ERβ Expression and Breast Cancer Risk Prediction for Women with Atypias
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Abstract
Estrogen receptor (ER) β is highly expressed in normal breast epithelium and a putative tumor suppressor. Atypical hyperplasia substantially increases breast cancer risk, but identification of biomarkers to further improve risk stratification is needed. We evaluated ERβ expression in breast tissues from women with atypical hyperplasia and association with subsequent breast cancer risk. ERβ expression was examined by immunohistochemistry in a well-characterized 171-women cohort with atypical hyperplasia diagnosed 1967–1991. Nuclear ERβ percent and intensity was scored in the atypia and adjacent normal lobules. An ERβ sum score (percent + intensity) was calculated and grouped as low, moderate, or high. Competing risks regression was used to assess associations of ERβ expression with breast cancer risk. After 15-year median follow-up, 36 women developed breast cancer. ERβ expression was lower in atypia lobules than normal lobules, by percent staining and intensity (both \( P < 0.001 \)). Higher ERβ expression in the atypia or normal lobules, evaluated by percent staining, intensity or sum score, decreased the risk of subsequent breast cancer by 2-fold (\( P = 0.04 \)) and 2.5-fold (\( P = 0.006 \)). High normal lobule ERβ expression conferred the strongest protective effect in premenopausal women: the 20-year cumulative incidence of breast cancer was 0% for women younger than 45 years with high versus 31% for low–moderate ERβ expression (\( P = 0.0008 \)). High ERβ expression was associated with a significantly decreased risk of breast cancer in women with atypical hyperplasia. These data suggest that ERβ may be a useful biomarker for risk stratification and a novel therapeutic target for breast cancer risk reduction. Cancer Prev Res; 8(11); 1084–92. ©2015 AACR.

Introduction
Estrogen receptor (ER) β is a member of the nuclear receptor superfamily of transcription factors that was identified in 1996 as the product of the ESR2 gene on chromosome 14q22-24 (1, 2). ERβ is distinct from ERα (ESR1 gene on chromosome 6), the form of the estrogen receptor that is assayed in routine clinical practice for all newly diagnosed breast cancers and used to determine treatment and prognosis (3, 4). ERα and ERβ share 96% homology in their DNA-binding domains but differ considerably at the hinge region, AF1 domain, and ligand-binding domain (2, 5). Unlike ERα, ERβ is highly expressed in normal breast epithelium but declines in expression in precancerous and cancerous breast lesions (6–13).

Furthermore, ERβ (specifically the full-length form, termed ERβ1) is postulated to function as a tumor suppressor of breast cancer as well as other cancers (14–17). Its expression is diminished or absent in invasive breast cancers compared with pre-invasive or benign lesions (8, 9, 12, 18–20). In breast cancer models, ERβ expression alone, or in combination with ERα, inhibits breast cancer cell proliferation and enhances sensitivity of ERα expressing breast cancer cells to the antiproliferative effects of selective estrogen receptor modulators (14, 21–24). Tumoral expression of ERβ is also associated with increased effectiveness of tamoxifen and aromatase inhibitor therapy (14, 25–30).

There is little data on the association of ERβ expression in benign breast disease (BBD) with subsequent breast cancer risk. Atypias of the breast increase the lifetime risk of breast cancer four-fold (31). In particular, given its possible tumor suppressor role, ERβ expression in breast tissues with atypia and a possible role for ERβ in mitigating breast cancer risk in high-risk individuals are of interest. The identification of novel biomarkers for risk prediction within this high-risk group of patients is desirable to ascertain those individuals at the highest risk, to better guide women in their choice of pharmacologic or surgical risk reduction strategies, and to identify pharmacologic targets to lower risk.

To better understand the role of ERβ in BBD and its possible impact on future breast cancer risk, we undertook this study in women with atypical hyperplasia and known long-term outcome with regard to subsequent development of breast cancer. Our aim was to examine the relationship of ERβ expression in the atypical epithelium and in the adjacent histologically normal lobules with the risk of future breast cancer.

Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerpreventionresearch.aacrjournals.org/).

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Materials and Methods

Patient cohort

With IRB approval, we studied breast tissues from women with atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH) from the Mayo Clinic Benign Breast Disease Cohort. The cohort and verification of atypical hyperplasia has been described previously (32). Among 334 women in the cohort diagnosed with atypia between 1967 and 1991, adequate tissue for ERβ staining was available for the 171 women who form the basis of this study. Median follow-up of this atypia subcohort was 15 (range, 1–36) years.

Histology and immunohistochemistry

The atypia tissue samples were characterized for the presence of unifocal versus multifocal atypia defined as more than one terminal ductal lobular unit clearly containing atypical hyperplasia (33). In addition, the degree of involution of the breast tissue was categorized as none, partial, or complete (34). Immunostaining and assessment for ERα and Ki67 was performed as previously described (32, 35). For this analysis of ERβ expression, the tissues studied included the epithelia of the atypical hyperplasia lesion (s), referred to as “the atypia,” and epithelia of histologically normal lobules from the same tissue section as the atypia, hereafter called normal or adjacent normal lobules.

The ERβ subcohort was defined after review of all the tissue sections by two pathologists (J.M. Carter and D.W. Visscher). Subsequently, ERβ immunohistochemistry was performed on archival formalin-fixed, paraffin-embedded tissue sections that were stained with an ERβ-specific monoclonal antibody (PPGS/10; Thermo Scientific) that is known to detect only the full-length form of ERβ (termed ERβ1) without cross-reacting with any of its splice variant forms (11, 36). This antibody also has been shown to be the most sensitive and specific commercially available ERβ antibody for use in immunohistochemical studies (11, 36, 37). In brief, sections were first deparaffinized in xylene, washed in decreasing concentrations of ethanol, and rehydrated in distilled water. Antigen retrieval was performed by treatment with a preheated, citrate-based solution [low-pH Target Retrieval Solution (Dako)] in a steamer at 98°C for 40 minutes. Staining was performed in a Dako Autostainer Plus as previously described (11).

Nuclear ERβ staining in epithelia was scored semiquantitatively by a single pathologist (J.M. Carter) blinded to patient identity as well as clinical characteristics and outcome. Both the atypical and adjacent histologically normal breast epithelia were scored for percentage of nuclei stained (scores 0–10; Thermo Scientific) – that is known to detect only the full-length form of ERβ (termed ERβ1) without cross-reacting with any of its splice variant forms (11, 36). This antibody also has been shown to be the most sensitive and specific commercially available ERβ antibody for use in immunohistochemical studies (11, 36, 37). In brief, sections were first deparaffinized in xylene, washed in decreasing concentrations of ethanol, and rehydrated in distilled water. Antigen retrieval was performed by treatment with a preheated, citrate-based solution [low-pH Target Retrieval Solution (Dako)] in a steamer at 98°C for 40 minutes. Staining was performed in a Dako Autostainer Plus as previously described (11).

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Statistical analysis

Descriptive statistics were reported with frequency and percentage for categorical variables and median (range) for continuous variables. Paired comparisons of ERβ expression between the atypia and adjacent normal lobules were performed using Wilcoxon signed-rank tests. Independent sample comparisons between the two types of atypia (ADH vs. ALH) used Wilcoxon rank-sum tests. Follow-up time was calculated from the date of the index benign biopsy until the diagnosis of breast cancer or until the earliest of the following: prophylactic mastectomy, last follow-up, or death. The cumulative incidence estimator was used to estimate the incidence of breast cancer while taking the competing risk of death into account (38). The association of ERβ expression with breast cancer risk was assessed using Fine and Gray competing risks regression with the Firth penalized bias-reduction method and was summarized with HR and 95% profile-likelihood confidence intervals (39). P < 0.05 was considered statistically significant. Correlation coefficients (r) were calculated using the Spearman rank method. Analysis was performed using SAS (Version 9.3) with the %phsreg macro and R (http://www.r-project.org), including the cmrsk package (40, 41).

Results

The median patient age was 56 years (range, 28–84 years). All women underwent excisional biopsy of the atypia lesion. Seventy-nine women had ADH and 92 had ALH. No women in this cohort received chemoprevention with endocrine therapy. One patient underwent bilateral prophylactic mastectomy 3 years after her atypia biopsy. During follow-up, 36 of the 171 women developed breast cancer at a median of 13 (range, 1–29) years.

ERβ expression, assessed by nuclear percent staining, intensity, and sum score, was lower in the atypia than in adjacent normal lobules (all P < 0.0001) as shown in Table 1 and illustrated in Fig. 1, which shows low and high ERβ expression, respectively, in the atypias (A and B) and in the adjacent normal lobules (C and D). ERβ expression was slightly lower in ADH than in ALH (Supplementary Table S1), particularly for nuclear percent staining (P = 0.0002), sum score (P = 0.0004), and sum score category (P = 0.001). However, ERβ expression in the adjacent normal lobules did not differ between ADH and ALH cases (data not shown).

Association of ERβ expression with other risk factors

The association of ERβ expression with age, lobular involution, and the number of atypical foci is summarized in Fig. 2. Generally, ERβ expression in either the atypia or normal lobules was

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independent of these factors. The only significant association was for age category with normal lobule ERβ expression, with significantly lower ERβ expression in women ≤55 years as compared to women >55 ($P = 0.03$). ERβ expression in the atypia was not significantly associated with the three variables.

Correlation of ERβ expression with other markers

Data were available on ERα and Ki67 for the atypia lesion only. ERα in the atypia was not correlated with ERβ expression in the atypia for either percent staining ($\rho = 0.02$) or intensity ($\rho = 0.08$). ERβ expression in the atypia lesion did show a trend ($P = 0.09$) toward an inverse association with Ki67 expression with 39% (12 of 31), 24% (21 of 86), and 14% (1 of 7) showing elevated Ki67 expression ($\geq$2% cells positive in the atypia) across the levels of low, moderate, and high ERβ sum score, respectively.

Association of ERβ with breast cancer risk

**ERβ in the atypia.** By sum score, 44 (26%) of atypias had low ERβ expression, 117 (68%) moderate expression, and 10 (6%) high expression. Higher nuclear ERβ expression in the atypia was associated with decreased breast cancer risk for all methods of evaluation, including nuclear percent staining ($P = 0.03$), intensity of staining ($P = 0.03$), and sum score ($P = 0.01$). Low nuclear ERβ expression (sum score, 0–2) in the atypia was associated with a 2-fold increased risk of subsequent breast cancer (HR: 2.0; 95% CI: 1.02–3.8; $P = 0.04$) compared with atypias with moderate–high expression (sum score, 3–7; Fig. 3A).

**ERβ in the normal lobules.** In the adjacent normal lobules, ERβ expression assessed by sum score was high in 96 (56%), moderate in 74 (43%), and low in 1 (0.6%). As the distribution was substantially different in normal lobules as compared with the atypia, low–moderate expression was compared with high expression in further analysis of the normal lobule scores. The normal lobule sum score showed a moderate correlation of $\rho = 0.39$ with atypia sum score within subject. Of those with low expression in the atypia, 28 of 44 (64%) showed low–moderate expression in the adjacent normal lobules, which was significantly more frequent ($P = 0.002$) than for the moderate–high atypia expression group at 47 of 127 (37%). However, there were also a substantial number of subjects discordant between the atypia and the normal lobules in terms of favorable ERβ expression ($x = 0.22$), with a favorable score for the normal lobules but not the atypia in 16 of 171 (9%) and a favorable score for the atypia but not the normal lobules in 47 of 171 (27%).

High ERβ expression in the normal lobules was also protective against future development of breast cancer, and as with the atypia lesion, nuclear percent staining ($P = 0.002$), intensity of staining ($P = 0.01$), and sum score ($P = 0.001$) were each significantly associated with risk. A low–moderate sum score (score, 0–5) conferred a HR of 2.5 (95% CI, 1.3–5.1) for future breast cancer risk versus a high sum score (score, 6–7), $P = 0.006$ (Fig. 3B).

**Multivariate analysis.** The potential for multivariate analysis was somewhat limited because of the small number of breast cancer events ($n = 36$). Yet, after adjustment for the key risk factors of age,
Figure 2.
The relationship between ERβ expression in the atypia (left) and in the normal lobules (right) with age, lobular involution, and the number of atypical foci.
degree of lobular involution, and number of foci of atypia, lower ERβ expression remained significantly associated with increased breast cancer risk, in both the atypia (adjusted HR, 2.3; 95% CI, 1.1–4.5; P = 0.007) and in the normal lobules (adjusted HR, 2.3; 95% CI, 1.1–4.8; P = 0.006). When both atypia and normal lobule ERβ expression were included in the same model with the above-mentioned covariates, their respective HRs showed some attenuation (adjusted HRs, 1.91 and 1.96; P = 0.07 and P = 0.08, respectively), yet each measure continued to show a trend.

We noted a slight shift in ERβ scores over time with higher scores observed in more recent years (normal lobule median sum score, 6 vs. 5 and atypia median sum score, 4 vs. 3 for 1982–1991 vs. 1967–1981, respectively, P < 0.01 for both). However, although these differences were statistically significant, the absolute differences were modest and HR estimates adjusting for year of BBD biopsy remained significant with only small attenuations relative to the unadjusted estimates (HR, 1.9; 95% CI, 0.9–3.6 for low vs. high–moderate scores in the atypia, and HR, 2.3; 95% CI, 1.2–4.9 for low–moderate vs. high scores in normal lobules).

To further explore whether considering ERβ expression from both the atypia and normal added value to either alone, three categories of ERβ expression were compared, derived from the combination of the binary variables for the atypia lesion (low or moderate–high) and the normal lobules (low–moderate or high; Fig. 4). Those with low expression in the atypia and low–moderate expression in the normal lobules (unfavorable/unfavorable) had the highest risk of future breast cancer with an estimated cumulative incidence of 29.2% at 20 years and an unadjusted HR of 3.7 (95% CI, 1.6–8.8) or an adjusted HR of 3.8 (95% CI, 1.6–9.5; P = 0.001) as compared with subjects with moderate–high expression in the atypia and high expression in the normal lobules (favorable/favorable) who had an estimated cumulative incidence of 10.4% at 20 years. Those with favorable expression levels for either the atypia or normal lobules but not both showed an intermediate degree of risk that was not significantly different from the most and least favorable categories (data not shown), although these analyses are limited by sample size.

**Effect of age on ERβ expression and breast cancer risk.** To explore the effect of hormonal status on the protective effect of higher ERβ expression, associations of ERβ expression and breast cancer development were determined within age strata roughly corresponding to pre-, peri-, and postmenopausal states based on age at benign biopsy. The effect of low ERβ expression in the atypia lesion was greatest for older patients. For women older than 55 years, the HR was 3.4 (95% CI, 1.1–10.3); for those between ages 45 and 55 years, the HR was 1.8 (95% CI, 0.7–4.6); and for those younger than 45 years, the HR was 1.1 (95% CI, 0.2–4.8) as shown in Fig. 5. In contrast, lower ERβ expression in normal lobules showed a stronger effect in younger women. In women younger than 45 years at biopsy, low–moderate versus high ERβ expression was strongly associated with future breast cancer risk with a HR of 15.2 (95% CI, 1.8 to >100). Smaller effects of ERβ expression in normal lobules were observed for individuals 45 to 55 (HR, 1.5; 95% CI, 0.6–3.8) and older than 55 years (HR, 2.3; 95% CI, 0.8–7.4) at the time of benign biopsy. Strikingly, no patient (0 of 15) younger than 45 years with high normal lobule ERβ expression developed breast cancer during follow-up versus 40% (6 of 15) with low–moderate expression.
Figure 5.
Association of ERβ expression in the atypia and adjacent normal lobules with subsequent breast cancer risk stratified by age groups.
with low–moderate normal lobule ERβ expression, \( P = 0.008 \), as shown in Fig. 5.

Discussion

Atypical hyperplasia is identified in 4% to 10% of benign breast biopsies (42–44). Recent data suggest that the absolute risk of future breast cancer imparted after a biopsy demonstrating atypia is about 30% at 25 years, comparable to the risk associated with mantle radiation prior to 31 years, a well-recognized indication for breast cancer risk reduction interventions (33, 45–47). While a prior benign breast biopsy showing atypia confers a substantial risk for the future development of breast cancer, currently used models to predict breast cancer risk are poorly applicable to these women, although a risk model incorporating benign breast biopsy histology recently has been published (48). In current practice, the use of cumulative incidence data is recommended when counseling women with atypical hyperplasia on their future risk of breast cancer and the number of atypical foci is reported as the best further discriminant of risk for these high-risk women (47).

Despite these advances, further individualization of risk prediction is needed, as the majority of these very high-risk women will not be diagnosed with breast cancer. To this end, we evaluated ERβ expression using a sum score incorporating both the extent and intensity of staining and found that preserved nuclear ERβ expression in the atypia and in the normal lobules of women with atypical hyperplasia was significantly associated with a decreased risk of subsequent breast cancer.

In our longitudinal cohort study, we found that when ERβ expression was diminished within the atypical epithelium, the risk of future breast cancer was doubled. Low ERβ expression in the adjacent normal lobules also was associated with a 2.5-fold increase in future breast cancer risk. Furthermore, high ERβ expression in the normal lobules was most protective against future breast cancer for women who were under 45 years of age (and likely premenopausal) at the time of their biopsy. To the best of our knowledge, this is the first study to evaluate ERβ expression and breast cancer risk in a well-defined cohort of women with long-term follow-up.

Shaaban and colleagues reported a case-control study in which they evaluated patients who were diagnosed with breast cancer at least 6 months after a prior benign breast biopsy and compared them to an age and year of biopsy-matched group of controls who had a benign biopsy between 1979 and 1999 and who did not develop cancer (20). In this study, ERβ expression was assessed in 54 cases and 71 controls in foci of usual type hyperplasia without atypia using the same antibody we used, specific for the full-length ERβ1 receptor. In the hyperplastic lesions of cases versus controls, they found a nonstatistically significant difference in mean nuclear percent staining for ERβ: 68% in the cases versus 81% in the controls. In 116 normal lobules evaluated for ERβ expression, 56 from patients who later developed cancer and 60 who did not, mean percentage nuclear staining was 89% in the cases versus 97% in the controls. These findings lend support to our hypothesis that high levels of ERβ expression in both the atypical lesion and adjacent normal breast tissue are protective against future breast cancer. To the best of our knowledge, no other case-control studies evaluating ERβ expression and subsequent breast cancer risk have been reported.

We confirmed that ERβ expression was lower in the atypia than in adjacent normal lobules whether assessed by nuclear percent staining, staining intensity, or sum score.Roger and colleagues evaluated 13 cases of atypia (12 ADH and one ALH), of which two were from patients with coincident cancer. They evaluated total ERβ expression with a polyclonal ERβ503 antibody and described a statistically significant decrease in the ERβ to EBr ratio in the lesionol epithelia versus both adjacent normal epithelia and normal lobules from reduction mammoplasties (8). Ellis and colleagues reported similar findings on ERβ expression in a study of ADH grouped with ductal carcinoma in situ (DCIS), and ALH grouped with lobular carcinoma in situ (LCIS) from both patients with and without cancer combined (10). This study used the 14C8 ERβ antibody, which also detects total ERβ, including splice variants, and described similar levels of ERβ expression in normal lobules from breast reduction specimens and patients with cancer and a steady decline in expression from BBD with usual hyperplasia to atypia combined with carcinoma in situ. Using a different ERβ1-specific antibody and categorization of staining similar to our methodology, Chantzi and colleagues found that ERβ1 expression was slightly, but not significantly, higher in 14 samples of normal breast tissue versus 16 cases of atypical hyperplasia (12). Unlike our study and another (10) in which there was no association between age and ERβ expression in the atypia or adjacent normal lobule, they further found that ERβ1 expression declined after menopause in normal breast lobules and BBD, including atypical hyperplasia as well as in DCIS.

Our finding of the dramatic protective effect on future breast cancer risk of high ERβ expression in the normal adjacent breast lobules in premenopausal patients is intriguing and raises several interesting hypotheses for further investigation. Might early intervention to preserve or create a high ERβ breast environment prior to menopause confer a risk-reducing benefit that extends for decades? Why is it that ERβ is so effective when patients are younger (premenopausal) and why is the effect so long lasting even after menopause? Is this analogous to the tamoxifen effect of 5 years of treatment affecting 20-year event rate? Would therapeutic targeting of ERβ represent a novel treatment for breast cancer prevention? These findings lend further support to the notion that ERβ functions as a potent tumor suppressor in the breast and lay the foundation for future studies aimed at addressing these questions.

Strengths of our study include use of an established and well-characterized patient cohort with long-term follow-up information on breast cancer events, as well as careful central pathology review and verification of cases. Limitations include the relatively modest absolute number of events and use of a manual, semiquantitative scoring system for assessing ERβ expression. Along with development of digital quantitation algorithms to permit semiautomated reads of immunohistochemical ERβ expression, confirmation of our findings in a validation cohort is needed prior to clinical application of these data.

Conclusions

Here, we show for the first time that preserved ERβ expression in atypical hyperplasia and within normal adjacent breast epithelium is protective against the future development of breast cancer. These data suggest that ERβ may be both a biomarker of elevated breast cancer risk and a potential target for therapeutic intervention. Analysis in a validation cohort to confirm our findings, and further investigation in a larger group of women at lower risk for breast cancer is indicated to confirm the role of ERβ as a novel...
biomarker of breast cancer risk. Studies are warranted to further elucidate the mechanisms by which ERγ functions in normal breast epithelial cells and/or alters the microenvironment surrounding atypical breast lesions, in order to elicit a breast cancer preventative effect. Finally, strategies aimed at enhancing ERγ expression levels and activating the tumor suppressive effects of this receptor appear promising for the prevention of breast cancer.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.M. Carter, M. Bois, M. Frost, L.C. Hartmann, D.W. Visscher, A.C. Degnim

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