Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Association for Academic Surgery

The Influence of Age on the Histopathology and Prognosis of Atypical Breast Lesions

Amanda R. Sergesketter, BS,[a] *Samantha M. Thomas, MS,*[b,c] *Oluwadamilola M. Fayanju, MD, MA, MPHS,*[a,b] *Carolyn S. Menendez, MD,*[a,b] *Laura H. Rosenberger, MD, MS,*[a,b] *Rachel A. Greenup, MD, MPH,*[a,b] *Terry Hyslop, PhD,*[b,c] *Edgardo R. Parrilla Castellar, MD, PhD,*[a,d] *E. Shelley Hwang, MD, MPH,*[a,b] *and Jennifer K. Plichta, MD, MS*[a,b,*]

[a] *Department of Surgery, Duke University Medical Center, Durham, North Carolina*
[b] *Duke Cancer Institute, Durham, North Carolina*
[c] *Department of Biostatistics and Bioinformatics, Duke University, Durham, North Carolina*
[d] *Department of Pathology, Duke University Medical Center, Durham, North Carolina*

ARTICLE INFO

Article history:
Received 8 December 2018
Received in revised form
8 March 2019
Accepted 22 March 2019
Available online xxx

Keywords:
Age
Atypical breast lesions
Breast atypia
Breast cancer risk

ABSTRACT

Background: Although several prognostic variables and risk factors for breast cancer are age-related, the association between age and risk of cancer with breast atypia is controversial. This study aimed to compare the type of breast atypia and risk of underlying or subsequent breast cancer by age.

Methods: Adult women with breast atypia (atypical ductal hyperplasia, atypical lobular hyperplasia, and lobular carcinoma *in situ*) at a single institution from 2008 to 2017 were stratified by age at initial diagnosis: <50 y, 50-70 y, and >70 y. Regression modeling was used to estimate the association of age with risk of underlying carcinoma or subsequent cancer diagnosis.

Results: A total of 530 patients with atypia were identified: 31.1% < 50 y ($n = 165$), 58.1% 50-70 y ($n = 308$), and 10.8% > 70 y ($n = 57$). The proportion of women with atypical ductal hyperplasia steadily increased with age, compared with atypical lobular proliferations ($P = 0.04$). Of those with atypia on needle biopsy, the overall rate of underlying carcinoma was 17.5%. After adjustment, older age was associated with a greater risk of underlying carcinoma (odds ratio: 1.028, 95% confidence interval: 1.003-1.053; $P = 0.03$). Of those confirmed to have atypia on surgical excision, the overall rate of a subsequent cancer diagnosis was 15.7%. Age was not associated with a long-term risk for breast cancer ($P = 0.48$) or the time to a subsequent diagnosis of carcinoma (log-rank $P = 0.41$).

Conclusions: Although atypia diagnosed on needle biopsy may be sufficient to warrant surgical excision, older women may be at a greater risk for an underlying carcinoma,

Presentation: Quickshot presentation at the Academic Surgical Congress in February 2019.

* *Corresponding author*. Department of Surgery, Duke University Medical Center, DUMC 3513 Durham, NC 27710. Tel.: +919 681 9156; fax: +919 660 8608.
E-mail address: jennifer.plichta@duke.edu (J.K. Plichta).

0022-4804/$ – see front matter
https://doi.org/10.1016/j.jss.2019.03.047

albeit the long-term risk for malignancy associated with atypia does not appear to be affected by age.

Introduction

Breast cancer is the most common noncutaneous malignancy in adult women across all age groups.[1] Age is a well-studied risk factor for invasive and *in situ* breast cancer, with both breast cancer incidence and death rates increasing with age.[2] This variation has been attributed, in part, to differences in treatment patterns among older women,[3-5] as well as additive cumulative risks from lifetime estrogen exposure and differences in intrinsic tumor biology.[6-8]

Breast atypia is a common diagnosis found in 10% of benign breast biopsies, and it carries an increased risk for the development of a subsequent breast malignancy.[9] Breast atypia represents a histopathologic spectrum, including atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and lobular carcinoma *in situ* (LCIS). While ADH and ALH have an estimated lifetime risk of breast cancer of 20%-30%,[10,11] a diagnosis of LCIS carries a lifetime risk of breast cancer that approaches 40%.[10,12,13] Current management of these lesions is controversial. While surgical excision may be recommended for many patients,[14] active surveillance may be preferred in certain populations and/or in the context of certain radiopathologic findings.[15,16] Thus, estimating the individual risk of underlying carcinoma among various cohorts is important to guide decision-making regarding active surveillance versus surgical excision.[13] Patient characteristics such as premenopausal status and use of hormone replacement therapy (HRT) have been shown to increase a woman's risk of cancer after an atypia diagnosis[15,17] and may influence management decisions. However, despite extensive research into how breast cancer biology, prognosis, and treatment strategies vary across age groups,[4,5,7,8,18-20] the effect of age on clinical outcomes after a diagnosis of atypia is not clearly defined. The aim of this study was to stratify types of breast atypia and risk of breast cancer by age.

Methods

After obtaining institutional review board approval, the medical records of adult women diagnosed with breast atypia (LCIS, ADH, or ALH) at a major academic institution from 2008 to 2017 were identified. Given the methods and scope of the research (retrospective chart review with minimal risk to participants), a waiver of informed consent was granted. Exclusion criteria were (1) patients with unknown age, (2) patients with prior histories or concurrent diagnoses of breast malignancy, and (3) males. Age groups were defined as <50, 50-70, and >70 y old at first atypia diagnosis. Patients with multiple types of atypia were coded according to their most advanced atypia as follows: (1) LCIS; (2) ADH; and (3) ALH. Demographic characteristics captured at the time of atypia diagnosis included age, body mass index (BMI), and breast cancer risk factors including family history (in a first- or second-degree relative), menopausal status, use of HRT or oral contraceptives, gravidity and parity, and alcohol and tobacco use. Diagnostic and therapeutic information, as related to their atypia and/or breast cancer diagnosis, was also captured. Of note, the management strategy for each patient was driven by surgeon-patient discussions, not institution-specific guidelines, although national guidelines at the time of the discussion were presumably considered.

Patient characteristics were summarized as *N* (%) for categorical variables and median (interquartile range) for continuous variables. Differences between age groups were tested using the Chi-square test or Fisher's exact test for categorical variables and the analysis of variance or Kruskal-Wallis test for continuous variables, as appropriate. Logistic regression was used to estimate the effect of age (as a continuous variable) on the odds of identifying an underlying carcinoma (ductal carcinoma *in situ* [DCIS] or invasive breast cancer) on excision after atypia on needle biopsy, after adjusting for select covariates; odds ratios (ORs) and 95% confidence intervals (CIs) are reported. Poisson regression was used to estimate the effect of age on the risk of a subsequent breast cancer diagnosis, after adjusting for select covariates; risk ratios (RRs) and 95% CI are reported. This model accounts for differences in patient observation time by including an offset value of the log-transformed follow-up time in months.

Time to a subsequent diagnosis of DCIS or invasive carcinoma was calculated as the time in months from the date of first atypia diagnosis to the date of subsequent carcinoma diagnosis (*in situ* or invasive) or the date of last follow-up for patients who did not develop a subsequent carcinoma. Patients who were found to have an underlying malignancy (DCIS or invasive carcinoma) on excision after their initial atypia biopsy were excluded from the time to subsequent diagnosis model. Median time to a subsequent carcinoma diagnosis and 5-y no-subsequent-carcinoma rates were estimated using the Kaplan-Meier method; differences between age groups were tested using the log-rank test. A Cox proportional hazards model was used to estimate the association of age (as a continuous variable) with time to subsequent diagnosis of DCIS or invasive carcinoma, after adjustment for covariates. Given the small number of deaths in the cohort during the follow-up period ($n = 14$), these were not accounted for as a competing risk in the multivariate modeling.

Only patients with available data for all covariates for a given analysis were included in each model, and effective sample sizes are reported for each table or figure. A *P*-value <0.05 was considered significant, and no adjustments were made for multiple comparisons. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

Table 1 – Select patient and breast disease characteristics by age group.

Characteristic	All patients ($n = 530$)	Age group (y)			P-value
		<50 ($n = 165$)	50-70 ($n = 308$)	>70 ($n = 57$)	
First atypia diagnosis					0.04
Atypical ductal hyperplasia	398 (75.1%)	115 (69.7%)	232 (75.3%)	51 (89.5%)	
Atypical lobular hyperplasia	62 (11.7%)	24 (14.5%)	34 (11%)	4 (7%)	
Lobular carcinoma *in situ*	70 (13.2%)	26 (15.8%)	42 (13.6%)	2 (3.5%)	
Most advanced atypia diagnosis[*]					0.21
Atypical ductal hyperplasia	396 (74.7%)	116 (70.3%)	231 (75%)	49 (86%)	
Atypical lobular hyperplasia	25 (4.7%)	9 (5.5%)	14 (4.5%)	2 (3.5%)	
Lobular carcinoma *in situ*	109 (20.6%)	40 (24.2%)	63 (20.5%)	6 (10.5%)	
Age (y), median (IQR)	54 (48-64)	45 (42-47)	58 (53-64)	75 (73-78)	<0.001
Age at first live birth, median (IQR)	25 (20-30)	28 (23-32)	24 (20-30)	21 (19-24)	<0.001
Menopausal status					<0.001
Pre	91 (17.2%)	84 (50.9%)	7 (2.3%)	0 (0%)	
Peri	31 (5.8%)	14 (8.5%)	17 (5.5%)	0 (0%)	
Post	360 (67.9%)	43 (26.1%)	262 (85.1%)	55 (96.5%)	
Use of hormone replacement therapy					<0.001
Yes, currently	19 (3.6%)	2 (1.2%)	12 (3.9%)	5 (8.8%)	
Yes, in the past	102 (19.2%)	8 (4.8%)	79 (25.6%)	15 (26.3%)	
No, never	297 (56%)	134 (81.2%)	144 (46.8%)	19 (33.3%)	
Not sure	105 (19.8%)	19 (11.5%)	69 (22.4%)	17 (29.8%)	
Parity, median (IQR)	2 (1-3)	2 (1-2)	2 (1-2)	3 (2-4)	<0.001
Family history of cancer					0.05
No	82 (15.5%)	17 (10.3%)	52 (16.9%)	13 (22.8%)	
Yes	424 (80%)	139 (84.2%)	243 (78.9%)	42 (73.7%)	
Germline genetic testing					<0.001
No or unknown	467 (88.1%)	130 (78.8%)	281 (91.2%)	56 (98.3%)	
Yes, negative	60 (11.3%)	33 (20%)	26 (8.4%)	1 (1.8%)	
Yes, mutation identified	3 (0.6%)	2 (1.2%)	1 (0.3%)	0 (0%)	
Diagnosis method of initial atypia					0.98
Surgical excision	59 (11.1%)	19 (11.5%)	34 (11%)	6 (10.5%)	
Needle biopsy	471 (88.9%)	146 (88.5%)	274 (89%)	51 (89.5%)	
Atypia on needle biopsy ± underlying malignancy on excision[†]					0.29
No	329 (82.5%)	107 (84.9%)	190 (82.6%)	32 (74.4%)	
Yes	70 (17.5%)	19 (15.1)	40 (17.4%)	11 (25.6%)	
Type of atypia on needle biopsy ± underlying malignancy on excision[†]					0.37
No underlying malignancy	329 (82.5%)	107 (84.9%)	190 (82.6%)	32 (74.4%)	
Underlying malignancy + first atypia ADH	53 (13.3%)	12 (9.5%)	32 (13.9%)	9 (20.9%)	
Underlying malignancy + first atypia ALH	6 (1.5%)	3 (2.4%)	2 (0.9%)	1 (2.3%)	
Underlying malignancy + first atypia LCIS	11 (2.8%)	4 (3.2%)	6 (2.6%)	1 (2.3%)	
Type of malignant diagnosis on excision[‡]					0.40
Ductal carcinoma *in situ*	43 (61.4%)	10 (52.6%)	27 (67.5%)	6 (54.5%)	
Invasive carcinoma	26 (37.1%)	9 (47.4%)	12 (30%)	5 (45.5%)	
Subsequent diagnosis of malignancy[§]					0.66
No	386 (84.3%)	124 (86.1%)	222 (82.8%)	40 (87%)	
Yes	72 (15.7%)	20 (13.9%)	46 (17.2%)	6 (13%)	
Type of atypia on initial biopsy ± subsequent diagnosis of malignancy[§]					0.58
No subsequent malignancy	386 (84.3%)	124 (86.1%)	222 (82.8%)	40 (87%)	

(*continued*)

Table 1 – (*continued*)

Characteristic	All patients ($n = 530$)	Age group (y)			*P*-value
		<50 ($n = 165$)	50-70 ($n = 308$)	>70 ($n = 57$)	
Subsequent malignancy + first atypia ADH	49 (10.7%)	11 (7.6%)	32 (11.9%)	6 (13%)	
Subsequent malignancy + first atypia ALH	10 (2.2%)	3 (2.1%)	7 (2.6%)	0 (0%)	
Subsequent malignancy + first atypia LCIS	13 (2.8%)	6 (4.2%)	7 (2.6%)	0 (0%)	
Type of subsequent malignancy diagnosis[‖]					0.93
Ductal carcinoma *in situ*	33 (45.8%)	10 (50%)	20 (43.5%)	3 (50%)	
Invasive carcinoma	39 (54.2%)	10 (50%)	26 (56.5%)	3 (50%)	

Data presented as *N* (%) unless otherwise specified. Percentages may not add up to 100 because of rounding or missing values.
IQR = interquartile range; ADH = atypical ductal hyperplasia; ALH = atypical lobular hyperplasia; LCIS = lobular cancer *in situ*.
[*] Patients with multiple types of atypia were coded according to their most advanced atypia as follows: (1) LCIS; (2) ADH; (3) ALH.
[†] Among women who were diagnosed with atypia by needle biopsy and underwent surgical excision ($n = 399$).
[‡] Among women who were found to have an underlying malignancy on surgical excision after needle biopsy with atypia ($n = 70$).
[§] Among women who were not found to have an underlying malignancy on surgical excision after needle biopsy with atypia ($n = 458$).
[‖] Among women who were diagnosed with a subsequent malignancy.

Results

Application of the defined inclusion and exclusion criteria resulted in the final study population of 530 women diagnosed with breast atypia from 2008 to 2017. The cohort included 165 women aged <50 y (31.1%), 308 women aged 50-70 y (58.1%), and 57 women aged >70 y (10.8%). Notably, there were 26 women younger than 40y (4.9%). For the overall cohort, the median age at diagnosis was 54 y (interquartile range: 48-64 y). Median follow-up time from the first atypia diagnosis was 49 mo (95% CI: 44-53.9 mo), and there were 14 deaths during this time period (2.6%): 1 patient after identification of an underlying breast cancer on excision (after needle biopsy with atypia), 3 after a subsequent diagnosis of breast cancer, and 10 without a breast cancer diagnosis at any time. Most women were postmenopausal at diagnosis (67.9%), and a family history of breast cancer in either a first- or second-degree relative was present in 80% of women (Table 1). Only 24 patients underwent a breast magnetic resonance imaging (MRI) within 18 mo of diagnosis, including 11 women aged <50 y (6.7%), 12 women aged 50-70 y (3.9%), and only 1 woman aged >70 y (1.8%). ADH was the most common initial histopathologic diagnosis in 75.1% of patients ($n = 398$), followed by LCIS in 13.2% ($n = 70$) and ALH in 11.7% ($n = 62$). Of note, 10 patients were diagnosed with pleomorphic LCIS specifically, which was equally distributed across all age groups (<50 y: 1.8%; 50-70 y: 1.9%; >70 y: 1.8%). The proportion of women with ADH steadily increased with age, compared with atypical lobular proliferations (overall $P = 0.04$) (Table 1).

Breast cancer risk factors by age

BMI varied by age, with a higher median BMI among women aged 50-70 y (<50 y: 26.9; 50-70 y: 29.4; >70 y: 26.4; $P = 0.004$). Women aged >70 y were less likely to drink alcohol currently (<50 y: 50.3%; 50-70 y: 46.8%; >70 y: 24.6%; $P = 0.03$) or use tobacco currently (<50 y: 6.7%; 50-70 y: 6.5%; >70 y: 0%; $P = 0.02$). Age at the first live birth was highest among younger women aged <50 y ($P < 0.001$). Given that women aged >70 y were more often postmenopausal at diagnosis ($P < 0.001$), they were also more likely to report a history of HRT ($P < 0.001$). Older women aged >70 y also had a higher median parity ($P < 0.001$). Younger women <50 y reported higher rates of oral contraceptive use (<50 y: 46.1%; 50-70 y: 42.2%; >70 y: 19.3%; $P = 0.003$) and were more likely to have a family history of breast cancer in either a first- or second-degree relative ($P = 0.05$). Germline genetic testing was uncommon overall (11.9% had testing) but was more common among women <50 y ($P < 0.001$) (Table 1). It was also more common among patients with LCIS (22.9% *versus* 9.6% of ADH and 12% of ALH; $P = 0.002$). Notably, only 3 patients had a germline genetic mutation (all BRCA1/2, all women <70 y).

Risk of underlying carcinoma by age

Fifty-nine (11.1%) patients were diagnosed with breast atypia by surgical excision, and 471 (88.9%) were diagnosed by needle biopsy. Of the women diagnosed with breast atypia by needle biopsy ($n = 471$), 399 underwent surgical excision, and 17.5% ($n = 70$ of 399) were found to have an underlying carcinoma (DCIS or invasive disease) at the time of excision (Table 1). Of the 70 women diagnosed with an underlying carcinoma, 61.4% had DCIS and 37.1% had invasive disease, which was similar between age groups ($P = 0.40$). For those with an underlying carcinoma, tumor stage, grade, and biomarkers were similar across all age groups (Table 2). After adjustment, increasing age was associated with an increased risk of underlying carcinoma at surgical excision (OR: 1.028; 95% CI: 1.003-1.053; $P = 0.03$). However, the type of atypia diagnosis ($P = 0.12$) and family history of breast cancer ($P = 0.52$) were not associated with underlying carcinoma at the time of surgical excision (Table 3). Of note, 72 patients diagnosed with atypia on needle biopsy did not undergo surgical excision at that time. Of the 59 women diagnosed with breast atypia by surgical excision, 3.4% ($n = 2$) were found to have an underlying breast cancer after additional surgery.

Risk of subsequent breast cancer and time to carcinoma by age

During the follow-up (median 49 mo) of the 458 women with atypia who did not have an underlying carcinoma at the time

Table 2 – Summary of those with atypia on needle biopsy and found to have an underlying malignancy at surgical excision (*n* = 70) by age group, including DCIS (*n* = 43) or invasive disease (*n* = 26).

	All patients (*n* = 70)	Age group (y)			P-value
		<50 (*n* = 19)	50-70 (*n* = 40)	>70 (*n* = 11)	
DCIS, estrogen receptor*					0.33
Positive	38 (88.4%)	9 (90%)	24 (88.9%)	5 (83.3%)	
Negative	3 (7%)	1 (10%)	1 (3.7%)	1 (16.7%)	
DCIS, progesterone receptor*					1.00
Positive	36 (83.7%)	9 (90%)	22 (81.5%)	5 (83.3%)	
Negative	5 (11.6%)	1 (10%)	3 (11.1%)	1 (16.7%)	
DCIS, grade*					0.25
1	7 (16.3%)	0 (0%)	5 (18.5%)	2 (33.3%)	
2	23 (53.5%)	7 (70%)	13 (48.1%)	3 (50%)	
3	2 (4.7%)	0 (0%)	1 (3.7%)	1 (16.7%)	
Invasive cancer, T stage*					0.75
T0	1 (3.8%)	0 (0%)	1 (8.3%)	0 (0%)	
T1	20 (76.9%)	7 (77.8%)	8 (66.7%)	5 (100%)	
T2	2 (7.7%)	0 (0%)	2 (16.7%)	0 (0%)	
Invasive cancer, N stage*					0.14
N0	20 (76.9%)	7 (77.8%)	11 (91.7%)	2 (40%)	
N1	1 (3.8%)	0 (0%)	0 (0%)	1 (20%)	
Invasive cancer, ER status*					-
Positive	21 (80.8%)	6 (66.7%)	11 (91.7%)	4 (80%)	
Negative	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Invasive cancer, PR status*					1.00
Positive	20 (76.9%)	6 (66.7%)	10 (83.3%)	4 (80%)	
Negative	1 (3.8%)	0 (0%)	1 (8.3%)	0 (0%)	
Invasive cancer, HER2 status					0.19
Positive	4 (15.4%)	0 (0%)	4 (33.3%)	0 (0%)	
Negative	17 (65.4%)	6 (66.7%)	7 (58.3%)	4 (80%)	
Unknown	5 (19.2%)	3 (33.3%)	1 (8.3%)	1 (20%)	
Invasive cancer, grade*					1.00
1	11 (42.3%)	3 (33.3%)	5 (41.7%)	3 (60%)	
2	8 (30.8%)	2 (22.2%)	4 (33.3%)	2 (40%)	
3	2 (7.7%)	0 (0%)	2 (16.7%)	0 (0%)	
Treatment with radiation therapy†					0.01
No	28 (40%)	12 (63.2%)	10 (25%)	6 (54.5%)	
Yes	39 (55.7%)	6 (31.6%)	28 (70%)	5 (45.5%)	
Treatment with chemotherapy‡					0.68
No	22 (84.6%)	8 (88.9%)	9 (75%)	5 (100%)	
Yes	2 (7.7%)	0 (0%)	2 (16.7%)	0 (0%)	
Treatment with endocrine therapy†					0.16
No	46 (65.7%)	12 (63.2%)	29 (72.5%)	5 (45.5%)	
Yes	21 (30%)	6 (31.6%)	9 (22.5%)	6 (54.5%)	
Treatment with endocrine therapy, if ER+ and/or PR+†					0.20
No	17 (24.3%)	4 (21.1%)	8 (20%)	5 (45.5%)	
Yes	39 (55.7%)	10 (52.6%)	25 (62.5%)	4 (36.4%)	

DCIS = ductal carcinoma *in situ*; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.
* Among women with known results/status.
† Among women who have either DCIS and/or invasive disease.
‡ Among women who have invasive disease only.

Table 3 – Adjusted logistic regression for underlying malignancy at surgical excision after needle biopsy with atypia (*n* = 367).

	Odds ratio (95% CI)	*P*-value	Overall *P*-value
Age (y)	1.028 (1.003-1.053)	0.03	0.03
Race/Ethnicity			0.42
Non-Hispanic white	Ref		
Non-Hispanic black	1.279 (0.699-2.339)	0.42	
First atypia diagnosis			0.12
Atypical ductal hyperplasia	Ref		
Atypical lobular hyperplasia	0.724 (0.269-1.953)	0.52	
Lobular carcinoma *in situ*	2.095 (0.965-4.552)	0.06	
Family history of cancer			0.52
No	Ref		
Yes	1.336 (0.556-3.209)	0.52	

Sixty-three of 367 patients included in this model were found to have an underlying malignancy at surgical excision after atypia on needle biopsy. Hispanic patients were excluded because of lack of events.
DCIS = ductal carcinoma *in situ*; CI = confidence interval.

of initial surgical excision, 15.7% (*n* = 72) developed a subsequent diagnosis of breast cancer (*in situ* or invasive), which was similar for all age groups (*P* = 0.66) (Table 1). Of those who subsequently developed breast cancer, 45.8% were diagnosed with DCIS and 54.2% with invasive disease, which did not differ by age group (*P* = 0.93) (Table 1). For those who subsequently developed breast cancer, tumor stage, grade, and biomarkers did not significantly differ by age (Table 4). After adjustment, age was not associated with a risk of subsequent breast cancer (*P* = 0.48). In addition, a family history of breast cancer (*P* = 0.30) and type of atypia (*P* = 0.14) were not associated with the risk of subsequent malignancy (Table 5). The 5-y no-subsequent-carcinoma rate was similar across all age groups (<50 y: 0.881, 50-70 y: 0.811, >70 y: 0.885; *P* = 0.41), and the time to a subsequent breast cancer diagnosis did not vary significantly by age group (log-rank *P* = 0.41; Figure, Table 6).

Breast cancer prevention (chemoprevention) after atypia by age

Of the 458 women not initially diagnosed with breast cancer after their atypia diagnosis, 92.4% (*n* = 423) had chemoprevention data available (Supplemental Table 1). Of note, 1 patient may have taken chemoprevention as a part of a clinical trial. Use of chemoprevention was uncommon across all age groups (10.6% received chemoprevention, *n* = 45), and none of the women aged >70 y received chemoprevention after their atypia diagnosis (*P* = 0.02). Further stratification by the type of atypia yielded similar findings (low utilization rates across all age groups and all atypia subtypes; *P* = 0.08; Supplemental Table 1). Notably, the reasons for receiving or not receiving chemoprevention were not available in this data set. Within this cohort of 458 women, 63 subsequently developed breast cancer (13.8%), including 55 in the no-chemoprevention group (55 of 378 = 14.6%) and 8 in the chemoprevention group (8 of 45 = 17.8%). The risk of a subsequent malignant diagnosis was not significantly different between age groups after stratifying by receipt of chemoprevention (*P* = 0.18).

Discussion

In this retrospective series of women with high-risk atypical breast lesions, we found that the age at diagnosis of atypia does not influence the long-term risk of a subsequent breast cancer. However, our data suggest that age at diagnosis may be associated with the type of atypia diagnosed at presentation and with the risk of identifying underlying carcinoma at surgical excision. These findings may inform patient counseling and tailor risk estimates for the subsequent development of cancer in this population.

With the standardization and acceptance of breast cancer screening, diagnoses of breast atypia have increased significantly in the past 2 decades.[9] Many women with atypia, in accordance with the National Comprehensive Cancer Network guidelines,[14] undergo surgical excision to rule out an underlying malignancy missed by a sampling error.[21] However, atypia has been shown to carry a spectrum of risk related to malignancy, and some low-risk populations may benefit from active surveillance when identified on needle biopsy.[10,11,13,15,17,21-26] To inform this decision-making, numerous retrospective studies have aimed to identify clinical and histopathologic risk factors that predict underlying carcinoma after a diagnosis of atypia on needle biopsy. For example, factors such as multiplicity of atypical lesions[26-28] and overall extent of atypia[13,15,26,27] have been linked with an increased risk of underlying carcinoma. However, whether demographic characteristics, such as age, influence a woman's risk of underlying malignancy remains controversial.[29]

For invasive carcinoma, the influence of age on cancer biology and prognosis has been well studied. While older women have been shown to have tumors with less aggressive behavior than younger women,[30] older age has been consistently linked to a higher incidence of breast cancer,[2] as well as a poorer prognosis.[31,32] These differences likely stem from multiple factors, including access to and uptake of both screening and standard treatment strategies,[3-5] as well as reported biological and genetic differences in tumors with age.[6-

Table 4 – Summary of those with a subsequent malignant diagnosis after atypia ($n = 72$) by age group, including DCIS ($n = 33$) or invasive disease ($n = 39$).

	All patients ($n = 72$)	Age group (y)			P-value
		<50 ($n = 20$)	50-70 ($n = 46$)	>70 ($n = 6$)	
DCIS, estrogen receptor*					0.29
Positive	29 (87.9%)	9 (90%)	18 (90%)	2 (66.7%)	
Negative	3 (9.1%)	1 (10%)	1 (5%)	1 (33.3%)	
DCIS, progesterone receptor*					0.19
Positive	28 (84.8%)	8 (80%)	18 (90%)	2 (66.7%)	
Negative	4 (12.1%)	2 (20%)	1 (5%)	1 (33.3%)	
DCIS, grade*					0.25
1	5 (15.2%)	0 (0%)	5 (25%)	0 (0%)	
2	15 (45.5%)	6 (60%)	8 (40%)	1 (33.3%)	
3	10 (30.3%)	4 (40%)	4 (20%)	2 (66.7%)	
Invasive cancer, T stage*					0.17
T0	1 (2.6%)	0 (0%)	1 (3.8%)	0 (0%)	
T1	26 (66.7%)	8 (80%)	16 (61.5%)	2 (66.7%)	
T2	8 (20.5%)	0 (0%)	8 (30.8%)	0 (0%)	
T3	1 (2.6%)	1 (10%)	0 (0%)	0 (0%)	
Invasive cancer, N stage*					0.16
N0	29 (74.4%)	6 (60%)	21 (80.8%)	2 (66.7%)	
N1	4 (10.3%)	3 (30%)	1 (3.8%)	0 (0%)	
N2	2 (5.1%)	0 (0%)	3 (11.5%)	0 (0%)	
Invasive cancer, ER status*					0.65
Positive	35 (89.7%)	9 (90%)	23 (88.5%)	3 (100%)	
Negative	3 (7.7%)	0 (0%)	3 (11.5%)	0 (0%)	
Invasive cancer, PR status*					0.81
Positive	31 (79.5%)	8 (80%)	20 (76.9%)	3 (100%)	
Negative	7 (17.9%)	1 (10%)	6 (23.1%)	0 (0%)	
Invasive cancer, HER2 status					0.39
Positive	7 (17.9%)	3 (30%)	4 (15.4%)	0 (0%)	
Negative	30 (76.9%)	6 (60%)	21 (80.8%)	3 (100%)	
Unknown	2 (5.1%)	1 (10%)	1 (3.9%)	0 (0%)	
Invasive cancer, grade*					0.72
1	11 (28.2%)	2 (20%)	9 (34.6%)	0 (0%)	
2	19 (48.7%)	5 (50%)	12 (46.2%)	2 (66.7%)	
3	5 (12.8%)	2 (20%)	3 (11.5%)	0 (0%)	
Laterality of subsequent malignancy compared with initial atypia					0.23
Ipsilateral	55 (76.4%)	18 (90%)	34 (73.9%)	3 (50%)	
Contralateral	15 (20.8%)	2 (10%)	10 (21.7%)	3 (50%)	
Unknown	2 (2.8%)	0 (0%)	2 (4.4%)	0 (0%)	
Treatment with radiation therapy†					0.09
No	40 (55.6%)	12 (60%)	22 (47.8%)	6 (100%)	
Yes	25 (34.7%)	6 (30%)	19 (41.3%)	0 (0%)	
Treatment with chemotherapy‡					0.31
No	27 (69.2%)	5 (50%)	19 (73.1%)	3 (100%)	
Yes	9 (23.1%)	4 (40%)	5 (19.2%)	0 (0%)	
Treatment with endocrine therapy†					0.80
No	27 (37.5%)	8 (40%)	16 (34.8%)	3 (50%)	
Yes	40 (55.6%)	10 (50%)	27 (58.7%)	3 (50%)	

(continued)

Table 4 – (continued)

	All patients ($n = 72$)	Age group (y)			P-value
		<50 ($n = 20$)	50-70 ($n = 46$)	>70 ($n = 6$)	
Treatment with endocrine therapy, if ER+ and/or PR+[†]					0.41
No	23 (31.9%)	7 (35%)	13 (28.3%)	3 (50%)	
Yes	37 (51.4%)	9 (45%)	26 (56.5%)	2 (33.3%)	

DCIS = ductal carcinoma *in situ*; HER2 = human epidermal growth factor receptor 2; ER = estrogen receptor; PR = progesterone receptor.
[*] Among women with known results/status.
[†] Among women who have either DCIS and/or invasive disease.
[‡] Among women who have invasive disease only.

[8] The genomic and biologic landscapes of atypia, DCIS, and invasive cancer have been shown to share similar cellular expression[33] and gene expression profiles,[34] suggesting that these diagnoses represent a histopathologic spectrum.[35] However, to date, few studies have assessed whether age similarly impacts atypia biology and outcomes in this high-risk population, and the ones that have been published yield conflicting results. While some studies show that an older age at diagnosis increases the risk of carcinoma at excision[15,21,25] and that younger age at diagnosis may be associated with an increased long-term risk for breast cancer,[26] other studies have found no significant association between age at diagnosis and cancer risk associated with atypia.[29,36,37]

Our study represents one of the largest single-institution retrospective series to assess patterns of atypia diagnoses and cancer outcomes by age. We demonstrated that the histology of the initial atypia diagnosis varied with age, with increasing prevalence of ADH in older women. However, this finding may be due to a disproportionate decrease in ALH and LCIS due to the progressive, age-related loss of lobules, where atypical lobular proliferations commonly reside. In addition, it could be that older women are more likely to have mammographic calcifications, which may lead to more needle biopsies, and ADH is often associated with mammographic calcifications. In contrast, ALH and LCIS typically lack specific imaging and/or clinical characteristics and are often considered incidental findings.

Furthermore, we demonstrated that older age may increase the risk of underlying carcinoma on excision after a diagnosis of atypia on needle biopsy, a finding which may inform the ongoing debate regarding active surveillance versus surgical excision as the optimal management strategy in this population. Our findings, in conjunction with previous reports identifying older age as a risk factor for carcinoma,[15,21,25] suggest that age may be key when stratifying risk to inform management decision-making. While active surveillance may be considered in younger women in certain clinical settings, surgical excision may be more appropriate in women diagnosed at an older age because of a higher risk of underlying malignancy.

Similar to previous studies identifying no association between age and cancer risk after a diagnosis of atypia,[29,36,37] we

Table 5 – Adjusted Poisson regression for a subsequent diagnosis of DCIS or invasive breast cancer ($n = 400$), adjusting for log-transformed follow-up time.

	Risk ratio (95% CI)	P-value	Overall P-value
Age (y)	1.008 (0.986-1.031)	0.48	0.48
Race/Ethnicity			0.56
Non-Hispanic white	Ref		
Non-Hispanic black	1.176 (0.685-2.019)	0.56	
Most advanced atypia diagnosis[*]			0.14
Atypical ductal hyperplasia	Ref		
Atypical lobular hyperplasia	0.482 (0.066-3.539)	0.47	
Lobular carcinoma *in situ*	1.612 (0.946-2.746)	0.08	
Chemoprevention	0.67 (0.298-1.509)	0.33	0.33
Family history of cancer			0.30
No	Ref		
Yes	1.522 (0.689-3.362)	0.30	

Sixty-six of 400 patients included in this model had a subsequent diagnosis of DCIS or invasive breast cancer. Hispanic patients were excluded because of lack of events.
DCIS = ductal carcinoma *in situ*; CI = confidence interval.
[*] Patients with multiple types of atypia were coded according to their most advanced atypia as follows: (1) LCIS; (2) ADH; (3) ALH.

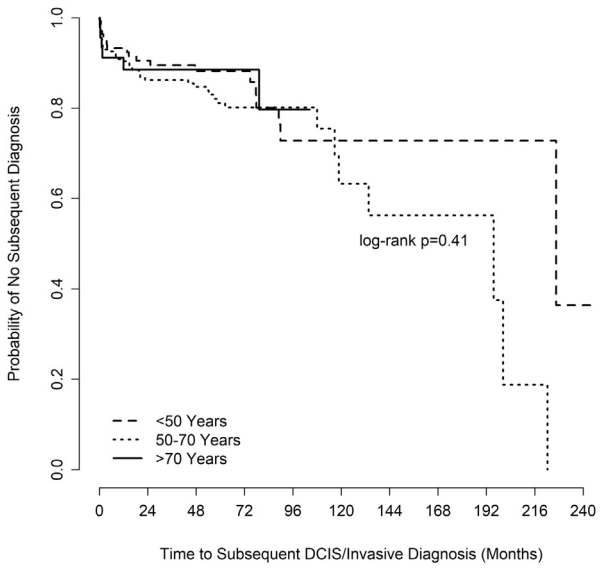

Fig – Unadjusted time to subsequent diagnosis of DCIS or invasive breast cancer by age group ($n = 447$). DCIS = ductal carcinoma *in situ*.

found that the long-term risk for developing DCIS or invasive cancer may be similar across all ages in women with preceding atypia, given a similar time period. In contrast, the baseline risk of breast cancer in general has been shown to increase with increasing age.[38] Based on these observations, one might predict that older women with atypia would be more likely to develop breast cancer within 5 y after their atypia diagnosis. However, our findings indicate these risk factors do not have an additive effect. Therefore, a woman's risk of breast cancer after atypia may be more closely related to an underlying predisposition rather than her chronologic age and suggests that similar ongoing surveillance strategies may be beneficial across all age groups (given a reasonable life expectancy). For ongoing surveillance of patients with atypia, the National Comprehensive Cancer Network guidelines recommend a clinical encounter every 6-12 mo, annual screening mammogram, and consideration of annual breast MRI. Based on our findings, these recommendations should be considered for all women with atypia and not dismissed based on age alone.

Our study additionally supports the notion that age may influence the recommendation or uptake of preventative treatment strategies for atypia. The significant risk reduction associated with chemoprevention in atypia patients has been demonstrated retrospectively[39] and in multiple clinical trials (e.g., National Surgical Adjuvant Breast and Bowel Project P-1,[40] Mammary Prevention.3,[41] International Breast Cancer Intervention Study-I,[42] and International Breast Cancer Intervention Study-II trials[43]), all of which reported substantial relative-risk reductions of 41%-79%.[9] However, only a minority of high-risk patients have been reported to use prophylactic endocrine therapy nationally despite the demonstrated benefits.[44,45] Similarly, we found a 10.6% overall chemoprevention uptake rate. Although no significant difference in the risk of a subsequent breast cancer diagnosis was noted with or without chemoprevention in our study, this may be related to the relatively short follow-up (median: 49 mo) and/or the small number of patients who received chemoprevention ($n = 45$). For patients with invasive breast cancer, use of endocrine therapy has been shown to be influenced by age, with reduced uptake of adjuvant endocrine therapy among older patients.[5,46] Similarly, in our study, we found that patients aged >70 y were less likely to receive chemoprevention, although the reasons for the difference in use are unclear (e.g., do patients decline treatment; are they poor candidates because of contraindications; or are providers not discussing or recommending treatment?). Understanding the association between age-related treatment patterns and use of endocrine therapy and that this association may extend to atypia patients may inform tailored counseling in high-risk populations.

There are some limitations to our study, many of which are inherent to its retrospective design and manual data entry. For example, data regarding clinical trial participation were limited, and although there was only documentation for 1 patient participating in a prevention trial, there could have been other patients who participated but did not have adequate documentation. While younger women <40 y represented a minority of our patient population ($n = 26$), we were unable to account for the reasons this young population underwent imaging because screening in this age group is generally outside of current guidelines. However, we did find that roughly one-third of patients underwent a breast MRI within 18 mo of diagnosis, which was more common among younger women, but we were unable to determine the indications for this imaging. Similarly, we were unable to determine if the atypical biopsies were thought to be concordant or discordant with the imaging findings, which may have affected the surgeon's decision to excise and/or breast cancer risk assessment. It is important to note that although recent national guidelines suggest surveillance may

Table 6 – Unadjusted time to subsequent diagnosis of DCIS or invasive breast cancer by age group ($n = 447$).

Age group	Total	Experienced subsequent carcinoma (%)	Median time-to subsequent carcinoma (95% CI)	5-y no-subsequent-carcinoma rate	Log-rank P-value
<50 y	140	20 (14.3%)	226.6 mo (226.6-NE)	0.881 (0.806-0.929)	0.41
50-70 y	261	46 (17.6%)	195.6 mo (118.8-222.3)	0.811 (0.745-0.862)	
>70 y	46	6 (13%)	NE (NE–NE)	0.885 (0.745-0.951)	
Total	447	72 (16.1%)			

DCIS = ductal carcinoma *in situ*; NE = nonestimable.

be indicated in select clinical settings, these guidelines notably changed during the study period, and excision was likely recommended to nearly all patients with atypia in the earlier years. In addition, geographic differences in patient populations (as related to differences in the proportions of certain races and ethnicities, and/or environmental exposures) may limit generalizability. Regardless, this study represents a foundation for further research into how patient characteristics, such as age, may differentially impact prognosis after a diagnosis of an atypical breast lesion. Future directions should include multicenter studies representing larger and more diverse populations with high-risk breast lesions and further explore some of the biologic differences in atypia that likely exist among various cohorts.

Conclusions

Among women with atypical breast lesions, age did not influence the long-term risk of a subsequent breast cancer. However, older women presented more commonly with ductal atypia and have a higher risk of underlying carcinoma at the time of initial surgical excision. Moreover, older women with atypia are less likely to use chemoprevention strategies. Additional research into the interrelationship of age, histologic subtype, and use of chemoprevention is necessary.

Acknowledgment

The database used for this study was created by Mary Beth Aschenbrenner, Chandra Almond, and Matthew Small. Data verification was performed by Madeline Thornton. R.A.G. is supported by the National Institutes of Health Office of Women's Research Building Interdisciplinary Research Careers in Women's Health K12HD043446 (Principal Investigator [PI]: Andrews). O.M.F. is supported by the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH) under Award Number 1KL2TR002554 (PI: Svetkey). This project and its authors (S.M.T., O.M.F., C.S.M., L.H.R., R.A.G., T.H., E.S.H., and J.K.P.) are all supported by the Duke Cancer Institute through NIH grant P30CA014236 (PI: Kastan). A.R.S. contributed to study design and conception, data collection, data analysis/interpretation, manuscript drafting, critical manuscript review, and final approval. S.M.T. contributed to data analysis/interpretation, critical manuscript review, and final approval. O.M.F., C.S.M., L.H.R., R.A.G., T.H., E.R.P.C., and E.S.H. contributed to data interpretation, critical manuscript review, and final approval. J.K.P. contributed to study design and conception, data analysis/interpretation, manuscript drafting, critical manuscript review, and final approval. All authors agreed to be accountable for all aspects.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. J.K.P. has a research project supported by the Color Foundation (PI: Plichta). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jss.2019.03.047.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68:7–30.
2. Society AC. *Breast Cancer Facts & Figures 2017-2018*; 2017. Atlanta, GA. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf.
3. Weiss A, Noorbakhsh A, Tokin C, Chang D, Blair SL. Hormone receptor-negative breast cancer: undertreatment of patients over 80. *Ann Surg Oncol*. 2013;20:3274–3278.
4. Shachar SS, Hurria A, Muss HB. Breast cancer in women older than 80 years. *J Oncol Pract*. 2016;12:123–132.
5. Strader LA, Helmer SD, Yates CL, Tenofsky PL. Octogenarians: noncompliance with breast cancer treatment recommendations. *Am Surg*. 2014;80:1119–1123.
6. Lodi M, Scheer L, Reix N, et al. Breast cancer in elderly women and altered clinico-pathological characteristics: a systematic review. *Breast Cancer Res Treat*. 2017;166:657–668.
7. Benz CC. Impact of aging on the biology of breast cancer. *Crit Rev Oncol Hematol*. 2008;66:65–74.
8. Brouwers B, Fumagalli D, Brohee S, et al. The footprint of the ageing stroma in older patients with breast cancer. *Breast Cancer Res*. 2017;19:78.
9. Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. *N Engl J Med*. 2005;353:229–237.
10. McEvoy MP, Coopey SB, Mazzola E, et al. Breast cancer risk and follow-up recommendations for young women diagnosed with atypical hyperplasia and lobular carcinoma in situ (LCIS). *Ann Surg Oncol*. 2015;22:3346–3349.
11. Collins LC, Aroner SA, Connolly JL, Colditz GA, Schnitt SJ, Tamimi RM. Breast cancer risk by extent and type of atypical hyperplasia: an update from the Nurses' Health Studies. *Cancer*. 2016;122:515–520.
12. King TA, Pilewskie M, Muhsen S, et al. Lobular carcinoma in situ: a 29-year longitudinal experience evaluating clinicopathologic features and breast cancer risk. *J Clin Oncol*. 2015;33:3945–3952.
13. Linsk A, Mehta TS, Dialani V, et al. Surgical upgrade rate of breast atypia to malignancy: an academic center's experience and validation of a predictive model. *Breast J*. 2017;24:115–119.
14. Bevers TB, Helvie MA, Bonaccio E, et al. NCCN guidelines: breast cancer screening and diagnosis (version 3.2018). 2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf. Accessed January 23, 2019.
15. Uzan C, Mazouni C, Ferchiou M, et al. A model to predict the risk of upgrade to malignancy at surgery in atypical breast lesions discovered on percutaneous biopsy specimens. *Ann Surg Oncol*. 2013;20:2850–2857.
16. Nguyen CV, Albarracin CT, Whitman GJ, Lopez A, Sneige N. Atypical ductal hyperplasia in directional vacuum-assisted

biopsy of breast microcalcifications: considerations for surgical excision. *Ann Surg Oncol*. 2011;18:752–761.
17. Menes TS, Rosenberg R, Balch S, Jaffer S, Kerlikowske K, Miglioretti DL. Upgrade of high-risk breast lesions detected on mammography in the Breast Cancer Surveillance Consortium. *Am J Surg*. 2014;207:24–31.
18. Newman LA. Breast cancer disparities: socioeconomic factors versus biology. *Ann Surg Oncol*. 2017;24:2869–2875.
19. Bickell NA, Weidmann J, Fei K, Lin JJ, Leventhal H. Underuse of breast cancer adjuvant treatment: patient knowledge, beliefs, and medical mistrust. *J Clin Oncol*. 2009;27:5160–5167.
20. Cluze C, Colonna M, Remontet L, et al. Analysis of the effect of age on the prognosis of breast cancer. *Breast Cancer Res Treat*. 2009;117:121–129.
21. McGhan LJ, Pockaj BA, Wasif N, Giurescu ME, McCullough AE, Gray RJ. Atypical ductal hyperplasia on core biopsy: an automatic trigger for excisional biopsy? *Ann Surg Oncol*. 2012;19:3264–3269.
22. Collins LC, Baer HJ, Tamimi RM, Connolly JL, Colditz GA, Schnitt SJ. Magnitude and laterality of breast cancer risk according to histologic type of atypical hyperplasia: results from the Nurses' Health Study. *Cancer*. 2007;109:180–187.
23. Pena A, Shah SS, Fazzio RT, et al. Multivariate model to identify women at low risk of cancer upgrade after a core needle biopsy diagnosis of atypical ductal hyperplasia. *Breast Cancer Res Treat*. 2017;164:295–304.
24. Peres A, Barranger E, Becette V, Boudinet A, Guinebretiere JM, Cherel P. Rates of upgrade to malignancy for 271 cases of flat epithelial atypia (FEA) diagnosed by breast core biopsy. *Breast Cancer Res Treat*. 2012;133:659–666.
25. Ko E, Han W, Lee JW, et al. Scoring system for predicting malignancy in patients diagnosed with atypical ductal hyperplasia at ultrasound-guided core needle biopsy. *Breast Cancer Res Treat*. 2008;112:189–195.
26. Degnim AC, Visscher DW, Berman HK, et al. Stratification of breast cancer risk in women with atypia: a Mayo cohort study. *J Clin Oncol*. 2007;25:2671–2677.
27. de Mascarel I, Brouste V, Asad-Syed M, Hurtevent G, Macgrogan G. All atypia diagnosed at stereotactic vacuum-assisted breast biopsy do not need surgical excision. *Mod Pathol*. 2011;24:1198–1206.
28. Rendi MH, Dintzis SM, Lehman CD, Calhoun KE, Allison KH. Lobular in-situ neoplasia on breast core needle biopsy: imaging indication and pathologic extent can identify which patients require excisional biopsy. *Ann Surg Oncol*. 2012;19:914–921.
29. Buckley E, Sullivan T, Farshid G, Hiller J, Roder D. Risk profile of breast cancer following atypical hyperplasia detected through organized screening. *Breast*. 2015;24:208–212.
30. Ebner F, van Ewijk R, Wockel A, et al. Tumor biology in older breast cancer patients–what is the impact on survival stratified for guideline adherence? A retrospective multi-centre cohort study of 5378 patients. *Breast*. 2015;24:256–262.
31. van de Water W, Markopoulos C, van de Velde CJ, et al. Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer. *JAMA*. 2012;307:590–597.
32. Bastiaannet E, Liefers GJ, de Craen AJ, et al. Breast cancer in elderly compared to younger patients in The Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients. *Breast Cancer Res Treat*. 2010;124:801–807.
33. Emery LA, Tripathi A, King C, et al. Early dysregulation of cell adhesion and extracellular matrix pathways in breast cancer progression. *Am J Pathol*. 2009;175:1292–1302.
34. Ma XJ, Salunga R, Tuggle JT, et al. Gene expression profiles of human breast cancer progression. *Proc Natl Acad Sci U S A*. 2003;100:5974–5979.
35. Bombonati A, Sgroi DC. The molecular pathology of breast cancer progression. *J Pathol*. 2011;223:307–317.
36. Mazzola E, Coopey SB, Griffin M, et al. Reassessing risk models for atypical hyperplasia: age may not matter. *Breast Cancer Res Treat*. 2017;165:285–291.
37. Vierkant RA, Degnim AC, Radisky DC, et al. Mammographic breast density and risk of breast cancer in women with atypical hyperplasia: an observational cohort study from the Mayo Clinic Benign Breast Disease (BBD) cohort. *BMC Cancer*. 2017;17:84.
38. Coopey SB, Acar A, Griffin M, Cintolo-Gonzalez J, Semine A, Hughes KS. The impact of patient age on breast cancer risk prediction models. *Breast J*. 2018;24:592–598.
39. Coopey SB, Mazzola E, Buckley JM, et al. The role of chemoprevention in modifying the risk of breast cancer in women with atypical breast lesions. *Breast Cancer Res Treat*. 2012;136:627–633.
40. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study. *J Natl Cancer Inst*. 2005;97:1652–1662.
41. Goss PE, Ingle JN, Ales-Martinez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med*. 2011;364:2381–2391.
42. Cuzick J, Forbes JF, Sestak I, et al. Long-term results of tamoxifen prophylaxis for breast cancer–96-month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst*. 2007;99:272–282.
43. Cuzick J, Sestak I, Forbes JF, et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet*. 2014;383:1041–1048.
44. Pinsky PF, Miller E, Heckman-Stoddard B, Minasian L. Use of raloxifene and tamoxifen by breast cancer risk level in a Medicare-eligible cohort. *Am J Obstet Gynecol*. 2018;218:606.e1–606.e9.
45. Bober SL, Hoke LA, Duda RB, Regan MM, Tung NM. Decision-making about tamoxifen in women at high risk for breast cancer: clinical and psychological factors. *J Clin Oncol*. 2004;22:4951–4957.
46. Daly B, Olopade OI, Hou N, Yao K, Winchester DJ, Huo D. Evaluation of the quality of adjuvant endocrine therapy delivery for breast cancer care in the United States. *JAMA Oncol*. 2017;3:928–935.