to have a prospective association with increased breast-cancer risk. Concerns in the past, however, were that these samples may be acellular and that not all women readily produce fluid.

The reason cytology sampling has not been used more widely until recently has to do with the difficulty of collecting breast samples. There are now emerging newer, more acceptable collection methods that overcome these difficulties. Before describing these technologies and alternative methods, it is helpful to examine the rationale for this tissue biomarker in more detail.

Validation of breast epithelial atypia biomarker

Our current understanding of cytomorphology of breast specimens was first reported more than 50 years ago. Dr. George Papanicolaou and colleagues published their research with exfoliative cytology samples of the breast in 1958.¹⁴ Dr. Papanicolaou carefully illustrated the cellular composition of both nipple aspirates and spontaneous nipple discharges in asymptomatic and symptomatic women. Dr. Papanicolaou proposed a five-tiered classification system for these cytologic findings. He concluded that, despite its limitations, cytologic examination should be performed in every case of spontaneous discharge. He suggested that the Papanicolaou technique could be used to detect carcinoma at an earlier, pre-clinical stage. This could be incorporated into the physical examination with little loss of time and without danger to the patient.

The logic of Papanicolaou's observations stemmed from breast anatomy and what is known about the genesis of breast cancer. Ductal epithelial cells compose the lining of the roughly 12 ducts that end in a woman's nipple. These ducts are part of a branching series of ductal-lobular units within the breast. It is believed that most invasive breast cancers begin from pre-cancerous lesions in these epithelial cells. These changes are now widely recognized to have a closer biologic association to elevated risk of developing breast cancer than other risk biomarkers.

The reliability of cytologic atypia as a breast-cancer risk biomarker is well established in the literature, starting with a major prospective study. In that research, Wrensch and Petrakis, et al, of the University of California-San Francisco studied 2,701 women followed for an average of 12.7 years and showed that asymptomatic women with atypia in NAF had a breast-cancer risk 4.9 times greater than women who did not yield NAF.¹¹ In 2001, a follow-up study confirming the original work was published based on following 7,600 women for 21 years.¹²

Three other studies found similar relative risks (RR) for women with atypia discovered through open biopsy or FNA:

- DuPont and Page (*NEJM*, 1985) found 5.3x RR with biopsy-proven atypia in 3,303 women followed for an average of 17 years.¹³
- Fabian (*JNCI*, 2000) found 5x RR with atypia discovered by FNA in 480 women followed for four years.²
- Hartmann (*NEJM*, 2005) found 4.2x RR with biopsy-proven atypia in 9,087 women followed an average of 15 years. Women under 45 had a 6.99x RR.¹
- Two recent studies looked at risk associated with the presence of epithelial cells in NAF, regardless of whether the cells were normal or atypical:
- Buehring, et al (*Epidemiology*, 2006) found 1.92x RR in 972 women followed for 25 years.¹⁵
- Baltzell (2008) found a 1.9x RR in 946 women followed for 20.7 years.¹⁶

The National Cancer Institute, the American Cancer Society, and the American Society of Breast Surgeons¹⁷ have all recognized cytologic atypia as an objective, valuable biomarker of breast-cancer risk.

State of the technology for breast-fluid collection

Mammary samples can be collected either invasively or non-invasively. Non-invasive methods include a manual-extraction approach and newer automated system, which appears to address problems associated with the manual method. The manual-collection method begins with the application of heat and massage to the breast, followed by use of a suction cup and attached syringe, or, in some cases, a breast pump. The complexity of the procedure is such that a physician is often required to perform it. The method can also be time consuming. For these reasons, providers often do not consider it practical, and its use is mainly in the research setting.

Next, an automated instrument uses the successive application of heat, massage, and suction, but a machine similar to a breast pump performs the cycle automatically. Adjustable breast cups fitted with disposable sample-collection cups are placed on both breasts simultaneously and are then adjusted around the nipple and areola. No topical anesthetic is needed beforehand. Because the procedure is automated, it takes only five minutes and can be performed by an assistant rather than a physician. These qualities make it more suitable for settings such as primary-care or OB-GYN offices. The system has undergone 510(k) clearance by the U.S. Food and Drug Administration (FDA). The approval states that "The collected fluid can be used in the determination and/or differentiation of normal versus premalignant versus malignant cells." A published prospective observational clinical trial found that the device was well tolerated, safe, and effective.¹⁸ Proctor, et al, demonstrated that results from NAF collected via the automated system are stratified equivalently to NAF samples collected manually (i.e., have the same percentage of non-yielders, acellular samples, atypia, and so on).

Nipple fluid can be obtained from many women, with reports of NAF production ranging from 25% to more than 95% of asymptomatic women.¹⁸ Breast tissue and ductal systems are influenced by hormones, which affect the ability to produce NAF. Other intrinsic breast characteristics can influence the ability to obtain NAF. On average, about 50%

Table 1. Breast cytology sample-collection methods.

	Periareolar FNA	Ductal lavage	Nipple aspirate fluid - Manual	Nipple aspirate fluid - Automated
Device	Syringe + needle	FirstCyte Micro Catheter (Hologic)	Syringe + suction cup	FDA-cleared system
FDA approval	N/A	Yes, high-risk only	No	Yes, 510(k)
Cytology interpretation	Routine cytopathologic evaluation	Unsatisfactory, benign, atypical, or malignant cells (certification required)	Unsatisfactory, benign, atypical, or malignant cells	Category 0-IV (negative, benign, hyperplasia, atypical, suspicious)
Performing	Physician	Physician (certification required)	Physician	Medical assistant
Time	45 minutes	1 hour	20 minutes	5 minutes

of women produce fluid. Women who do not produce are termed "non-yielders." They have the lowest risk of developing breast cancer. Those that do produce NAF commonly have an acellular specimen; that is, no epithelial cells were exfoliated with the fluid. This is a normal result indicating that the woman's risk is only slightly higher than someone who does not produce fluid. The epithelial cells lining the breast ducts are constantly producing and reabsorbing NAF at similar

rates, so often there is no accumulation of NAF to collect. Slight changes in the ducts can cause the cells to produce more NAF than they can absorb, resulting in a slight accumulation. Again, studies have shown that these women (i.e., "non-yielders") have a statistically decreased breast-cancer risk compared to women who do yield NAF.^{11,12}

Invasive approaches to collecting specimens include random periareolar FNA and ductal lavage (DL). Some of

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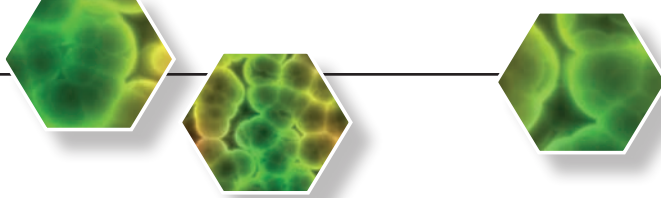
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the earliest descriptions of the FNA technique were published by Drs. Ward and Marshall in a cohort of high-risk women from the University of Utah in 1990.¹⁹ After the breast skin is numbed with a local anesthetic, the needle is inserted into each quadrant of the breast, approximately one centimeter (1 cm) from the areola. The needle is then repositioned eight to 10 more times in all areas within the quadrant. The procedure is generally performed by an interventional radiologist or cytopathologist, making it impractical for wide clinical use.

Like FNA, DL is not considered a practical option for risk screening of the type discussed herein, for multiple reasons. Most importantly, its FDA clearance limits its use to women already known to be at high risk.²⁰ In other words, it is not indicated for women who have no known risk factors, a cohort that constitutes 50% to 70% of women who will develop breast cancer, the group most in need of risk assessment. Another limitation of DL is that clinicians must complete a specialty-training program to perform the procedure. The procedure involves the insertion of a small catheter into the ducts emerging from the nipple, flushing with saline,

and subsequent collection of the flushed saline containing any ductal cells. Pathologists must also be certified to evaluate and report results because evaluation involves precise differentiation between different grades of atypia.

Table 2. Automated nipple-aspirate fluid classification system

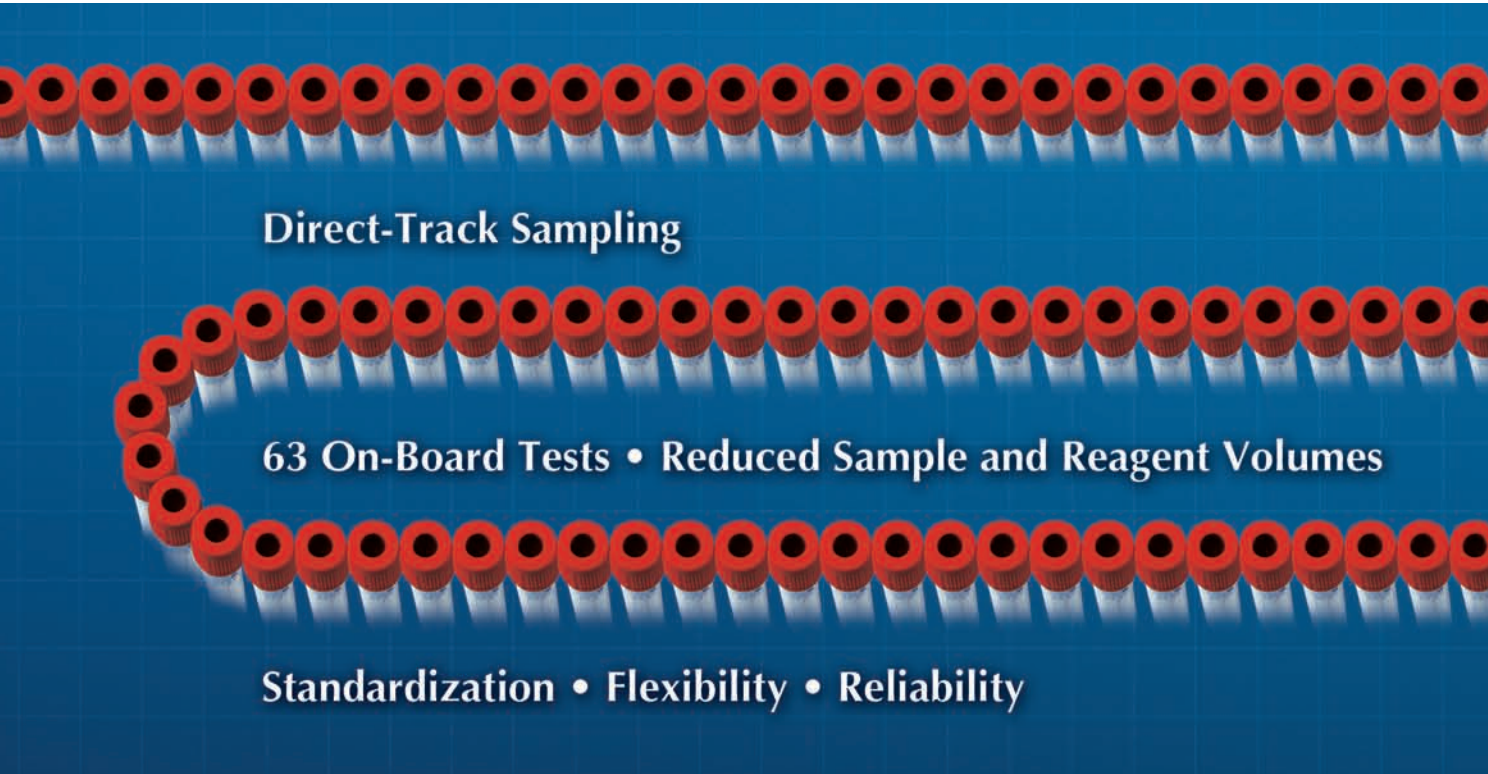
Category	Interpretation	Characteristics
Category 0	Negative for atypical or malignant cells.	No or <10 ductal cells. Foam cells, or foam cells in a background of proteinaceous debris. Acellular slides with only proteinaceous debris (see Figure 1).
Category I	Benign — normal ductal epithelial cells identified	Normal ductal epithelial cells, with or without foam cells. Some ductal cells will display apocrine metaplasia (see Figure 2).
Category II	Benign — hyperplastic ductal epithelial cells identified	Cell distribution predominately in cohesive groups with >10-50 cells. Minimal nuclear changes. Fine chromatin (see Figure 3).
Category III	Atypical	Distinct nuclear enlargement, increasing N/C ratio, irregular nuclear borders and nuclear variation. Course chromatin. Prominent chromocenters (see Figures 4, 5).
Category IV	Suspicious for malignancy	Single cells and groups of cells with nuclear features suspicious for cancer (see Figure 6).

In contrast, cytological examination of NAF does not require special certification because the results are used for risk stratification only, not pathologic diagnosis. Results are reported in just five categories focused on the presence or absence of atypia with no need to determine grades of atypia. Therefore, most laboratories with routine cytology capability can evaluate and report NAF status after brief training.

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Spontaneous nipple secretions or discharges

Spontaneously secreted or discharged fluid is different from NAF, both for purposes of pathologic evaluation and in the clinical origins. Spontaneously secreted or discharged fluid is a symptom, whereas the NAF discussed herein is collected from asymptomatic women. Although the causes are not well understood, spontaneous secretions can be symptoms of conditions ranging from mastitis and hormonal imbalances to tumors. Most likely, they occur because of endocrine-related changes or use of particular medications.

It must be emphasized that a cytologic evaluation does not in any way replace mammograms, manual exam, or other diagnostic tests. Nipple aspirate fluid cytology results are not diagnostic. Breast NAF is a means of risk assessment, and its routine clinical use should be confined to asymptomatic women with a normal breast examination. Although breast NAF cytology was designed to detect cytologic changes associated with benign breast lesions, there will certainly be breast cancers which cannot be detected by NAF. In the absence of information on sensitivity and specificity for detection of carcinoma, NAF should be considered a method of risk assessment only, and this must be emphasized to women undergoing the procedure to ensure that a benign NAF does not result in false reassurance, causing a woman to ignore symptoms of breast cancer or neglect screening tests of proven value such as mammography.

Best practice: specimen acquisition, transport, and labeling

The discussion from this point forward assumes the use of an automated system for collecting NAF because of its practical advantages over other methods. Collection will most likely take place in a primary-care or OB-GYN office or at a breast center. NAF evaluation is particularly appropriate for asymptomatic, pre-menopausal women ages 25 to 55 — the same group for whom cervical-cancer screens are recommended. Much of the rationale for this age range, including breast density and the virulence of cancer in younger women, has already been described. Another relevant factor is that post-menopausal women tend to produce less NAF. There is no specific cutoff age at which the test is suddenly not useful. Post-menopausal women can continue to benefit from NAF evaluation as long as they produce NAF, though the test is less meaningful for older women who are non-yielders. Also, NAF evaluation can begin earlier than 25 for patients with other known risk factors. As with cervical Pap tests, breast-health screening would ideally be recommended as part of a woman's regular health check-up.

Specific directions for handling samples prior to submission to the laboratory are as follows: Samples are collected with a custom, non-cell-binding swab that is supplied as part of the collection kit for the automated device. The swab is placed directly into a non-gyn liquid-based cytology (LBC) fixative vial for transport to a pathology lab.

Clinicians have the option of submitting separate vials for

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each breast's sample, or submitting the samples together in a single vial. The argument for submitting separate vials is that if an actual malignancy is revealed, the clinician will want to know which breast is affected. Absent this possibility, there is no advantage for risk-assessment purposes to submitting separate vials. A woman with atypia in one breast has a nearly equal chance of developing breast cancer in either breast due to the "field effect" whereby both breasts together constitute a single organ. Because of the diagnostic circumstance just mentioned, labels should indicate whether a patient's two samples are pooled or placed in different vials.

Best practice: slide preparation and staining

It is preferable to prepare NAF slides with liquid-based cytology, or LBC, technique, using cellular concentration and monolayer slide method. This approach aids interpretation, because it optimizes cellularity. While cytocentrifugation yields acceptable slides, a portion of the sample might not be deposited onto the slide, so some cells may be lost with this method. Cell block preparation should be avoided with NAF samples because the samples are normally hypocellular. All breast-cytology slides should be stained with the Papanicolaou stain.

Best practice: slide screening and interpretation

Macrophages (foam cells), squamous cells (nipple contaminate), ductal epithelial cells, and less frequently, inflammatory

cells and blood are among the cell types pathologists will observe in NAF samples. Only a small percentage of NAF samples from asymptomatic women — from 0.7% to 2.7%, according to studies — are likely to display atypia. "Abnormal" samples are those that display atypia, suspicious cells, or malignant cells. These samples are somewhat easier to differentiate than "normal" samples, which include those with acellular, normal epithelium, or hyperplasia. In normal, asymptomatic patients, NAF is generally acellular or hypocellular.

The pathologist's role in interpretation of NAF, especially from automated collections, is very different than when interpreting diagnostic samples, such as those obtained from FNA or open biopsy. 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. An automated system-collected sample is used for risk assessment purposes only, so no clinical impressions will accompany the sample, nor will any treatment course be based directly on the finding. Screening is generally defined as systematic testing for the early detection of cancer 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.

Reporting specimen adequacy with NAF results

Early work on nipple-fluid cytology by Drs. Papanicolaou¹⁴ and King²¹ and, later, by Procter¹⁸ had proposed classification schemes in which the first category, Category 0, was an inadequate or non-diagnostic sample. In the newest classification scheme described below, for breast-cancer risk assessment only, Category 0 instead indicates a meaningful result. This is because of an evolution in thinking about hypocellular and acellular NAF samples.

It is now recognized that hypocellular samples are normal, and many women will produce samples that are acellular. In addition, many women will produce no NAF at all. None of these circumstances are considered "unsatisfactory," "inadequate," or "non-diagnostic" today. Normal findings indicate only a slightly elevated cancer risk over women who produce no NAF at all. Only abnormal findings (atypia or suspicious for malignancy) indicate a significantly increased risk.

There is no expectation that women with healthy glands or ducts will produce fluid or, if they do, that epithelial cells will be present in the sample. Thus, it is not considered mandatory for the pathologist to provide a specimen-adequacy statement in the situations just described.

There is still an important quality-assurance role for adequacy statements when they might convey useful information about a lab's NAF-processing quality. A lab that consistently

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produces “blank” slides may be doing so because samples are being collected or processed improperly. In such a case, management should be notified so the situation can be researched and addressed.

Recommended classification system for reporting NAF results

There are several reasons for reporting NAF results via a standardized classification system:

- 1) Results can be communicated clearly and unambiguously.
- 2) Physicians often want their staffs to alert them to any results requiring their immediate attention. A NAF- classification system can aid this process by concisely and clearly differentiating between benign, atypical, and suspicious results.
- 3) Classification categories reduce complication in physician reports.
- 4) A classification system helps labs and other healthcare providers easily compile statistical reports, electronically or otherwise.

Conclusion

Pathologists can play a key role in understanding the genetic and metabolic differences unique to the individual patient. This knowledge could then be used to tailor a custom program of prevention that offers maximum potential and minimizes possible side effects. These findings do not take the place of standardized screening programs but can supplement the current personal and family history for a given patient. Much progress has been made in identifying treatments and lifestyles for prevention of breast cancer; but until recently, there was no practical, effective means of risk assessment to identify appropriate candidates for these approaches.

The majority of women who develop breast cancer have no identifiable risk factors. A finding of epithelial atypia, either by histology or cytology, has long been recognized as an important breast-cancer risk biomarker; but, to date, there has not been a practical way to apply this knowledge to the general population as a screen. With NAF cytology, we might have the opportunity to identify and refer high-risk women for enhanced surveillance programs earlier, and offer a woman and her physician the chance to make more informed decisions about minimizing her risk of breast cancer. □

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