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EXPERT
REVIEWS

Screening for breast cancer risk in the obstetric/gynecological setting: a breast surgeon's perspective

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Despite recent gains in screening and detection of breast cancer risk in postmenopausal women in the USA, there are still significant challenges in current risk assessment methods and patient management in premenopausal women. A finding of atypia in this patient population, with either a histological or cytological determination, has been shown to confer a four- to fivefold increase in relative risk for developing breast cancer. Currently, 75% of women in the USA who develop breast cancer have no identifiable risk factors, other than age. By screening a premenopausal, asymptomatic population in the obstetric gynecological setting, it is possible to find women at a significantly increased risk of developing breast cancer. Identifying women at increased risk will help clinicians and their patients to better make informed decisions regarding risk reduction and management options.

KEYWORDS: atypia • breast cancer screening • HALO™ System • nipple aspirate fluid

Excluding skin cancers, breast carcinoma is the most common type of cancer in women, accounting for nearly one in three cancer cases diagnosed every year in the USA [1]. According to the American Cancer Society, approximately 211,000 new cases of invasive breast cancer in women were diagnosed in 2005, with an additional 58,000 cases of *in situ* cancer.

The most widely used screening tool for breast cancer risk factors is the Gail model, which includes a personal history of breast abnormalities, family history of breast cancer among first-degree relatives, onset of menarche before the age of 12 years, and nulliparity or first pregnancy after the age of 30 years, to estimate the relative risk of developing breast cancer. The Gail model and all other risk assessment models are of limited value, since 70% of women who develop breast cancer have no identifiable risk factors other than age [2].

The goal of screening is early detection, and would ideally lead to reductions in morbidity and mortality. This goal has been achieved in cardiovascular disease. Screening for hypertension and elevated levels of cholesterol has led to the identification of increased risk of disease before symptoms develop. With this

screening program, the mortality from heart disease subsequently decreased by over 40%. Approximately half the decline in US deaths from coronary heart disease from 1980 to 2000 may be attributable to reductions in major risk factors [3].

Another example of successful screening is Papanicolaou (Pap) test screening for cervical cancer, arguably the most successful cancer screening test ever developed. After widespread adoption, the Pap test resulted in a 75% reduction in mortality for cervical cancer [101].

Although cytologic screening for breast cancer risk is in its early stages of development, there are similarities to the Pap test. Both tests are based on cytologic examination of changes in epithelial cells. Just as epithelial cells of the cervix undergo a transition from normal to invasive cancer, breast epithelial cells progress through a similar spectrum from normal, to hyperplasia, to atypia, to *in situ* cancer, to invasive 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 a future breast cancer [4]. It has been well established that identification of atypical cells in fluid from nipple aspirates, as

well as fine needle aspiration [5], is associated with the same magnitude of increased risk for future breast cancer as was observed from open biopsies [4].

Thus, the finding of atypia in nipple aspirate fluid (NAF) identifies a subgroup of women who are at increased risk for breast cancer. 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 diagnostic tests and, in selected cases, preventative efforts may be indicated. These findings lead us to conclude that widespread screening for breast cancer risk with NAF on an annual basis, which increases the sensitivity of the test, in premenopausal women could lead to major improvements in the early detection of breast cancer and reductions in breast cancer mortality.

One of the major challenges facing this new technology is determining what group of physicians will take the leadership role in the application of this technology. We are of the opinion that the obstetrician–gynecologist is ideally suited for this role. Just as the obstetrician–gynecologist screens for cervical cancer risk during the well woman visit, it would seem logical to include examination of NAF in the yearly well woman examination.

The obstetrician–gynecologist is the physician that most women associate with evaluation of breast problems. If a woman has breast concerns, or finds a lump in her breast, she is most likely to call her obstetrician–gynecologist for evaluation. Additionally, the obstetrician–gynecologist usually takes the responsibility for scheduling screening mammograms and reporting results. According to the most recent American College of Obstetricians and Gynecologists Guidelines for Women's Health Care, Breast Disorders, 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.

Overview of the breast cancer screening market

In screening for breast cancer risk, the current gold standard is mammography. There are approximately 30 million mammograms performed annually in the USA, at a cost of US \$2.2 billion. Despite the current utilization rates of mammography, data from the American Cancer Society Surveillance Research shows that the incidence rate of breast cancer has decreased from 182,800 new cancer cases in the year 2000 to 178,480 in 2007, a 2.4% reduction, and the number of breast cancer deaths decreased from 40,800 to 40,460, a total of 0.8% reduction in 7 years. Most of the decrease in incidence and death rates has been in postmenopausal women.

The role of screening mammography in subsequent reduction in mortality from breast cancer has been estimated at between 28 and 65% in independent statistical models of breast cancer incidence and mortality. Adjuvant treatment contributed the balance of the reduction in breast cancer mortality [6].

Current screening guidelines from the American Cancer Society suggest that a woman with no known risk factors should start annual mammograms at 40 years of age, but if she is at increased risk, as early as age 30 is recommended.

In general, mammographic sensitivity is lower in premenopausal women than in older women. Multiple factors have been suggested as contributing to this lower sensitivity, including higher breast density, faster tumor growth rate and differences in the distribution of breast cancer risk factors [7]. Mammography is currently being enhanced by new procedures, including digital image evaluation software and other technologies. Additionally, MRI is demonstrating the potential for highly discrete diagnosis of soft tissue tumors [8].

Recent recommendations by the American Cancer Society guidelines on MRI state that women at high risk for breast cancer should start screening with MRI and mammograms as early as the age of 30 years. Mammograms are less effective in younger, premenopausal women, often due to breast density, which reduces the sensitivity of the mammogram. A combination of mammogram, ultrasound and MRI increases the combined sensitivity to approximately 94% [9].

The major advantage of screening with NAF is that atypia can be identified before cancer is detected by imaging technology. Women who are found to have atypia on NAF would undergo more aggressive follow-up, and would be candidates for treatment with tamoxifen, which has been demonstrated to provide high-risk women with a 50% reduction in the risk of future breast cancer [10].

Another method for collecting ductal epithelial cells is ductal lavage, an invasive procedure limited to high-risk women. This is an outpatient procedure, in which a microcatheter is inserted directly into the nipple using a saline solution for a lavage and aspiration. The collected cells are sent for cytological analysis just like a NAF sample, and findings of atypia confer the same elevation of risk as in NAF.

Genetic testing for breast cancer screening includes genetic testing for *BRCA1* and *BRCA2* abnormalities that may predispose a woman to breast cancer, but these genetic abnormalities are present in only 5% of women who develop breast cancer [11].

Clinical efficacy of NAF cytology & the HALO™ System

Similar to screening for cervical cancer with the Pap test, NAF is used to identify patients with atypia from an asymptomatic population, which will occur in approximately 1% of the screening population. Infrequently, a frank carcinoma will be found and will require further diagnostic testing [12].

Manual collection of NAF for cytologic evaluation varies widely in terms of efficacy, reproducibility, ease of use and patient acceptance. For widespread acceptance of NAF as a breast cancer screen, the method for collection of NAF should be consistent, reproducible, reliable, efficient and cause minimal patient discomfort. The HALO™ System (NeoMatrix, CA, USA) has been FDA approved for screening asymptomatic

women for breast cancer risk through the collection of NAF for cytological evaluation. 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 study reviewed the clinical trial of the HALO System and found that the device was well tolerated, safe and effective [13].

The HALO NAF collection system has adjustable breast cups with disposable sample collection cups, which are placed simultaneously on each breast and manually adjusted to fit snugly around the nipple and areola. Using a combination of warmth, compression and vacuum, the NAF is collected. Approximately 50% of women are nonsecretors, and will not produce a sample. These women have a lower relative risk compared with women with a finding of atypia [12].

The collected samples are sent in a liquid-based cytology vial to a pathology laboratory for cytological review. It is well recognized that cytological assessment of epithelial changes is imperfect, whether in cervical or NAF samples. Cytological findings considered 'normal' are classified as acellular, normal epithelium or hyperplasia. Findings of atypia, suspicious cells or malignant cells are considered 'abnormal' and are not as challenging to differentiate. Only findings of abnormal cells are associated with a significant increase in breast cancer risk, which simplifies the interpretation process.

The sensitivity and specificity of NAF are comparable with those of cervical cytology. According to the National Cancer Institute (NCI), when atypical squamous cells of undetermined significance are used as the threshold, sensitivity of the cervical pap is approximately 68% and specificity is approximately 75% [102]. A report in *Cytopathology* indicates that nipple fluid cytological sensitivity in multiple studies ranged from 40 to 70% with a mean detection rate of 66.1%. The study conducted reported findings on nipple discharge cytology with sensitivity of 55.6%, specificity of 100%, positive predictive value of 100% and negative predictive value of 88.9%. The study reported that nipple discharge cytology is as specific as concomitant fine needle aspiration cytology, but is slightly less sensitive in detecting papillomas or malignant lesions [14]. As with the Pap test, repeated interval testing is expected to improve sensitivity.

The proposed age range for NAF screening in premenopausal asymptomatic women with no other known risk factors is 30–55 years. The frequency of screening should coincide with periodic well woman visits. If there are other known risk factors, such as family history, it may be appropriate to start screening earlier. The rationale for NAF screening in these age ranges is due to a number of reasons. Few women are routinely screened by mammogram before age 40, yet breast cancer is particularly virulent in younger women. Breast density negatively impacts the sensitivity of mammograms in women under 50 years of age. Postmenopausal women produce less NAF, but mammography is more effective.

A recent journal article showed that women diagnosed with breast cancer between 50 and 60 years of age have seen a significantly greater decrease in tumor size and percentage of positive

nodes at time of diagnosis compared with younger women. The authors believe that this data could be related to ineffective screening of younger women, as well as younger women having biologically more aggressive tumors [15].

Conclusion

The majority of women who develop breast cancer have no identifiable risk factors other than age. A finding of atypia, either cytologically or histologically, has long been recognized as an important breast cancer risk factor, but to date there has not been a practical way to apply this knowledge to the general asymptomatic population as a screen. With the addition of a noninvasive, office-based method of collecting NAF in the primary care setting, we have the opportunity to find and refer more high-risk women into breast centers with enhanced surveillance programs earlier to help them avoid a life-threatening battle with breast cancer.

Expert commentary

The obstetrician–gynecologist has a unique opportunity to initiate a discussion of breast cancer risk assessment with their patients. The challenge for physicians screening for atypia is managing the patient with an abnormal result. In most cases, the obstetrician–gynecologist will refer their patient to a breast surgeon, radiologist or comprehensive breast center.

A finding of atypia is an objective measure of risk, and organizations ranging from the NCI, the American Cancer Society and the American Society of Breast Surgeons [103] recognize the use of a finding of atypia as a risk assessment tool that will help clinicians and their patients to make informed decisions regarding risk reduction and management options.

Patients with atypia discovered by NAF cytology will follow the same care path as patients with histological atypia. By focusing on the small group of patients who have been identified as high risk, the use of enhanced diagnostic methods such as ultrasound and MRI may be justifiable to make a better determination of current breast health. If the enhanced diagnostic methods find a lesion, the care path for the patient is well established.

In women with atypia without palpable or imageable lesions, the care path is more complex. To determine the appropriate patient management plan, a comprehensive risk assessment should be performed. Risk factors should be considered according to the contribution of individual risk factors to the overall picture and degree that they increase risk. Factors that increase risk slightly, such as early menarche, HRT use, BMI and alcohol intake should be weighted less than a family history, especially if there is a first-degree relative with premenopausal breast cancer or two or more relatives with breast cancer. Some studies suggest that family history may dramatically increase risk if coupled with atypia, while other studies do not demonstrate this synergistic relationship. Until this is better understood, to

be conservative, family history should be considered a potential increase in risk above and beyond atypia [16]. Genetic counseling may be considered if appropriate. There have been several publications on managing the high-risk breast cancer patient that detail suggested care paths [17].

After a comprehensive risk assessment is completed, the patient and clinician use this information to determine an appropriate care path for management of this high-risk patient. There are different ways of approaching patient management that will depend upon the clinician's experience and judgment, as well as the woman's risk tolerance and concern level. For many women, the care path might be a conservative management plan with increased surveillance through more frequent mammograms, screening ultrasound and/or screening breast MRI. A conservative plan may also include lifestyle counseling and informed decisions regarding the use of HRT. With increased surveillance and enhanced imaging, if a cancer does develop, it can be reassuring to the patient that it is more likely to be caught at an earlier and more treatable stage.

A moderate management plan may incorporate the use of a chemopreventative agent such as tamoxifen in addition to the conservative plan described above. The Study of Tamoxifen And Raxolifene (STAR) trial was one of the largest breast cancer prevention trials ever conducted, and it demonstrated that using tamoxifen or raloxifene reduced the incidence of breast cancer by 50%. In the breast cancer prevention trial studying over 13,000 patients, tamoxifen was shown to be particularly valuable in patients with atypia. Tamoxifen as a preventive therapy reduced the risk of developing invasive breast cancer in women with atypia by 86% [10].

Where there are multiple risk factors, an aggressive management plan may add a surgical approach that may dramatically reduce the risk of developing breast cancer. Surgical options include ductal excision, prophylactic mastectomy and/or prophylactic oophorectomy, the latter usually reserved for patients who test positive for a mutation in the *BRCA* genes.

Five-year view

The study of NAF has been well characterized with a cytological finding of abnormalities and increased risk of breast cancer. Many research organizations, including the NCI, are supporting research to identify biomarkers in NAF, including DNA, RNA and the use of proteomics [18]. If these research efforts are successful, NAF may have more utility than a risk stratification tool and may have the ability to identify cancers earlier, characterize lesions, and possibly become a companion diagnostic tool for new chemopreventative strategies.

Information resources

- American Cancer Society website; information and resources on breast cancer.
www.cancer.org
- National Cancer Institute website; provides information on all types of cancer.
www.nci.nih.gov
- The American Society of Breast Surgeons; support for cell-based risk assessment for breast cancer screening.
www.breastsurgeons.org/officialstmts/officialstmt4.shtml
- American Society of Clinical Oncology.
<http://breastca.asco.org/portal/site/cancerportals>

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Key issues

- It has been shown that 70% of women in the USA who develop breast cancer have no identifiable risk factors other than age.
- Premenopausal women generally have dense breasts that render screening mammography less effective than in postmenopausal women.
- A comparison of screening for cervical cancer and screening for breast cancer is relevant, since both cancers have similar origins in the epithelial cells that line the interior surface of the cervix and the interior epithelial lining of the breast ducts and lobules.
- With the introduction of cervical screening with the Papanicolaou test, the mortality rate in the USA from cervical cancer has dropped by over 75%.
- The obstetrician–gynecologist is uniquely positioned to perform a breast cancer screening test for asymptomatic women during their well woman visit.
- A finding of atypia in nipple aspirate fluid (NAF) is well recognized as an indicator of increased risk for breast cancer, with a four- to fivefold increase in relative risk.
- A new, FDA-cleared, noninvasive device for acquiring NAF for cytological evaluation has been introduced to the obstetrician–gynecologist market for screening for breast cancer risk.
- A well-established care path exists within the comprehensive breast center for management and treatment of high-risk women, such as those identified by NAF with atypia.

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