Atypia in Random Periareolar Fine-Needle Aspiration Affects the Decision of Women at High Risk to Take Tamoxifen for Breast Cancer Chemoprevention

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Abstract

Random periareolar fine-needle aspiration (RPFNA) is a research procedure designed to (*a*) evaluate short-term breast cancer risk in women at high risk for developing breast cancer, and (*b*) track response to chemoprevention. Of import, cellular atypia in breast RPFNA is prospectively associated with a 5.6-fold increase in breast cancer risk in women at high risk. Among 99 women attending a clinic for high-risk breast cancer, we explored the effects of RPFNA cytology results on decision making pertaining to the use of tamoxifen for breast cancer chemoprevention. No patient with nonproliferative or hyperplastic cytology subsequently elected to take tamoxifen. Only 7% of subjects with borderline atypia elected to take tamoxifen. In contrast, 50% with atypia elected to take tamoxifen. These results suggest that the provision of a biomarker of short-term risk can affect the motivation to take tamoxifen for chemoprevention. This conclusion is informative given that tamoxifen, due to its side effects, is often underused by women at high risk of developing breast cancer. Further research is needed to determine the mechanisms through which RPFNA results affect the decision to use tamoxifen, or any other breast cancer chemopreventive agent. (Cancer Epidemiol Biomarkers Prev 2007;16(5):1032–4)

Introduction

Tamoxifen is approved by the U.S. Food and Drug Administration for reducing breast cancer risk among women with a 5-year calculated Gail model risk of >1.66%. A meta-analysis of data from the Breast Cancer Prevention Trials and other trials show that tamoxifen reduces breast cancer risk by 38% (1, 2). Preliminary results from the Study of Tamoxifen and Raloxifene trial replicate the ~50% reduction in breast cancer risk found in the Breast Cancer Prevention trials (3). Overall, the benefits of tamoxifen outweigh the side effects among women with increased breast cancer risk, such as those with a strong family history of breast cancer and/or atypia (4, 5).

Despite the potential benefits of tamoxifen, a majority of women at high risk decline tamoxifen chemoprevention due to its known side effects, such as endometrial cancer, pulmonary embolism, stroke, and deep-vein thrombosis (4, 6-12). To date, studies investigating the decision of women at high risk to accept or decline tamoxifen chemoprevention have not integrated the role of response biomarkers in decision making. Biomarkers are currently being developed to improve our ability to predict short-term breast cancer risk and response to chemoprevention.

Random periareolar fine-needle aspiration (RPFNA) is a research procedure designed to (*a*) evaluate short-term breast cancer risk in women at high risk for developing breast cancer, and (*b*) track response to chemoprevention (13, 14). RPFNA yields informative cells in 82% to 88% of women at high risk and, importantly, the presence of cellular atypia in breast RPFNA is prospectively associated with a 5.6-fold increase in breast cancer risk in women at high risk (13, 15). In this study, we tested whether the presence of atypia in RPFNA influenced whether women at high risk decided to take tamoxifen chemoprevention.

We predicted that women found to have atypia through RPFNA would be more likely to decide to use tamoxifen than women not found to have atypia. This prediction was based on the hypothesis that women found to have atypia would likely perceive themselves at higher risk for breast cancer than women without atypia; in turn, and consistent with major models of health behavior change (16-18), women who view themselves at higher breast for cancer risk should be more inclined to want to reduce their risk and hence elect to use tamoxifen (6, 19, 20). These findings would suggest that risk biomarkers can have an important influence on the decision of women at high risk to undergo chemoprevention.

Materials and Methods

Informed Consent. The study was approved by the Institutional Review Board at Duke University, in accordance with assurances filed with and approved by the Department of Health and Human Services.

Eligibility. To be eligible for RPFNA, women were required to have at least one of the following major risk factors for breast cancer: (*a*) 5-year Gail risk calculation >1.7%, (*b*) prior biopsy exhibiting atypical hyperplasia, lobular carcinoma *in situ*, or ductal carcinoma *in situ*, (*c*) known BRCA1/2 or suspected mutation carrier, or (*d*) prior contralateral breast cancer. In subjects with prior invasive cancer, ductal carcinoma *in situ*, or radiation, only the contralateral breast was aspirated, as the cell yield from radiated breast tissue is uniformly poor. Clinical variables evaluated included age, menopausal status, hormone and oral contraceptive use, parity, age of menarche and menopause, lactation history, family cancer history (including breast, ovarian, colon, and prostate), and radiation and other environmental exposures.

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Table 1. Characteristics of patient samples (*N* = 99)

Characteristics	Outcome mean, no. (%)
Average age in years (range)	46 (29-64)
Race	
Caucasian	86 (87)
African American	10 (10)
Ashkenazi Jewish	3 (3)
Menopausal status	
Postmenopausal	25 (25)
Pre/Perimenopausal	74 (74)
Hormone replacement use	
Current	4 (4)
Ever use	13 (13)
Never use	82 (82)
Prior abnormal biopsies (total)	32 (32)
Lobular carcinoma *in situ*	4 (4)
Ductal carcinoma *in situ*	12 (13)
Atypical ductal hyperplasia	16 (16)
Known BRCA1 mutation carrier	3 (3)
Known BRCA2 mutation carrier	1 (1)

RPFNA and Cytologic Assessment. RPFNA was done as previously published (15). All investigators were trained by Carol Fabian in the use of RPFNA. Slides for cytology were prepared by filtration and Papanicolaou stained as described previously (13). A minimum of one epithelial cell cluster with at least 10 epithelial cells was required to sufficiently determine pathology; the most atypical cell cluster was examined and scored (13). Cells were classified qualitatively as nonproliferative, hyperplasia, or hyperplasia with atypia (21). Cytology preparations were also given a semiquantitative index score through evaluation by the Masood cytology index (22-24). As previously described, cells were given a score of 1 to 4 points for each of six morphologic characteristics that include cell arrangement, pleomorphism, number of myoepithelial cells, anisonucleosis, nucleoli, and chromatin clumping; the sum of these points computed the Masood score: ≤10, nonproliferative (normal); 11 to 12, hyperplasia; 13, high-grade hyperplasia; 14 to 17, atypia; >17, suspicious cytology (13, 22-24). The number of epithelial cells were quantitated and classified as <10 epithelial cells (insufficient quantity for cytologic analysis), 10 to 100 cells, 100 to 500 cells, 500 to 1,000 cells, 1,000 to 5,000, and >5,000 cells. Morphologic assessment, Masood cytology index scores, and cell counts were assigned by a blinded, single dedicated pathologist (C.M. Zalles; ref. 13).

Results

Original Population Screened. One hundred and seventy-three women underwent initial RPFNA at Duke University Medical Center from March 2003 to June 2006. All women consented to tamoxifen chemoprevention at the time they consented to initial RPFNA.

Selection of Subjects from the Screened Population and Criteria for Exclusion. Of the original 173 subjects, 144 subjects had sufficient epithelial cells for cytologic testing in all initial RPFNA determinations. Forty-five of 144 subjects with sufficient initial RPFNA cytology were excluded from this analysis for the following reasons: (*a*) 9% (13/144) of subjects elected to take tamoxifen chemoprevention prior to undergoing initial RPFNA, (*b*) 17% (25/144) had contralateral breast cancer within 5 years of study entry, (*c*) 5% (7/144) elected to have prophylactic mastectomy, or (*d*) had clinical contraindications to tamoxifen (e.g., a history of thromboembolic events).

Number of Women Eligible for Study. Ninety-nine of the original 173 subjects were eligible for this study. The clinical characteristics of eligible subjects are listed in Table 1. Eighty-seven percent (86/99) of the subjects were Caucasian, 3% (3/99) were of Ashkenazi Jewish descent, and 10% (10/99) were African American. Twelve percent (12/99) had prior ductal carcinoma *in situ*, 4% (4/99) had prior lobular carcinoma *in situ*, 16% (16/99) had prior atypia, 4% (4/99) were known BRCA1/2 mutation carriers, and 63% (63/99) had a Gail model score of >1.7.

Study Schedule. All 99 subjects were initially offered tamoxifen chemoprevention and declined. Subjects underwent initial RPFNA within 3 months after declining tamoxifen. On initial RPFNA, 52% (51/99) of subjects had nonproliferative (normal) or hyperplastic cytology (Masood <13), 30% (30/99) had borderline atypia (Masood = 14), and 18% (18/99) had atypia (Masood >15). All subjects with atypia on initial RPFNA had a 6-month and 12-month repeat RPFNA.

Subject Decision Making. All 99 subjects were offered tamoxifen after receiving initial RPFNA results. No subjects (0/51) with nonproliferative or hyperplastic cytology (Masood <13) subsequently elected to take tamoxifen. Only 7% (2/30) of subjects with borderline atypia (Masood = 14) elected to take tamoxifen. In contrast, 50% (9/18) with atypia (Masood >15) elected to take tamoxifen. All 18 subjects with cytologic atypia on initial RPFNA had atypia on 6-month repeat RPFNA. The Kruskal-Wallis test indicated that there was a significant difference in the proportion of patients deciding to take tamoxifen chemoprevention based on the level of atypia ($P < 0.001$).

Characteristics of Women with Atypia who Chose for or against Using Tamoxifen. Among the 18% (18/99) of women who had atypia on initial RPFNA, 50% (9/18) elected to take tamoxifen. Among these nine women, 67% (6/9) decided to begin tamoxifen chemoprevention after the initial atypical RPFNA and 33% (3/9) chose to take tamoxifen after they had had two atypical RRFNA (initial RPFNA and 6-month repeat RPFNA). Among the nine women who chose not to take tamoxifen, 89% (8/9) had one atypical RPFNA and 11% (1/9) had three atypical findings on RPFNA (initial RPFNA, 6-month repeat RPFNA, and 12-month repeat RPFNA).

Table 2. Characteristics of patients with atypia that elected to use or not use tamoxifen

Women with atypia on RPFNA, Masood >15 (*n* = 18)	Elected to use tamoxifen (*n* = 9)	Elected not to use tamoxifen (*n* = 9)
Average age in years (range)	46 (39-56)	43 (33-50)
Race		
Caucasian	5 (56%)	9 (100%)
African American	4 (44%)	0 (0%)
Ashkenazi Jewish	0 (0%)	0 (0%)
Median Gail score (range)	2.8 (1.3-5.4)	2.5 (0.9-12.9)
Subjects eligible for Gail risk assessment	4/9 (44%)	7/9 (78%)
Menopausal status		
Postmenopausal	1 (11%)	1 (11%)
Pre/Perimenopausal	8 (89%)	8 (89%)
Hormone replacement use		
Current	0 (0%)	1 (11%)
Ever	0 (0%)	0 (0%)
Never	9 (100%)	8 (89%)
Oral contraceptive use		
5 y or greater	4 (44%)	5 (56%)
1-5 y	4 (44%)	3 (33%)
Never	1 (11%)	1 (11%)
Prior abnormal biopsies		
Lobular carcinoma *in situ*	1 (11%)	0 (0%)
Ductal carcinoma *in situ*	2 (22%)	1 (11%)
Atypical ductal hyperplasia	2 (22%)	2 (22%)
No abnormalities	4 (44%)	6 (67%)

We compared whether women who accepted versus those who declined tamoxifen in this cohort at high-risk differed on demographic characteristics, Gail score, menopausal status, hormone replacement therapy use, oral contraceptive use, and history of abnormal biopsy (Table 2). The number of subjects electing to take tamoxifen was too small to test for a correlation between any of these variables and the decision to accept tamoxifen chemoprevention.

Discussion

We investigated whether the use of RPFNA might assist women in decision making about chemoprevention. We found that the presence of atypia in initial RPFNA was associated with a marked increase in the decision to take tamoxifen (50% elected to use tamoxifen) compared with women who had borderline atypia (7%) or nonproliferative (normal) cells (0%). Of import, all of our 99 subjects included in this study initially declined tamoxifen chemoprevention before initial RPFNA. The decision to use tamoxifen after initial RPFNA suggests the causal relationship between RPFNA feedback and the decision to use tamoxifen.

These findings are important because they suggest that providing women with biomarker feedback to stratify the level of breast cancer risk, in this case, atypia through RPFNA, might help them make decisions about tamoxifen use. Indeed, the complex trade-off between the risks and benefits of tamoxifen chemoprevention has left many women hesitant to take tamoxifen. What is left unclear is the precise mechanisms through which RPFNA affected decisions. For example, did the feedback affect perceptions of risks and worry? Did the feedback modify the saliency of the benefits versus the risks of tamoxifen such that those who were told they had atypia focused more on the benefits whereas those with normal results focused more on the risks? Understanding these mechanisms would help provide insights on how biomarkers might affect decisions about breast cancer chemoprevention.

Although the presence of histologic atypia predicts response to tamoxifen chemoprevention (3), there are no established response biomarkers to track the response to tamoxifen. The presence of persistent atypia on repeat RPFNA cytology after the initiation of tamoxifen could provide evidence that tamoxifen is insufficient for eliminating atypia but does not preclude a preventive benefit. The Breast Cancer Prevention trials showed a 50% reduction in the incidence of endoplasmic reticulum–positive breast cancer in women at high risk who took tamoxifen (1). Therefore, not all women will benefit from tamoxifen prevention. It is important to communicate to patients that tamoxifen may not benefit all women at high risk with atypia. Whether such feedback will affect the decision to take tamoxifen, in addition to understanding how biomarkers affect decisions, remain important future questions to address.

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