



TITLE: Nipple Aspiration or Ductal Lavage Cytology
in Risk Assessment of Breast Cancer

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NIPPLE ASPIRATION OR DUCTAL LAVAGE CYTOLOGY IN RISK ASSESSMENT OF BREAST CANCER

INTRODUCTION

The California Technology Assessment Forum has been asked to review the published data regarding the efficacy and safety of nipple aspirate and ductal lavage cytology in risk assessment of breast cancer.

BACKGROUND

Breast cancer is the most common cancer in women, and the second leading cause of cancer death. In the year 2000, it is estimated that nearly 200,000 new cases of breast cancer were diagnosed in the United States (Port *et al*, 2001). The vast majority of breast cancers are thought to start in the epithelial lining of the milk duct or lobule (Morrow *et al*, 2002). The pathogenesis of breast cancer most likely involves a prolonged sequence of morphologic alteration from normal breast epithelium through phases of hyperplasia, atypical hyperplasia, and carcinoma in situ to cancer (Wrensch *et al*, 1993).

Studies have found that histological findings of hyperplasia and atypical hyperplasia in breast biopsies are associated with a two to five-fold increased risk of subsequent breast cancer (Dupont *et al*, 1993). In a more recent report (Fabian *et al*, 2000), the finding of cytologic atypia in a random fine-needle aspiration of the breast in a group of high-risk women was associated with a five-fold increase in the relative risk of breast cancer development. Previous studies have also demonstrated that the increased risks associated with proliferative or atypical histo-pathological findings may be modified by other risk factors, particularly a positive family history of breast cancer. For example, in a 17-year follow-up study of women with benign breast biopsies, 103 (77%) of the 134 women who later developed breast cancer had had previous proliferative epithelium, with or without atypia (Dupont and Page, 1985).



BACKGROUND, continued

It has been shown in randomized trials (e.g. Fisher *et al*, 1998) that with the appropriate use of chemoprophylactic agents such as tamoxifen, breast cancer can be prevented in women at increased risk of the disease. As a result, researchers and clinicians are looking for effective techniques of early breast cancer detection and risk assessment. Although mammographic screening is an effective tool for breast cancer detection, it has some well described limitations, and has not been advocated alone as a technique for identifying and risk stratifying high-risk women (Kerlikowske *et al* 2003). In addition, mathematical models such as the Gail Model (Gail *et al*, 1989) that have been developed to predict breast cancer risk have been found to be better at assessing population-based risk rather than individual risk (Domchek, 2002).

Given the association between atypical cells and the subsequent development of breast cancer, and the important new developments in the chemoprevention of breast cancer, there has been increasing interest in technologies that can easily and accurately collect ductal epithelial cells from women for the purpose of breast cancer risk assessment. 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. This review will focus on NAF and ductal lavage.

Nipple Aspiration and Ductal Lavage of the Mammary Ducts

Nipple aspiration can be used to collect fluid containing epithelial cells for cytological analysis. Papanicolaou *et al* (1958) first studied the use of nipple aspirate cytology in detection of breast cancer using a maternal breast pump to obtain nipple aspirate fluid from more than 2,000 women. He found a few unsuspected cancers. Sartorius (1973; 1977) developed a simple breast pump with which he obtained nipple aspirate fluid in >60% of women in a breast clinic. The device consisted of a plastic cup placed over the cleansed nipple and attached by a short plastic tube to a 15-mL syringe. While the subject compressed her breast between both hands, the plunger of the syringe was withdrawn and held until fluid appears at the nipple surface.



Nipple Aspiration and Ductal Lavage of the Mammary Ducts, **continued**

Nipple aspirate fluid (NAF) can be obtained from the breast ducts in a significant proportion of patients with or without breast complaints (Wrensch *et al*, 1992). Four factors have been associated with increased likelihood of obtaining breast fluid: (1) age 35-50 years; (2) early age at menarche; (3) non-Asian versus Asian ethnicity; and (4) history of parity and/or lactation.

Ductal lavage is designed to increase the number of ductal cells for cytological analysis. It has been investigated both as a risk assessment tool and as a diagnostic tool, particularly for patients who are at high risk of breast cancer but without palpable or mammographic abnormalities. In contrast with NAF, ductal lavage requires a disposable microcatheter and experienced medical personnel (Klein and Lawrence, 2002). Nipple aspiration is first used to identify fluid-yielding mammary ducts. These ducts are then lavaged using a microcatheter inserted into the nipple opening of the individual mammary ducts. After saline is infused, the ductal lavage fluid is withdrawn. The fluid is then examined microscopically for cytological abnormalities. Training in the technique is proctored by a physician and involves successful completion of 6 to 10 cases per day (Cancer Update, 2001; www.producthealth.com). Cytologic preparation and interpretation of ductal lavage specimens are very similar to those used for breast fine-needle aspiration, nipple discharge and nipple aspirate fluid samples (Morrow *et al*, 2002). Ductal lavage specimens are divided into five categories: (1) inadequate cellular material for diagnosis (ICMD); (2) benign; (3) mild changes; (4) marked changes; (5) and malignant. For risk assessment, the cytological abnormality of interest is the finding of atypical hyperplasia. Overall, ductal lavage has been found to have significantly better cell yields as compared with nipple aspiration, collects cells from the entire ductal system and can localize abnormal cells to a specific ductal structure.



TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

The Pro-Duct Catheter used in ductal lavage (Pro-Duct Health, Inc., Menlo Park, CA) received FDA approval on April 10, 2000 as substantially equivalent (for the indications for use) to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Devices Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act. The indications for use statement reads; “The Pro-Duct Catheter is designed to perform contrast radiography of breast milk ducts. The Pro-Duct Catheter also enables the collection of breast milk duct fluid for cytological evaluation. The collected fluid can be used in the determination and/or differentiation of normal versus premalignant versus malignant cells.”

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

There are few published studies of nipple aspiration or ductal lavage cytology. No randomized controlled clinical trials of nipple aspiration or ductal lavage cytology have been published. There have been no published studies using biopsy techniques (e.g., excisional or fine needle aspiration biopsy) to confirm a diagnosis of atypical hyperplasia based on ductal lavage. Since nipple aspiration or ductal lavage cytology is employed in patients without suspicious dominant masses or mammographic abnormalities, there is no obvious target area of the breast for biopsy confirmation. In some patients with malignant cells on ductal lavage, surgical resection of the lavaged duct or a portion of the adjacent breast has been undertaken. However, there are no studies with long-term follow-up correlating the findings of ductal cytology with surgical pathology.



TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes (continued)

The final outcome of interest for nipple aspiration or ductal lavage is decreased morbidity and mortality from breast cancer. For risk stratification, an intermediate outcome for nipple aspiration or ductal lavage would be a change in patient management, such as intensified screening/surveillance, use of a chemopreventive agent (e.g. tamoxifen), or prophylactic mastectomy. None of the published studies of nipple aspiration or ductal lavage report on changes in patient management, surgical pathological confirmation, or down-staging of malignancy.

Level of evidence: 3,5. TA criterion 2 is not met.

TA Criterion 3: The technology must improve net health outcomes.

Breast Cancer Risk Assessment

Wrensch *et al* (1992) reported on an epidemiological study suggesting that atypical hyperplasia is associated with an increased risk of subsequent breast cancer. In a prospective study of breast cancer risk in relation to nipple aspirate fluid cytology, 2,701 white women volunteers from the San Francisco Bay Area who underwent nipple aspiration were followed for 10-18 years. Follow-up was complete for 87% (n = 2,343) of the cohort, representing 29,961 person-years and an average of 12.7 years of follow-up. About 23% of nipple aspirates contained proliferative epithelium, (i.e. hyperplasia (19%) and atypia (4%)). The subsequent breast cancer incidence was 4.4% (104 of 2,343). Women with cellular atypia in nipple aspirate fluid had a relative risk of developing breast cancer that was 4.9 times greater than women whose breasts did not yield nipple aspirate fluid. Women with a family history of breast cancer and cellular atypia had a relative risk that was 18 times greater than that for women without cellular atypia on nipple aspirate fluid (O'Shaughnessy *et al*, 2002). The findings regarding risk of subsequent breast cancer were strongest for and indeed largely confined to women aged 25-54 years at the time of specimen collection. Among women age 55 years and older, no significant or consistent differences were found in the risk of breast cancer by the different cytological diagnoses.



TA Criterion 3: The technology must improve net health outcomes (continued)

Breast Cancer Risk Assessment (continued)

The authors concluded that cytological findings of epithelial hyperplasia and atypical hyperplasia in nipple aspirates of breast fluid are associated with an increased risk of breast cancer. As noted, only 4.4% of women developed breast cancer. The authors caution that the study results cannot be generalized to the population at large because the study population was not randomly selected, but was largely composed of volunteers and a smaller proportion of women with breast complaints. Also, only white women were studied. Wrensch *et al* (1992) concluded, “At present, we do not advocate the use of this technique as a routine diagnostic procedure. In the future, as clinicians and researchers gain more experience with nipple aspirate cytology, it may become possible to augment clinical counseling of women about their breast cancer risks, incorporating risk estimates based on nipple aspirate cytology.”

Dooley *et al* (2001) report on a prospective, multicenter trial designed to compare ductal lavage with nipple aspiration with regard to safety, tolerability, and the ability to detect abnormal breast epithelial cells in women at high risk of breast cancer. Women enrolled in the study were at an elevated risk for breast cancer as determined by a 5-year Gail risk of invasive breast cancer development of at least 1.7% prior history of breast cancer, ductal carcinoma *in situ* or lobular carcinoma *in situ*, or a documented mutation in the BRCA1 gene or the BRCA2 gene. All women had a mammogram and a clinical breast exam interpreted as "not suspicious for breast cancer" within 12 months of entry into the study. Women who were taking tamoxifen or raloxifene were excluded. Seventy-two percent of the subjects underwent the study procedures in an outpatient facility; the rest were under general anesthesia during another planned procedure. Ductal lavage was attempted immediately after nipple aspiration on all ducts that yielded NAF. Ductal orifices were sometimes enlarged with a dilator. After the microcatheter was inserted to a maximum depth of 1.3 cm, a total of 1-3 ml of 1% lidocaine was infused intraductally in most subjects. Normal saline was then infused (2-6 mL) and the breast compressed to facilitate recovery of fluid. The mean volume of NS infused during ductal lavage in this study was 14mL, and the mean volume collected was 5mL. Surgical oncologists mainly performed the ductal cannulations.



TA Criterion 3: The technology must improve net health outcomes (continued)

Breast Cancer Risk Assessment (continued)

A total of 507 women were enrolled and 700 breasts were studied. Fifty-seven percent had a history of breast cancer and 39% had a Gail risk of breast cancer of 1.7% or more. The mean age was 51.9 years and 84% of the women were white. Eighty-four percent of participants had fluid-yielding ducts; 82% of these were successfully cannulated. Of these, 24% were found to have atypia (17% mild and 6% marked), 54% had benign cytology, and <0.5% had frankly malignant cells identified. Of the lavaged participants, 22% had an inadequate specimen as compared with 73% of NAF samples. Subjects with abnormal findings on ductal lavage were not statistically significantly different from those with benign or inadequate cellular material for diagnosis with respect to history of breast cancer, number of first degree relatives with breast cancer, age at menarche, biopsy history or use of hormone replacement therapy.

All subjects who underwent nipple aspiration and ductal lavage in the office setting were asked to complete a 100-mm visual analog scale immediately after the procedure; with 0 mm representing “no pain” and 100 mm representing “most severe pain”. The median rating was 8mm for nipple aspiration and 24 mm for ductal lavage. Fifty-one percent reported ductal lavage as less comfortable than mammography. There were no serious procedure related events during the trial.

The authors conclude that: “Ductal lavage is a safe and well-tolerated procedure that is a more sensitive method of detecting cellular atypia than nipple aspiration. Detection of intraductal cellular abnormalities can provide women at elevated risk for breast cancer and their physicians additional information to aid their decision about risk reduction therapy and ongoing surveillance.” (Dooley *et al*, 2001)

O’Shaughnessy *et al*, 2002 and others have proposed clinical management pathways that incorporate the findings of ductal lavage into the clinical decision algorithm.



TA Criterion 3: The technology must improve net health outcomes (continued)

Breast Cancer Risk Assessment (continued)

However, there are no published studies examining the benefits and risks of employing these strategies in women with epithelial hyperplasia or atypia on cytology of nipple aspirate or lavage. At this time, published studies do not demonstrate that nipple aspiration or ductal lavage cytology result in more prompt or accurate diagnosis of breast cancer or a change in medical management or treatment of the high-risk patient in a way that benefits the patient. As O’Shaughnessy *et al* (2002) state: “These guidelines (that suggest incorporating ductal lavage results into clinical management of high risk women) represent the **opinions** (emphasis added) of physicians experienced in breast carcinoma risk assessment and ductal lavage, and are offered for consideration rather than as an evidence-based protocol dictating standards of care.”

TA criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

The established method of risk assessment for breast cancer involves obtaining a woman’s clinical history (e.g. current age, age at menarche, age at first live birth, number of prior breast biopsies, presence of atypical hyperplasia, and number of first-degree relatives with breast cancer). These historical features are sometimes put into various statistical models to yield a quantitative estimate of breast cancer risk (Gail *et al*, 1989; Fabian *et al*, 2000). More recently, testing of high-risk women for genetic mutations in *BRCA1* and *BRCA2* has been undertaken to enhance risk assessment. Fabian and colleagues (2000) reported on use of random periareolar fine-needle aspiration (FNA) biopsies to evaluate the cytological appearance of epithelial cells in 480 women with a family history of breast cancer, prior precancerous biopsy, and/or prior invasive cancer. Twenty of these women subsequently developed breast cancer. Cytological evidence of hyperplasia with atypia in the FNA and a 10-year Gail model risk estimate were independently predictive of the subsequent cancer development or detection in this high-risk cohort.



TA Criterion 4: The technology must be as beneficial as any established alternatives (continued)

The cytomorphology from random FNAs is being explored as a surrogate end point biomarker in breast cancer chemoprevention trials (Fabian *et al*, 2000).

Published studies do not compare nipple aspiration or ductal lavage cytology to these established methods of breast cancer diagnosis or risk assessment. Therefore, it is impossible to conclude that these technologies improve the net health outcomes as much as or more than the established alternatives.

TA criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

Published data concerning nipple aspiration and ductal lavage are limited. Studies have not yet demonstrated the efficacy of these technologies in improving net health outcomes in the investigational setting. Whether nipple aspiration or ductal lavage will be effective in improving health outcomes when used to assess risk or to diagnose patients in the community setting under conditions of usual medical practice remains to be demonstrated.

TA criterion 5 is not met.



RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA TEC Medical Advisory Panel completed a review of this topic in 2002 and determined that it did not meet TEC criteria.

Centers for Medicare and Medicaid Services (CMS)

CMS does not have a published national or local policy regarding ductal lavage and/or nipple aspiration.

American Society of Breast Surgeons

The American Society of Breast Surgeons has released an Official Statement, which notes:

“The American Society of Breast Surgeons supports the use of ductal lavage as a cell-based risk assessment tool in high-risk or borderline-risk women to assist them in making more informed decisions regarding risk reduction and management options. This information can help to guide consideration of a variety of management options ranging from risk reduction therapy (tamoxifen or enrollment in the STAR trial) to closer surveillance or even prophylactic mastectomy. Practitioners using ductal lavage should be prepared to counsel patients about the results, offer psychological support, and be able to further evaluate the patient when atypia is identified. The American Society of Breast Surgeons cautions that the cytologic interpretation of breast epithelial cells must be standardized to ensure accurate risk assessment information. Ductal lavage is not a cancer detection technique and should not replace standard cancer screening methods. Long-term studies are necessary to better define the risk assessment contribution of cytologic atypia detected via these and other methods. The American Society of Breast Surgeons encourages participation in such trials.”



CONCLUSION

Breast cancer is the second most common cancer in women and a significant cause of morbidity and mortality. Over the past several years, a number of new techniques have been developed to improve the early detection of breast cancer. In spite of these advances, the impact of early detection on breast cancer mortality has been disappointing. As a result, investigators are searching for methods that will help identify women at high risk of developing breast cancer so that they can be prospectively offered increased surveillance, chemoprevention, or in some cases prophylactic mastectomy.

It is thought that the majority of breast cancers originate in the epithelial lining of the breast ductal system, and that breast tumorigenesis features the evolution of breast ductal cells from normal to hyperplastic, followed by the development of atypical hyperplasia. Furthermore, multiple studies have shown that the presence of atypical hyperplasia in breast tissue is a risk factor for the development of breast cancer. Ductal lavage is a safe, relatively non-invasive method for assessing the presence of atypical hyperplasia, in women at high risk of breast cancer. Therefore, it may prove helpful to patients and clinicians as a risk assessment tool for deciding which patients are more likely to benefit from chemoprevention of breast cancer. However, there are not yet any published studies that report on clinical outcomes of women undergoing ductal lavage. The relative risk for atypical hyperplasia detected in this setting has not yet been conclusively documented, and the outcomes of a change in clinical management as a result of information from ductal lavage have not been rigorously evaluated. How useful ductal lavage will prove to be as a tool for the diagnosis of breast cancer also remains to be seen.

In sum, the promise of ductal lavage appears to be considerable, but too many questions remain unanswered. If patients and doctors are to have evidence-based answers to these questions in the future, nipple aspiration and ductal lavage should be used in the context of clinical trials that are focused on breast cancer prevention and detection.

Currently, TA criteria 2-5 are not met.



RECOMMENDATION

It is recommended that nipple aspiration cytology and ductal lavage cytology do not meet California Technology Assessment Forum TA criteria.

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