Comparison of Ductal Lavage and Random Periareolar Fine Needle Aspiration as Tissue Acquisition Methods in Early Breast Cancer Prevention Trials

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Abstract

Purpose: Short-term phase I and phase II breast cancer prevention trials require tissue acquisition at baseline and after intervention to evaluate modulation of potential biomarkers. Currently used tissue acquisition methods include ductal lavage (DL), random periareolar fine needle aspiration (RPFNA), and core needle biopsy. The optimum method to retrieve adequate samples and the most accepted method by study participants is not known.

Experimental Design: We compared RPFNA and DL as breast tissue acquisition methods for short-term breast cancer prevention trials by evaluating sample adequacy and tolerability in subjects who participated in two prospective phase II breast cancer prevention trials. Eighty-six women at increased risk for breast cancer were included in this study and underwent baseline DL and RPFNA. High risk was defined as having a 5-year Gail score of >1.67% or a history of atypical hyperplasia (AH), lobular carcinoma, or breast cancer.

Results: Median age was 54.5 years (range, 39-75 years); 75% of the women were postmenopausal. About 51% of the women yielded nipple aspiration fluid, and breast fluid samples via DL were retrieved in 73% of these subjects. Of these samples, 71% were adequate samples (greater than 10 epithelial cells). However, when the entire cohort was considered, only 31% of the subjects had adequate samples. RPFNA was also attempted in all subjects, and sample retrieval rate was 100%. Out of these, 96% of the subjects had adequate samples. In DL samples, AH rate was 3.7% was and hyperplasia (H) rate was 11.1%. In RPFNA samples, AH rate was 12.9%, and H rate was 24.7%. Cytology findings in RPFNA samples correlated with age, menopausal status, and breast cancer risk category (previous history of lobular carcinoma in situ). Both procedures were well tolerated, and no complications occurred among participants.

Conclusions: Considering that the main endpoint for short-term prevention trials is the modulation of biomarkers, it is important to optimize adequate sample acquisition; therefore, RPFNA is a more practical option for future phase I and II breast cancer prevention trials compared with DL.

In the pivotal National Surgical Adjuvant Breast and Bowel Project Phase I (NSABP-P1) trial, tamoxifen was reported to reduce the incidence of breast cancer by ~50% in women who were at increased risk of developing this disease and is currently the only Food and Drug Administration–approved agent for risk reduction of breast cancer (1). However, that study also showed that tamoxifen did not reduce the risk of estrogen receptor–negative breast cancer, and that its use was associated with side effects, such as increased risk of endometrial cancer and thromboembolic events, which, to an otherwise healthy individual, might not be acceptable.

Therefore, current studies in breast cancer prevention are evaluating other potential agents that can also target ER-negative breast cancer and that have a better safety profile (2). Short-term phase I and II breast cancer prevention trials offer a convenient model to evaluate potential preventive agents and to identify intermediate and surrogate end point biomarkers. These studies require breast tissue acquisition at baseline and after the intervention (i.e., the potential preventive drug) to evaluate modulation of potential biomarkers by the agent (3).

Therefore, it is important to use the least invasive, yet optimal tissue acquisition method to obtain adequate samples. Currently used tissue acquisition methods include ductal lavage (DL), random periareolar fine needle aspiration (RPFNA), and core needle biopsy (4). The optimum method to retrieve adequate breast tissue samples for biomarkers analysis and the most accepted method by study participants are not known.
In this study, our aim was to compare RPFNA and DL as breast tissue acquisition methods for short-term breast cancer prevention trials by evaluating sample adequacy and tolerability in subjects who participated in two prospective phase II breast cancer prevention trials.

Materials and Methods

Study subjects. A total of 98 pre- and postmenopausal women at increased risk for developing breast cancer were registered into two prospective, short-term phase II breast cancer prevention trials, using celecoxib or anastrazole. The primary end points of these studies were to evaluate the feasibility of obtaining samples via RPFNA and DL in high-risk women; secondary end points included modulation of proliferation biomarkers in breast tissue of high-risk women. Out of these, 86 subjects had baseline samples available and were thus included in the study. Subjects were recruited between March 2003 and December 2005 from the Breast Cancer High Risk Clinic at The University of Texas M. D. Anderson Cancer Center. Both studies were reviewed and approved by the Institutional Review Board, and all subjects signed an informed consent. Subject population characteristics are shown in Table 1. High risk was defined as having a 5-year Gail score of >1.67% or a history of atypical hyperplasia (AH), lobular carcinoma in situ (LCIS), or a previous history of breast cancer. DL and RPFNA were attempted in all subjects before the initiation of the study prevention agent. Subjects had to have one intact breast without prior surgery or radiation therapy.

Acquisition and processing of DL and FNA samples. DL was attempted in all subjects. Subjects with a previous history of breast cancer underwent the procedure in their unaffected breast. The DL procedure was done as previously described (5). Briefly, topical cutaneous anesthesia with EMLA cream was applied to the surface of the nipple and covered with an occlusive dressing for ~30 min before the procedure. The nipple was then dekeratinized using a mild abrasive gel. After massaging the breast for ~1 min, a suction cup (Pro Duct Health, Inc.) fitted with a 10-mL syringe was placed over the nipple, and a small amount of suction (~7.10 mL) was applied. Nipple aspiration fluid (NAF)—yielding ducts were cannulated using a microcatheter (Pro Duct Health). After the microcatheter was inserted, 1 to 3 mL of 1% lidocaine was infused intraductally for additional anesthesia. Intermittent breast massage was done after instillation with ~2 mL of saline for affluent collection, and this was repeated four to five times so that the total affluent volume was ~10 mL of ductal affluent. The recovered ductal affluent was placed into tubes containing CytoLyte solution.

The RPFNA was done after the DL procedure in the same breast on the same day. Subjects with a previous history of breast cancer underwent the procedure in their intact opposite breast. The RPFNA procedure was done as previously described (6, 7). In all women, four RPFNA passes were done two each at the 3 o’clock and 9 o’clock positions in each breast. Briefly, a 1.5-in., 23-gauge needle attached to a 10-mL syringe was used. The needle was inserted ~1 to 2 cm away from the areola, at 3 o’clock and later at 9 o’clock. Following injection of 2 mL of 1% lidocaine, the aspiration needle was moved in multiple directions to ensure sampling of most of the breast tissue, with emphasis on areas of dense breast tissue, where proliferative glandular tissue is often present. All the FNA samples were pooled in 5 mL of Cytoyte solution. After each aspiration, firm pressure was applied to the aspiration site to prevent hematoma formation. A cold pack was also applied to the breast for ~10 min after completion of FNA.

Cytologic specimens were prepared using the thin preparation (ThinPrep) technique (Cytyc Corporation). Six to eight slides were prepared from each pooled FNA specimen. One slide was stained with Papanicolaou stain for cytologic diagnosis; the remaining slides were saved in the tissue bank for marker studies per the protocol.

Cytologic evaluation. Sample adequacy was defined as having equal or greater than 10 epithelial cells. Cytologic diagnosis was made on the basis of previously published criteria (5). The categories used were nonproliferative epithelium (NPE), hyperplasia (H; with or without atypia), and malignant lesion.

Cell numbers were quantified as described previously by directly counting epithelial cells clusters (groups containing >10 cells), single cells, and cells in small groups (groups containing nine or fewer cells; ref. 5). All cells within 10 representative epithelial cell clusters were counted and averaged. If more than 10 clusters were present, the cells within 10 randomly selected clusters were counted and averaged. The average number of cells was then multiplied by the total number of clusters present. Single cells and cells in small groups were counted by selecting a representative field from each quadrant of the sample. The types and numbers of single cells and cells in small groups were determined by randomly selecting up to 200 cells and by counting and typing all observed cells. The percentage of epithelial cells present alone and in small groups was determined by this method. The total number of epithelial cells was determined by adding the number of epithelial cells in cluster and the number of those present along and in small groups.

Statistical methods. Patient characteristics were tabulated and compared between cytology groups using the Kruskall-Wallis test or Fisher’s exact test, as appropriate. The association between RPFNA and DL cytology was assessed using the McNemar’s test.

Results

Subject characteristics. Eighty-six subjects who were found to be eligible were enrolled in the study and underwent baseline DL and RPFNA the same day. Subject characteristics are shown in Table 1. Briefly, the median age was 54 (range, 39-75 years). About 76% of the women were postmenopausal, and 24% were premenopausal. Approximately 53% of the women had never used hormone replacement therapy.

Risk factors for breast cancer included increased 5-year Gail risk of >1.67% in 20% (17:86), history of AH in 16% (14:86),
history of LCIS in 15% (13:86), and history of previous invasive breast cancer with an intact contralateral breast in 49% (42:86) of the subjects.

**Tissue acquisition adequacy for DL and FNA.** DL was attempted at baseline in all 86 subjects. In 51% (44:86) of the subjects, NAF could be retrieved. We were able to cannulate and retrieve samples from NAF-yielding ducts in 73% (32:44) of the subjects. Two of the NAF-yielding patients had bilateral aspirations bringing the total number of samples to 34. We were also able to cannulate and retrieve samples from non-NAF–yielding ducts in four subjects, which left us with 38 cannulated ducts and samples. About 71% (27:38) of these samples did have adequate epithelial cells. However, when the entire cohort is considered, sample adequacy was only 31% (27:86).

RPFNA was also attempted at baseline in all 86 subjects. Breast tissue was retrieved in all subjects (100%). Eleven subjects underwent bilateral RPFNA totaling the sample size to 97 samples. About 96% (93:97) of the samples had adequate number of epithelial cells.

The cell count for DL was an average of 5,215 epithelial cells per subject (range, 49-31,199 epithelial cells) and an average of 10,614 epithelial cells per subject (range, 70-45,640 epithelial cells) for RPFNA.

**Cytology findings in DL and RPFNA and clinical correlations.** Exactly 93 RPFNA and 27 DL samples from 86 subjects were available for cytologic review. Altogether, we had 26 matched samples. The same dedicated cytopathologist (N.S.) reviewed all slides in all cases. All RPFNA samples and their corresponding DL samples were adequate for cytologic evaluation (greater than 10 epithelial cells).

Generally, aspirates of NPE were mildly cellular, with the epithelial cells arranged in small clusters or flat sheets with uniform, small, rounded nuclei and moderate to abundant cytoplasm. Apocrine cells and histiocytes were present in some of the cases (Fig. 1). Hyperplastic epithelial changes were moderately cellular, with the epithelial cells forming complex or three-dimensional clusters. Nuclei were enlarged and overlapping, with dense chromatin and an irregular nuclear membrane (Fig. 2).

In DL samples, the AH rate was 3.7% (1:27), and H rate was 11.1% (3:27; Fig. 2B). In RPFNA samples, the AH rate was 12.9% (12:93), and H was rate 24.7% (23:93; Fig. 2A). When categorized together, AH + H rate was 14.8% (4:27) in DL and 37.6% (35:93) in RPFNA samples.

When the relationship between the number of cells obtained and the presence of a proliferative findings in our matched samples (adequate DL and RPFNA samples in the same subject) was evaluated, we expected a higher cell number in proliferative samples. The median cell number in nonproliferative DL samples was 1,162 (range, 49-9,996), and the median cell number in RPFNA samples was 10,892 (range, 70-45,640). The median cell number in proliferative DL samples was 14,644 (range, 5,579-31,199), and the median cell number in PRFNA samples 13,265 (range, 1,225-28,413).
We evaluated whether there is an agreement between RPFNA and DL cytology. We have observed that the cytology of the DL samples was not different than the cytology of the RPFNA samples from the same subject (McNemar’s test, \( P = 0.22 \); Table 2). For example, if a subject was found to have a proliferative sample via RPFNA, the corresponding DL sample was also proliferative.

Given the small number of samples, separate analysis for AH versus H versus normal cytology could not be done. We also evaluated whether there is a significant difference for age across RPFNA cytology groups and whether there is an association between RPFNA cytology and other patient characteristics. We have found that cytology findings in RPFNA samples were significantly correlated with age (\( P = 0.02 \)), menopausal status (\( P = 0.01 \)), and breast cancer risk category (previous history of LCIS; Kruskall-Wallis test or Fisher’s exact test, as appropriate, \( P = 0.03 \); Table 3).

**Tolerability.** Pain score on a 1 to 10 scale, with 0 demonstrating lack of pain and increased numerical score indicative of worsening pain, was documented after each procedure (DL and RPFNA) and compared for the same subject. The overall median pain score was 2.8 (range, 0-10) for the DL procedure and 2.0 (range, 0-7) for the FNA procedure. No procedure-related bleeding, infection, or perforation was observed for either procedure. Both procedures were well tolerated by study subjects.

**Discussion**

In this present study, we have shown that both RPFNA and DL are highly tolerable procedures (none of our subjects experienced bleeding, pain, or other complications with either procedure), and that once adequate samples are obtained, cytology was similar in DL and RPFNA samples. However, when the entire subject cohort was considered, the success rate of obtaining adequate samples was higher for the RPFNA versus the DL procedure.

Compared with long-term phase III breast cancer prevention trials, the advantage of short-term breast cancer prevention trials is that they do not require a large cohort of participants, are conducted over shorter periods of time, and are therefore more cost-effective. Cancer incidence is not the end point;

**Table 2. Tabulation of FNA and DL cytology**

<table>
<thead>
<tr>
<th></th>
<th>DL cytology atypical hyperplasia or hyperplasia, n (%)</th>
<th>Normal, n (%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNA Atypical hyperplasia or hyperplasia</td>
<td>3 (75.0)</td>
<td>5 (23.8)</td>
<td></td>
</tr>
<tr>
<td>Nonproliferative epithelium</td>
<td>1 (25.0)</td>
<td>16 (76.2)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

**Table 3. Sample characteristics by FNA cytology**

<table>
<thead>
<tr>
<th></th>
<th>All, n (%)</th>
<th>Atypical hyperplasia, n (%)</th>
<th>Hyperplasia, n (%)</th>
<th>Normal, n (%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>97</td>
<td>12</td>
<td>23</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Age Minimum</td>
<td>39 (—)</td>
<td>39 (—)</td>
<td>39 (—)</td>
<td>42 (—)</td>
<td>0.02</td>
</tr>
<tr>
<td>Median</td>
<td>54 (—)</td>
<td>49 (—)</td>
<td>55 (—)</td>
<td>55 (—)</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>75 (—)</td>
<td>58 (—)</td>
<td>71 (—)</td>
<td>75 (—)</td>
<td></td>
</tr>
<tr>
<td>Menopause Peri/Premenopause</td>
<td>25 (25.8)</td>
<td>7 (53.8)</td>
<td>6 (26.1)</td>
<td>10 (17.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>72 (74.2)</td>
<td>5 (41.7)</td>
<td>17 (73.9)</td>
<td>48 (82.8)</td>
<td></td>
</tr>
<tr>
<td>HRT N</td>
<td>51 (52.6)</td>
<td>10 (83.3)</td>
<td>13 (56.5)</td>
<td>27 (46.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Y</td>
<td>46 (47.4)</td>
<td>3 (16.7)</td>
<td>10 (43.5)</td>
<td>31 (53.4)</td>
<td></td>
</tr>
<tr>
<td>HRT months Minimum</td>
<td>0 (—)</td>
<td>0 (—)</td>
<td>0 (—)</td>
<td>0 (—)</td>
<td>0.17</td>
</tr>
<tr>
<td>Median</td>
<td>0 (—)</td>
<td>0 (—)</td>
<td>0 (—)</td>
<td>9.5 (—)</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>480 (—)</td>
<td>168 (—)</td>
<td>300 (—)</td>
<td>480 (—)</td>
<td></td>
</tr>
<tr>
<td>Previous breast cancer N</td>
<td>41 (42.2)</td>
<td>5 (41.7)</td>
<td>11 (47.8)</td>
<td>22 (37.9)</td>
<td>0.72</td>
</tr>
<tr>
<td>Y</td>
<td>56 (57.7)</td>
<td>7 (58.3)</td>
<td>12 (52.2)</td>
<td>36 (62.1)</td>
<td></td>
</tr>
<tr>
<td>Breast feed N</td>
<td>60 (61.9)</td>
<td>9 (75.0)</td>
<td>12 (52.2)</td>
<td>35 (60.3)</td>
<td>0.42</td>
</tr>
<tr>
<td>Y</td>
<td>37 (38.1)</td>
<td>3 (25.0)</td>
<td>11 (47.8)</td>
<td>23 (39.7)</td>
<td></td>
</tr>
<tr>
<td>Risk group AH</td>
<td>17 (17.5)</td>
<td>4 (33.3)</td>
<td>3 (13.0)</td>
<td>9 (15.5)</td>
<td></td>
</tr>
<tr>
<td>Breast cancer Gail</td>
<td>42 (43.3)</td>
<td>2 (16.7)</td>
<td>11 (47.8)</td>
<td>29 (50.0)</td>
<td></td>
</tr>
<tr>
<td>LCIS</td>
<td>24 (24.7)</td>
<td>1 (8.3)</td>
<td>6 (26.1)</td>
<td>15 (25.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Site L</td>
<td>14 (14.4)</td>
<td>5 (41.7)</td>
<td>3 (13.0)</td>
<td>5 (8.6)</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>49 (50.5)</td>
<td>7 (58.3)</td>
<td>11 (47.8)</td>
<td>29 (50.0)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

NOTE: Four subjects were excluded from the analysis due to inconclusive cytologic diagnosis (\( n = 1 \)) and insufficient cells in FNA samples (\( n = 3 \)).
instead, the aim of short-term prevention trials is to evaluate tissue surrogate end point biomarkers and the effect of potential preventive agents on such biomarkers over time (8). Besides, being used to monitor response to a preventive intervention, biological markers can also be useful in breast cancer risk assessment and ideally should be associated with subsequent breast cancer development. For these reasons, adequate breast tissue acquisition is important to evaluate biological markers in obtained samples. Tissue acquisition methods should be as noninvasive as possible, cost-effective, and provide optimal samples to evaluate proposed biomarkers.

Current tissue acquisition methods include breast core needle biopsy, RPFNA, nipple aspiration, and DL (4). However, the optimal method is not known. In this study, our aim was to compare RPFNA and DL as breast tissue acquisition methods for short-term breast cancer prevention trials by evaluating sample adequacy and tolerability in subjects who participated in two prospective phase II breast cancer prevention trials.

Ductal lavage is a relatively noninvasive method where natural milk duct openings are cannulated with a microcatheter to retrieve ductal fluid (9, 10). One large study compared the feasibility and sample adequacy for DL versus nipple aspiration (5). In that study, 500 high-risk women underwent DL, and 83% produced NAF, of which 92% had successful duct cannulation. Of the successfully cannulated women, 78% had adequate samples for cytologic assessment. Thus, only 60% of the entire study population had evaluable samples. Several other studies, including our study, reported a lower rate (30–56%) of evaluable samples in the entire cohort (11–13). It should be noted that in the study of Dooley et al. (5), 28% of the patients underwent this procedure under general anesthesia. In one study, reasons for nonevaluable samples included no NAF production in 23% of the patients, not being able to cannulate the duct in 5% of the patients, and inadequate cells for cytologic assessment in 16% of the patients (12).

Our epithelial cell count number in DL samples was within the range of what has been reported previously. For example, Dooley et al. reported a median epithelial cell count of 4,000 (range, 24,143–0,000) per duct (14). Other studies failed to show this high cell count (14). Studies also evaluated cytomorphology and reported an 18% to 21% rate of mild atypia and a 6% to 8% rate of marked atypia (5, 12, 13, 15). The AH rate observed in the present study was slightly lower. This could be due to the fact that with patients at very high risk, such as deleterious BRCA mutation carriers were not included in our study.

We found, as did other investigators (13), a low percentage of women producing NAF; this could be partly due to the mostly postmenopausal subject population or the fact that some of our subjects with previous history of breast cancer had received prior chemotherapy. In one study, NAF production was 36%, and reduced NAF production was associated with postmenopausal status (13). However, we did not find a correlation between NAF production and any of the clinical subject characteristics, most probably due to the small subject numbers in each category (data not shown). If NAF was produced and ducts were cannulated, about 70% of our DL samples were adequate for cytologic analysis.

As previously reported by others (5, 16), we were also able to cannulate non-NAF–yielding ducts. One of four of these samples was adequate for cytologic assessment. The inability to produce NAF does not rule out potential hyperplasia; in fact, a study has shown that hyperplasia with atypia found by RPFNA was present in cases where NAF could not be retrieved (17). Therefore, if technically possible, non-NAF–yielding ducts should also be considered for cannulation.

The RPFNA is a method where no specific lesion is targeted; it instead assesses a large area of breast tissue to detect a field effect in the entire breast. It has been reported that when proliferative changes are present in the breast, these proliferative changes are seen in a multifocal and multicentric pattern (18–20). This is particularly useful for short-term prevention trials because the aim of these studies is not to biopsy or treat a certain abnormal lesion, but rather to induce antiproliferative or biomarker changes throughout the high-risk breast. Several studies have reported on the rate of hyperplasia with or without atypia in high-risk individuals ranging from 20% to 50% (6, 17, 21, 22). These studies also revealed that sample adequacy was rather high, with up to 97% of subjects having adequate samples for cytologic assessment (6, 17, 21, 22). In one study reported by Fabian et al. (6), the hyperplasia with atypia rate was 12% during initial aspiration in a high-risk cohort of 480 women. About 94% of the subjects had adequate samples for cytologic assessment. Our sample adequacy in this present study was 97%, in concordance with what has been previously reported.

The RPFNA procedure is well tolerated among women participating in breast cancer prevention trials, and the risk of infections requiring oral antibiotics is reported to be <1% (6, 7). In a prospective phase II chemoprevention trial, the compliance was very high, and 114 out of 119 patients returned for the second RPFNA (23). In our current cohort, none of our subjects developed hematoma, infection, or post-procedure pain requiring analgesic administration.

One other study to date has compared cytomorphology in RPFNA versus DL samples in high-risk women and concluded that RPFNA was more likely to yield evaluable samples, but once a cellular DL sample was obtained, the morphology of cells obtained was similar (24). Specifically, samples were adequate in 60% of the presenting patients. In this study, cytomorphology was assessed and compared using three different criteria: standard, National Cancer Institute, and the Masood scoring system. Atypical cytology was found in 15% of the DL samples and 31% of the RPFNA samples (24).

Several other studies have evaluated the breast core needle biopsy method to obtain breast tissue for biomarker analysis in high-risk women (25–28). Tissue adequacy ranged between 66% and 79% (25, 28). However, accrual to these studies was reported to be difficult. Currently, there are no studies comparing the core biopsy method to DL or RPFNA.

In summary, this is a prospective study comparing DL and RPFNA as tissue acquisition methods in short-term prevention trials. We have shown that both RPFNA and DL are highly tolerable procedures (none of our subjects experienced bleeding, pain, or other complications with either procedure). We have also shown that once adequate samples are obtained, cytomorphology was similar in DL and RPFNA samples. Overall, when the entire subject cohort is considered, the success rate of obtaining adequate samples was higher for the RPFNA versus the DL procedure. Considering that the main end point for short-term prevention trials is modulation of biomarkers, it is important to optimize adequate sample acquisition; therefore, RPFNA is a more practical option for future phase I and II breast cancer prevention trials compared with DL.
References

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