Report

Failure of high risk women to produce nipple aspirate fluid does not exclude detection of cytologic atypia in random periareolar fine needle aspiration specimens

Priyanka Sharma1, Jennifer R. Klemp1, Marie Simonsen1, Chezna M. Welsko1, Carola M. Zalles3, Bruce F. Kimler2, and Carol J. Fabian1
1Department of Internal Medicine, Division of Hematology/Oncology; 2Department of Radiation Oncology, University of Kansas Medical Center, Kansas City; 3Hutchison Hospital, Hutchison, KS, USA

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Summary

Introduction. Evidence of hyperplasia with atypia found both on random periareolar fine needle aspiration (RPFNA) and in nipple aspirate fluid (NAF) fluid are associated with an increased risk for breast cancer.

Aim. In this study, we report the correlation of NAF production with cytological assessment of ductal cells obtained by RPFNA.

Methods. 113 women at high risk for development of breast cancer attending the Breast Cancer Prevention Clinic at the University of Kansas Medical Center underwent a single NAF collection attempt and RPFNA.

Results. NAF was successfully collected in 51% of women. There was no significant difference in age, 5-year Gail risk assessment, menopausal status, hormone use, family history of breast cancer, history of prior atypical hyperplasia/LCIS or history of contralateral DCIS/invasive breast cancer between women who produced NAF and those that did not. The only significant difference between the two groups was in history of prior lactation ($p = 0.018$). Twenty-seven of the 113 subjects were found to have hyperplasia with atypia by RPFNA. Prevalence of atypia by RPFNA was 31% in women who produced NAF versus 16% in those who did not ($p = 0.07$).

Conclusion. Although prevalence of RPFNA atypia was numerically higher in NAF producers than non-producers the difference did not reach statistical significance. Failure to produce NAF does not exclude the presence of hyperplasia with atypia by random periareolar fine needle aspiration.

Introduction

Breast intraepithelial neoplasia (IEN) is a biomarker currently being employed in risk stratification, as well as in cohort selection and response evaluation in Phase II chemoprevention trials [1–5]. The most accurate and acceptable method of sampling breast tissue for the detection of occult IEN is controversial, and subject of intense study and debate [6–9].

We have previously reported that random periareolar fine needle aspiration (RPFNA) provides sufficient epithelial cells for cytologic evaluation in 95% of high risk women undergoing this procedure; and that RPFNA cytology was an independent risk factor which could be used to stratify women with elevated Gail risk into moderate and very high short-term risk groups [10]. In that prospective study, high risk women with RPFNA evidence of hyperplasia with atypia...
exhibited a 5-fold increase in short term risk of DCIS or invasive cancer compared to those without hyperplasia with atypia.

Nipple aspirate fluid (NAF) collection is a non-invasive procedure which has been reported to provide adequate epithelial cells for evaluation in 21–53% of women [11, 12]. The rate of NAF production following manual massage attempt has been reported between 56 and 83% [11, 12–15] and is influenced by both cohort selection and number of attempts [12, 13, 16]. Klein et al. reported that 56% of women produced NAF during a first aspiration attempt but 80% produced NAF after a maximum of five attempts [13]. In a prospective study [12], detection of hyperplasia with atypia in NAF fluid was associated with a 2-fold increase in risk of developing breast cancer relative to women without NAF production. In the same study NAF-producing women with normal cytology exhibited an increase in risk of breast cancer by a factor of 1.4 relative to women who did not produce NAF. These observations indicate that NAF production itself may be associated with an increased risk of breast cancer development. However, prior studies have also demonstrated that factors not generally associated with increased breast cancer risk, including young age (35–50 years) and prior lactation, also influence NAF production [17].

Ductal lavage is another means of sampling breast tissue and has been reported to be a more reliable method than NAF collection alone for obtaining epithelial cells for evaluation in high risk women [11]. However, ductal lavage is generally only performed once a NAF-producing duct has been identified [7]. The proportion of high risk women exhibiting atypia after a successful ductal lavage (23%) is similar to the proportion of high risk women found to have hyperplasia with atypia in the prospective FNA series (21%) [10, 11]. Although follow up of women for development/detection of breast cancer was not reported in the ductal lavage multinstitutional study, ductal lavage is currently being suggested by some investigators as a supplementary risk assessment tool [6–8].

Since women who fail to produce NAF are unlikely to undergo ductal lavage, there is no published information regarding the prevalence of occult atypia in women who produce NAF versus women who do not produce NAF. In this cross-sectional cohort study, we sought to determine if NAF production in high risk women undergoing RPFNA correlated with cytologic pattern and more importantly if failure to produce NAF was associated with the absence of hyperplasia with atypia in RPFNA samples.

**Methods**

**Cohort selection and eligibility**

Women enrolled in this study were high risk women attending the University of Kansas Medical Center Breast Cancer Prevention Clinic. This study was performed after approval by the University of Kansas Medical Center Human Subjects Committee, in accord with an assurance filed with and approved by the Department of Health and Human Services. Subjects signed an informed consent prior to each breast aspiration.

To be eligible for NAF and RPFNA, women must have been judged as high risk by one or more of the following criteria: (1) Family history of breast cancer (one or more first degree relatives or two or more second degree relatives); (2) a prior biopsy showing atypical hyperplasia or lobular carcinoma in situ; (3) prior treated contralateral invasive breast cancer or DCIS; or (4) >50% mammographic breast density. For women with prior DCIS or invasive breast cancer, NAF collection and RPFNA was performed only on the uninvolved breast. Subjects that received cytotoxic therapy must have completed treatment at least 12 months prior to the procedures. Prior antihormone therapy must have been completed at least six months prior to the procedures. Sixteen subjects who had previously been on a Phase II chemoprevention trial of the third generation selective estrogen receptor modulator (SERM) arzoxifene must have been off-study for at least six months prior to NAF collection attempt or RPFNA.

All subjects must have had a normal mammogram within six months of the procedures as well as a clinical breast exam judged not suspicious for breast cancer on the day of the RPFNA procedure.

**Gail risk assessment**

The projected probability of developing in situ or invasive cancer at 5 years was calculated for each subject according to the Gail model [18, 19].