Risk factors for breast cancer development by tumor characteristics among women with benign breast disease

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Abstract

Background: Among women diagnosed with invasive breast cancer, 30% have a prior diagnosis of benign breast disease (BBD). Thus, it is important to identify factors among BBD patients that elevate invasive cancer risk. In the general population, risk factors differ in their associations by clinical pathologic features; however, whether women with BBD show etiologic heterogeneity in the types of breast cancers they develop remains unknown.

Methods: Using a nested case-control study of BBD and breast cancer risk conducted in a community healthcare plan (Kaiser Permanente Northwest), we assessed relationships of histologic features in BBD biopsies and patient characteristics with subsequent breast cancer risk and tested for heterogeneity of associations by estrogen receptor (ER) status, tumor grade and size. The study included 514 invasive breast cancer cases (median follow-up of 9 years post-BBD diagnosis) and 514 matched controls, diagnosed with proliferative or non-proliferative BBD between 1971-2006, with follow-up through mid-2015. Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained using multivariable polytomous logistic regression models.

Results: Breast cancers were predominantly ER-positive (86%), well- or moderately-differentiated (73%), small (74% <20mm) and stage I/II (91%). Compared to patients with non-proliferative BBD, proliferative BBD with atypia conferred risk for ER-positive (OR=5.48, 95%CI=2.14-14.01) with only one ER-negative case); p-heterogeneity=0.45. Presence of columnar cell lesions (CCLs) at BBD diagnosis was associated with a 1.5-fold increase in risk of both ER-positive and ER-negative tumors, with a 2-fold increase (95%CI=1.21-3.58) observed among postmenopausal women (56%), independent of proliferative BBD status with and without atypia. We did not identify statistically significant differences in risk factor associations by tumor grade or size.

Conclusion: Most tumors that developed after a BBD diagnosis in this cohort were highly treatable low-stage ER-positive tumors. CCL in BBD biopsies may be associated with moderately increased risk, independent of BBD histology, and irrespective of ER status.

Introduction

It is well established that benign breast diseases (BBDs) increase risk of breast cancer in women [1]. In the U.S., biopsy-confirmed BBD diagnoses are 4-times more common than invasive breast cancers, affecting ~1 million women annually. BBDs include a range of pathologies with approximately 30% comprising proliferative BBD lesions (PDWA, proliferative disease i.e., without atypia) and 65% encompassing non-proliferative benign lesions [2, 3]. Proliferative BBD with atypia (atypical hyperplasia) represent 3-4% of BBD diagnoses, have been associated with a 4-5 fold increased breast cancer (BC) risk [3, 4], and considered as an indication for possible chemoprevention [5].

Since women diagnosed with BBD comprise a large proportion of future breast cancer cases (~30%), it is important to identify factors associated with subsequent BC [3]. Having undergone a clinically-indicated breast biopsy, women with BBD provide the opportunity for evaluation of whether histopathologic features increase BC risk independently of other patient characteristics. Providing accurate invasive BC risk estimates for BBD patients could improve clinical management of this large group of women, including determination of whether watchful waiting, surgery, or chemoprevention should be offered [3]. In a model that predicted overall BC risk for BBD patients, key risk factors were parity/age at first birth and family history of breast cancer, as well as histologic features, including columnar cell lesions (CCLs), radial scars, sclerosing adenosis, and lobular involution [6]. Within the Kaiser BBD study, previous analyses examined associations of lifestyle, reproductive and pathologic characteristics that are associated with subsequent risk of breast cancer [7],[8]; however, whether risks associated with these factors are similar or vary by the

characteristics of the tumors diagnosed among BBD patients is not well understood and has not been previously assessed.

Breast cancer is a heterogeneous disease, with data strongly supporting different associations of risk factors such as parity and genetic susceptibility loci by tumor subtypes defined by hormone receptor status and other clinical/pathologic features [9-12]. Whether similar etiologic heterogeneity exists for breast cancer arising in BBD patients is unknown, and to date very few cohort studies have been able to assess this hypothesis [7, 13, 14]. We therefore assessed patient and BBD histopathological features associated with BC risk and evaluated whether relationships varied by tumor characteristics.

Methods

Study population

We utilized data from a previously designed case-control study of BBD and breast cancer risk [7], nested within a BBD cohort from Kaiser Permanente Northwest (KPNW), which provides medical care for approximately ½ million members located in Southwest Washington and Northwest Oregon. The source population was comprised of women who had biopsy-confirmed BBD diagnosed between August 3, 1971 and December 31, 2006 (N=15,395; age range 21-85 years), one control had a BBD diagnosis in 2012. Invasive breast cancer diagnoses were obtained through record linkage with the KPNW Tumor Registry, as previously described [7]. Briefly, cases were defined as women diagnosed with invasive breast cancer at least one year after BBD diagnosis, and with no prior history of *in situ* lesions. The follow-up rate for the KPNW Tumor Registry since its inception in 1960 has been excellent, accounting for 98% of patients (living or dead) even if they are no longer health plan members. Controls were women with a biopsy for BBD who were alive but had not developed breast cancer during the same follow-up calendar period as that for the corresponding cases. For each case, a control case was randomly selected using risk-set sampling with replacement, matched at age at diagnosis of BBD (±1 year) and, implicitly, given the risk-set sampling, on duration of membership of KPNW [15]. In addition, each control was required not to have undergone a mastectomy before the date of diagnosis of breast cancer for her matched case. If a selected control did not have breast tissue for evaluation or had no risk factor information, a replacement control was selected. There were 514 cases and 514 matched controls available for these analyses.

Tumor characteristics

We obtained information on the following variables from the KPNW Tumor Registry: date of invasive breast cancer diagnosis, date of death, tumor histology and behavior using ICD-O coding, grade, AJCC clinical staging variable, tumor size, lymph node status. Immunohistochemistry (IHC) data on key markers were obtained for ER (which has been measured on cases since the mid-1970s), PR (first measured in 1983) and HER2 status (first measured in 1988). The percentage of tumors analyzed for ER status increased from 0% in 1980, to 18% in 1989, 54% in 1994, and 85% in 2006; HER2 status was available on 43% of tumors until 2001 and on 68% from 2002 onward.

Risk factor information

Risk factor data were captured using routine medical records, which include information on clinic visits, prescriptions, operations and laboratory testing. These data were linked using the KPNW unique health record numbers to identify each individual member. From these records, data were available for various exposures. We focused on established or suspected breast cancer risk factors, specifically: family history of breast cancer, age at menarche, parity, age at first birth, body mass index (BMI) at benign biopsy, menopausal status, and menopausal hormone use. KPNW has a well

characterized mammography screening program and by 1993 more than 75% of women over 45 had had a screening mammogram [16]. For this reason, we also report characteristics stratified by this date (**Supplemental Table 1**).

BBD histology was assessed according to the Page classification criteria [1], as follows: **proliferative disease with atypia (ADH),** if atypical hyperplasia (either ductal or lobular) was present; **proliferative disease without atypia**, if epithelial hyperplasia without atypia (either moderate or florid) OR fibroadenoma (either complex-no atypia or complex-atypia) OR sclerosing adenosis OR radial scar OR papilloma was present; **non-proliferative**, if non-proliferative lesion (either cysts, fibrosis, or apocrine metaplasia) OR mild epithelial hyperplasia without atypia OR fibroadenoma was present. Pathologist assessment of biopsies was blinded to case-control status as previously described [8]. CCL pathology and terminal duct lobular unit (TDLU) involution status were additionally ascertained on digitized BBD H&E images using the Aperio Scanscope system. Furthermore, as involution status is not typically reported in clinical pathology, we obtained more detailed semi-quantitative measures of TDLU involution previously reported to be associated with breast cancer risk among BBD patients (see **Supplemental Methods**).

Multiple imputation

We used multiple imputation to impute missing data for risk factors. The largest amount of missingness (21%) was seen for the age at menarche variable (see Supplemental Methods and Appendix A). We did not impute missing data on MHT use, as the % missingness was too large (45%) to allow for stable imputation. All variables that were correlated or associated with the outcome variables or that were potentially related to the missingness of other imputed variables were included in the imputation models (see Supplemental Methods)[17, 18]. Variables were imputed as continuous and later categorized for further analyses. Multiple imputations were performed using IVEware (0.3 version, https://www.src.isr.umich.edu/software/iveware-documentation/iveware-with-sas/). Details of imputation steps are delineated in a flow chart (**Supplementary Figure 1 and Appendix A in Supplemental Material**). All calculations presented in this paper were conducted for 5 imputed datasets separately; estimates from the different imputed datasets were combined and variances were computed using Rubin's formula as implemented in SAS 9.4, PROC MIANALYZE.

Statistical analysis

Descriptive statistics of demographic and tumor characteristics by calendar year of BBD diagnosis and age at breast cancer diagnosis were assessed using Chi-squared or Fisher's exact tests. Conditional logistic regression and unconditional logistic models adjusted for the matching factors yielded similar estimates (**Supplemental Table 2).** We therefore present odds ratios (ORs) and 95% confidence intervals (CIs) for demographic, reproductive or tissue factors (explanatory variables) for overall breast cancer risk from unconditional regression models. The unconditional logistic regression models included matching factors, as well as continuous age at BBD diagnosis and follow-up period from BBD diagnosis to breast cancer diagnosis; other key risk factors included in the models were: family history of breast cancer in 1st degree relatives, history of bilateral oophorectomy, and parity. For the main analysis to determine associations by breast cancer subtype (comparing ER, PR and HER2 status or clinicopathologically defined subtypes), we used polytomous logistic regression models adjusted for matching factors and using the same variables as for the overall BC model. Heterogeneity between factors was assessed using polytomous logistic regression analyses restricted to cases (case-only analyses) with the tumor characteristics (ER, tumor size and grade) as the outcome variable. Models were also stratified by menopausal status. A $p \leq 0.05$ was considered statistically significant and all tests were two-sided. All analyses were performed using SAS V9.4.

Results

Tumor characteristics by patient characteristics, age at breast cancer diagnosis and BBD calendar year at diagnosis

Characteristics of the BBD patients are detailed in **Supplemental Tables 1 and 2**. The median age of BBD diagnosis was 51.5 years and over 60% of cases were diagnosed between 1980-1999. As mammography screening became more common after 1993, we observed an increased frequency of proliferative disease without atypia (38.5 vs 27.6%) and with atypia (7.3 vs 4.0%, **Supplemental Table 1)** subsequent to 1993**.** We also observed increased detection of prevalent breast cancer and a stage shift, with a 12% increase in diagnosed stage I tumors after 1993 (**Supplemental Table 1).** The median follow-up between BBD and breast cancer diagnosis was 9.0 years (IQR=4.4, 15.8 years), with a median age at breast cancer diagnosis of 62.7 years. Descriptive characteristics of the BBD patients subsequently diagnosed with breast cancer, overall, and stratified by age at breast cancer diagnosis, are presented in **Table 1**. Most cases were older than 50 years (87%) at diagnosis. Breast cancers were mostly diagnosed from 1996-2005, and 55% of cases were diagnosed within 10 years of their initial BBD diagnosis.

Table 1 Characteristics of BBD histology among breast cancer cases, overall and by age at breast cancer diagnosis (N=514)

			Age at breast cancer diagnosis					ER status				
	Cases		≤50 years (N=69)		>50 years (N=445)			ER+ (N=391)		ER- (N=64)		
	N	%	N	%	N	%	P	N	%	N	%	P
Age at BBD, years												
<40	90	17.5	41	59.4	49	11.0	**<0.0001**	61	15.6	13	20.3	0.83
40-49	141	27.4	28	40.6	113	25.4		113	28.9	17	26.6	
50-59	145	28.2	0	0	145	32.6		111	28.4	19	29.7	
60-69	86	16.7	0	0	86	9.3		65	16.6	8	12.5	
≥70	52	10.1	0	0	52	11.7		41	10.5	7	10.9	
mean (SD)	52.2 (12.5)		37.5 (6.9)		54.4 (11.6)			52.4 (12.5)		51.7 (12.9)		
median (IQR)	51.5 (42.6, 60.8)		39.0 (34.9, 42.9)		53.6 (46.1, 62.1)			51.7 (42.8, 61.0)		50.6 (42.8, 59.8)		
Year of BBD diagnosis							0.062					0.92
1971 - 1979	95	18.5	19	27.5	76	17.1		50	12.8	10	15.6	
1980 - 1989	173	33.7	16	23.2	157	35.3		134	34.3	20	31.3	
1990 - 1999	161	31.3	25	36.2	136	30.6		134	34.3	22	34.4	
2000 – 2006[#]	85	16.5	9	13.0	76	17.1		73	18.7	12	18.8	
BBD histology							0.22					0.39
Normal/Non-proliferative	324	63.0	50	72.5	274	61.6		243	62.2	43	67.2	
Proliferative without atypia	163	31.7	16	23.2	147	33.3		127	32.5	20	31.3	
Proliferative with atypia	27	5.3	3	4.4	24	5.4		21	5.4	1	1.6	
Year of breast cancer diagnosis							**<0.0001**					0.53
1973 - 1990	72	14.1	22	31.9	51	11.4		21	5.4	3	4.7	
1991 - 1995	68	13.2	10	14.5	58	13.0		49	12.5	12	18.8	
1996 - 2000	101	19.7	17	24.6	84	18.8		81	20.7	17	26.6	
2001 - 2005	116	22.6	11	15.9	106	23.7		104	26.6	12	18.8	
2006 - 2010	106	20.6	5	7.3	101	22.6		91	23.3	14	21.9	
2011 - 2013	51	9.9	4	5.8	47	10.6		45	11.5	6	9.4	
Years from BBD to breast cancer diagnosis							**<0.0001**					0.55
≤10	284	55.3	54	78.3	230	51.7		198	50.6	35	54.7	
>10	230	44.8	15	21.7	215	48.3		193	49.4	29	45.3	
mean (SD)	10.8 (7.9)		7.3 (6)		11.4 (8)			11.6 (8)		10.5 (8.3)		
median (IQR)	9.0 (4.4, 15.8)		5.6 (2.9, 9.4)		9.8 (4.7, 16.3)			10.0 (5.3, 16.4)		8.7 (3.3, 15.7)		
Tumor size/mm							0.13					0.63
<10	143	28.9	26	37.7	117	27.5		90	23.9	16	26.2	

10-20	211	42.6	29	42.0	182	42.7		173	45.9	24	39.3	
>20	141	28.5	14	20.3	127	29.8		114	30.2	21	34.4	
Missing	19		0		19			14		3		
Tumor grade[c]							0.14					**<0.0001**
Well differentiated	141	34.7	14	31.8	127	34.9		134	39.3	5	8.6	
Moderately differentiated	159	38.9	13	29.6	146	40.1		149	43.7	6	10.3	
Poorly differentiated	108	26.4	17	38.6	91	25.0		58	17.0	47	81.0	
Not determined	106		25		81			50		6		
ER							**0.026**					--
Negative	64	14.1	12	24.5	52	12.8		--	--	--	--	
Positive	391	85.9	37	75.5	354	87.2		--	--	--	--	
Missing/Unknown	59		20		39			--	--	--	--	
PR							0.53					**<0.0001**
Negative	131	28.9	16	32.7	115	28.4		73	18.7	58	90.6	
Positive	323	71.2	33	67.4	290	71.6		317	81.3	6	9.4	
Missing/Unknown	60		20		40			1		0		
HER2[d]							0.99					**0.0028**
Negative	224	79.4	17	73.9	207	79.9		203	81.5	20	62.5	
Positive	50	17.7	4	17.4	46	17.8		38	15.3	12	37.5	
Equivocal	8	2.8	2	8.7	6	2.3		8	3.2	0	0.0	
Missing/Unknown	232		46		186			142		32		
Regional lymph nodes							0.98					0.11
Negative	337	73.6	47	73.4	230	73.6		264	74.6	36	64.3	
Positive	121	26.4	17	26.6	104	26.4		90	25.4	20	35.7	
Missing	56		5		51			37		8		
Tumor histology							0.54					0.14[b]
Ductal	439	83.5	59	85.5	370	83.2		322	82.4	54	84.4	
Lobular	48	9.3	8	11.6	40	9.0		39	10.0	4	6.3	
Mixed ductal/lobular	26	5.1	2	2.9	24	5.4		23	5.9	2	3.1	
Other	11	2.1	0	0.0	11	2.5		7	1.8	4	6.3	
Tumor stage							0.46					0.30[b]
I	262	58.0	32	62.8	230	57.4		223	59.3	29	47.5	
II	150	33.2	13	25.5	137	34.2		120	31.9	25	41.0	
III	29	6.4	4	7.8	25	6.2		24	6.4	5	8.2	
IV	11	2.4	2	3.9	9	2.2		9	2.4	2	3.3	
Missing	62		18		44			15		3		

Note: Among all cases, 13.4% were diagnosed with breast cancer by 50 years old versus 86.6% were diagnosed after age at 50 years. Fifty-nine cases who had missing ER status were excluded from

analyses with ER status. P values from Chi-square test except where noted; cases with missing tumor characteristics were excluded from reported % and tests; p values less than 0.05 are in bold font. P values from Fisher exact test. [c]Patients with tumor grade as "Not determined" were excluded from analysis. [d]Patients with equivocal HER2 were excluded from analysis. Involution and columnar cell lesions associations were adjusted for all factors above line indicated in OR*. [#]One control had a BBD diagnosis in 2012. BBD, benign breast disease; ER, estrogen receptor status; HER2, human epidermal growth factor; IQR, inter-quartile range; PR, progesterone receptor status; SD, standard deviation

Tumors diagnosed in this population were predominantly small (71.6% ≤20mm), well or moderately differentiated (73.6%), ER-positive (85.9%), PR-positive (71.2%), HER2-negative (79.4%), lymph node negative (73.6%), and of ductal histology (83.5%). The invasive cases were overwhelmingly of low stage, with <10% of cases being diagnosed as stage III or IV. As expected, ER status differed significantly by age at breast cancer diagnosis, with a higher proportion (24.5%) of ER-negative breast cancers diagnosed among women ≤50 compared to those older than 50 (12.8%). We also assessed whether there were differences in tumor characteristics by calendar period before and during/after 1993 [16]. Of the tumor characteristics evaluated, HER2 status showed a statistically significant difference by BBD diagnosis before and during/after 1993, with a higher proportion of HER2 negative cases diagnosed after 1993 compared to prior years (84.2 vs 73.9%, **Supplemental Table 1**). After 1993 significantly more of the tumors occurred among women ≥50 years of age, were of smaller size (10-20mm;44.4% during/after 1993 vs 34.8% before 1993), and had no or mild involution (48.93% during/after 1993 vs 36.56% before 1993, **Supplemental Table 1)**. Histologic grade data were not routinely reported prior to 1993.

Breast cancer risk factors among women with BBD

Association results for all cases combined for established risk factors, including BBD characteristics, are shown in **Supplemental Table 2**. We found that younger age at first full term birth and history of bilateral oophorectomy were inversely associated with breast cancer risk, whereas positive family history of breast cancer in a 1st degree relative, increasing severity of BBD histology and presence of CCL at BBD diagnosis were associated with increased breast cancer risk (**Supplemental Table 2)**. A representative image of CCL is shown in **Figure 1**. CCL with atypia, also known as flat epithelial atypia, is a more severe lesion that has been suggested to be associated with increased risk of breast cancer [3]; however, we were unable to assess this association in the present study as only 2 controls and 1 case had flat epithelial atypia. Lobular involution, which has been proposed in other BBD patient populations as a key risk factor for subsequent breast cancer [6, 19], was weakly inversely associated with breast cancer risk in our population [complete vs no involution, OR (95%CI) = 0.89 (0.65, 1.24)]. Neither radial scar nor sclerosing adenosis conferred a significant risk among those with proliferative BBD disease (data not shown).

Breast cancer risk by ER status among women with BBD

Risk associations by ER status for patient characteristics and histologic features of BBD are presented in **Table 2**. Most tumors were ER-positive, which limited power to detect heterogeneity; as a result, patterns of association observed for overall invasive breast cancer were generally consistent with those observed for ER-positive breast cancer risk. Having an age at first birth <30 years was associated with reduced risk of ER-positive (OR=0.69, 95%CI=0.49-0.98), but not ER-negative (OR=1.08, 95% CI=0.51-2.30) breast cancer (p-heterogeneity=0.24). Compared with patients with non-proliferative BBD, those with proliferative BBD with atypia had a greater than five-fold increased risk for ER-positive disease (OR=5.48, 95% CI=2.14-14.01). There was only one ER-negative case, hence, too

few cases to provide a reliable estimate in this subgroup. After accounting for BBD histology, the presence of CCLs at BBD diagnosis was associated with a 1.5-fold increased risk for both ER-positive (95% CI=1.03-2.29) and ER-negative (95% CI=0.73-3.07) tumors (p-heterogeneity=0.94).

Table 2. Multivariable associations between select patient characteristics and histologic features with breast cancer risk by ER status (N=969)

Variable	Controls (N=514)		Cases, ER+ (N=391)		ER+ vs. Controls OR (95% CI)*	Cases, ER- (N=64)		ER- vs. Controls OR (95% CI)*	*P*-het†
	N	%	N	%		N	%		
Age at first full-term birth/years									
Nulliparous/≥30	108	20.9	88	27.6	1.00 (Ref)	13	20.3	1.00 (Ref)	0.24
< 30	406	79.1	231	72.4	**0.69 (0.49, 0.98)**	51	79.7	1.08 (0.51, 2.30)	
P-value					**0.038**			0.84	
Family history of breast cancer									
No	434	84.4	257	80.7	1.00 (Ref)	50	77.5	1.00 (Ref)	0.56
Yes	80	15.6	62	19.3	1.30 (0.89, 1.88)	14	22.5	1.60 (0.77, 3.33)	
P-value					0.17			0.20	
History of bilateral oophorectomy									
No	429	83.4	346	88.6	1.00 (Ref)	55	85.9	1.00 (Ref)	0.42
Yes	85	16.6	45	11.4	**0.59 (0.38, 0.90)**	9	14.1	0.82 (0.37, 1.80)	
P-value					**0.015**			0.62	
BBD histology									
Normal/Non-proliferative	384	74.7	243	62.2	1.00 (Ref)	43	67.2	1.00 (Ref)	0.45
Proliferative without atypia	124	24.1	127	32.5	**1.70 (1.25, 2.30)**	20	31.3	1.49 (0.84, 2.67)	
Proliferative with atypia	6	1.2	21	5.4	**5.48 (2.14, 14.01)**	1	1.6	---	
P-trend					**<0.0001**			---	
Subjective impression of involution									
None/mildly involuted (0-24%)	235	45.7	187	47.8	1.00 (Ref)	27	42.2	1.00 (Ref)	0.85
Partially involuted (25-74%)	75	14.6	78	20.0	1.38 (0.93, 2.04)	12	18.8	1.48 (0.70, 3.13)	
Completely involuted (≥75%)	135	26.3	84	21.5	0.87 (0.61, 1.24)	15	23.4	1.07 (0.53, 2.13)	
No TDLU observed	69	13.4	42	10.7	0.69 (0.43, 1.10)	10	15.6	1.28 (0.57, 2.91)	
P-trend					0.68			0.90	
Columnar cell lesions[c]									
None	450	87.9	328	84.1	1.00 (Ref)	53	82.8	1.00 (Ref)	0.94
Present with/without atypia	62	12.1	62	15.9	**1.54 (1.03, 2.29)**	11	17.2	1.50 (0.73, 3.07)	
P-value					**0.034**			0.27	

59 cases who had missing ER status were excluded from modeling analyses. Averaged frequencies and percentages. Women with zero-TDLU observed were not included in trend tests or heterogeneity tests. [c]Two controls and two cases were missing for columnar cell lesions. *OR and 95% CI estimates were calculated using polytomous logistic regression models adjusted for categorized BBD diagnosis calendar year as a trend, continuous age at BBD and follow-up period from BBD diagnosis to breast cancer diagnosis, family history of breast cancer in 1st degree relatives, history of bilateral oophorectomy, BBD histology, and parity. †*P*-heterogeneity were calculated from case-case analyses. Involution and columnar cell lesions associations were adjusted for all factors above line indicated in OR*.BBD, benign breast disease; CI, confidence interval; ER, estrogen receptor; OR, odds ratio.

While breast cancer risk associations for patient and histologic characteristics were generally consistent by tumor grade, we found suggestive evidence that higher levels of involution were inversely associated with reduced risk among well-differentiated tumors (complete vs no involution, OR (95%CI) = 0.51 (0.29, 0.90), **Supplemental Table 3**); this association was not evident among moderately or poorly differentiated tumors; p-het=0.054. Associations for patient and histologic characteristics by tumor size (≤20mm indicating small and >20mm larger tumors) are presented in **Supplemental Table 4**. We did not observe any significant heterogeneity by tumor size, although associations of severity of BBD histology (P<0.0001) and presence of CCLs (P=0.038) with increased breast cancer risk were somewhat stronger among patients with smaller tumors.

Breast cancer risk by menopausal status at BBD diagnosis and before and after 1993

We performed additional analyses stratified by menopausal status using factors that have been significantly associated with breast cancer risk, in our study population (**Table 3**). The association of CCLs with elevated breast cancer risk was most apparent for postmenopausal women (OR=2.08, 95% CI=1.21, 3.58); p-het=0.09.

Table 3: Associations between key risk factors and breast cancer risk stratified by menopausal status at BBD diagnosis

	Premenopausal women, N= 449 (43.6%)‡					Postmenopausal women, N= 579 (56.4%)‡					
	Control N= 217 (21.1%)		Case N= 233 (22.5%)		Multivariable model*	Control N= 297 (28.9%)		Case N= 282 (27.5%)		Multivariable model*	
Variable	N‡	%‡	N‡	%‡	OR (95% CI)*	N‡	%‡	N‡	%‡	OR (95% CI)*	*P*-het†
Age at first full-term birth/years											
Nulliparous/ ≥30	57	26.3	83	35.7	1.00 (Ref)	50	17.0	56	20.0	1.00 (Ref)	0.35
< 30	160	73.7	150	64.3	**0.59 (0.38, 0.90)**	247	83.0	226	80.0	0.81 (0.47, 1.38)	
P-value					**0.015**					0.43	
Family history of breast cancer											
No	190	87.5	186	80.0	1.00 (Ref)	244	82.2	225	79.9	1.00 (Ref)	0.28
Yes	27	12.5	47	20.0	1.75 (1.00, 3.07)	53	17.8	57	20.1	1.18 (0.76, 1.83)	
P-value					0.052					0.46	
History of bilateral oophorectomy											
No	--	--	--	--	--	212	71.3	221	78.3	1.00 (Ref)	--
Yes	--	--	--	--	--	85	28.7	61	21.7	**0.66 (0.44, 0.99)**	
P-value					--					**0.044**	
BBD histology											
Normal/Non-proliferative	178	81.9	157	67.5	1.00 (Ref)	206	69.5	167	59.4	1.00 (Ref)	0.47
Proliferative without atypia	37	17.2	67	28.7	**2.06 (1.27, 3.33)**	87	29.2	97	34.2	1.41 (0.97, 2.03)	
Proliferative with atypia	2	0.9	9	3.9	**5.45 (1.14, 26.15)**	4	1.4	18	6.4	**5.65 (1.86, 17.14)**	
P-trend					**0.015**					0.41	
Columnar cell lesions‡											
None	179	83.2	188	81.1	1.00 (Ref)	271	91.3	238	84.6	1.00 (Ref)	0.09
Present with/without atypia	36	16.9	44	18.9	1.09 (0.65, 1.82)	26	8.7	43	15.4	**2.08 (1.21, 3.58)**	
P-value					0.73					**0.008**	

‡Averaged frequencies and percentages. ‡Two controls (all premenopausal women) and two cases (1 pre- a postmenopausal women) were missing for columnar cell lesions.*OR and 95% CI estimates were calculate using unconditional logistic regression models adjusted for continuous age at BBD and follow-up period f BBD diagnosis to breast cancer diagnosis, categorized BBD calendar year as a trend, family history of bre cancer in 1st degree relatives, BBD histology, and parity. Postmenopausal women were additionally adjust history of bilateral oophorectomy. †P-heterogeneity were calculated from multivariable analyses comparin versus post-menopausal women. BBD, benign breast disease; CI, confidence interval; OR, odds ratio.

Discussion

There are few BBD cohort studies with comprehensive follow-up and detailed characteristics on subsequently diagnosed invasive tumors. Among a large, well-characterized cohort of patients diagnosed with BBD, we expanded upon previous analyses in this population [7],[8] that evaluated associations of well-established breast cancer risk factors and BBD features with breast cancer risk to determine herein if there exists possible etiologic heterogeneity using tumor characteristic data obtained from the longstanding high quality Kaiser tumor cancer registry [16]. Determining risk associations by tumor subtypes has been increasingly recognized as an important area of research [20, 21]. We comprehensively analyzed histopathologic features of the BBD biopsy and clinicopathologic characteristics of the breast tumors that developed subsequent to BBD diagnosis. We found that most breast cancers diagnosed among BBD patients within this general community healthcare plan were the low stage, ER-positive tumors that tend to be highly responsive to treatments. Compared with patients with non-proliferative BBD, those with proliferative BBD with atypia had an over five-fold increased risk of ER-positive breast cancer. Our analyses provided limited evidence for heterogeneity in risk factor associations that we evaluated by tumor characteristics. Importantly, histology and presence of CCLs at the time of BBD were independently associated with subsequent breast cancer risk irrespective of ER status, or tumor size or grade. These data provide further support for CCLs as a breast cancer risk factor, especially for postmenopausal BBD patients.

Patient characteristics and breast cancer risk

We extended prior findings by evaluating etiologic heterogeneity for risk factors thought to be most relevant for subsequent risk among BBD patients. Consistent with multiple studies of women diagnosed with sporadic breast cancer [9-12] and with the Mayo Clinic BBD cohort [6], we observed that parity/age at first birth was significantly associated with future breast cancer risk. Also consistent with limited data from other BBD cohorts [6], we found that history of bilateral oophorectomy was associated with reduced breast cancer risk, whereas positive family history of breast cancer in a 1st degree relative tended to be associated with increased breast cancer risk. We were able to further evaluate potential etiologic heterogeneity in risk associations, because our BBD study is nested within a single, large, well-defined population with access to healthcare and with a long-standing tumor tissue registry that has collected data since the 1960's. Although the number of ER-negative tumors was limited, we confirmed patterns of association by ER status that have also been observed among women diagnosed with sporadic breast cancers [9-12]. For example, early age at first birth showed an inverse association with ER-positive tumors suggesting that reproductive risk factor associations among BBD patients may be similar to those observed in the general population.*DH*

It has long been established that ADH is a high-risk precursor lesion, conferring a 4-5-fold increase in risk of breast cancer development [3]. Indeed, our analysis of BBD patients showed that compared to non-proliferative lesions, a diagnosis of ADH was associated with over 5-fold increased breast cancer risk; however, this association was limited to risk of ER-positive breast cancer, with little or no risk observed for ER-negative disease. Limited data from cohorts have reported on the relation of ADH by hormone receptor subtype. Consistent with our results, a previous population-based case-control study, CASH, found that history of any benign breast disease was associated only with increased risk of ER-positive luminal A tumors (OR = 1.89, 95% CI 1.43-2.50) [22]. These findings support the hypothesis that benign lesions are more likely to be hormone receptor positive with less genomic instability [23-26]. Moreover, the finding that ADH might be more relevant for ER-positive breast cancer risk is also consistent with hormonal chemoprevention trials which show a significant reduction in risk in women diagnosed with ADH [5, 27].

Proliferative BBD without atypia

Proliferative disease without atypia is a conglomerate of multiple different pathologies. Radial scars are proliferative lesions that visually appear similar to tumors on mammograms. Pathologically, they are associated with epithelial elements and/or other proliferative lesions such as sclerosing adenosis. Recent analyses in two Swedish cohorts recruited through mammography screening programs from 2001-2013 with over 75,000 subjects did not find any significant heterogeneity when evaluating the associations of non-proliferative or proliferative BBD lesions with risk of molecularly defined subtypes of breast cancer; however, a limitation in this study was that there was no separation of proliferative lesions with or without atypia [28]. Our analysis using the Page classification of BBD histology showed that PDWA was associated with increased risk of both ER+ and ER- disease. This is consistent with the hypothesis that these lesions serve as precursor lesions in the natural history of breast cancer [3]. The Nurses' Health Study and the Mayo BBD study showed radial scars to be one of the PDWA lesions associated with breast cancer risk, with an almost 2-fold increased risk [6, 29]. The Nurses' Health study cohorts showed an independent association after adjusting for BBD histology. After restricting analyses to BBD patients with proliferative disease, we did not find a significant increase in risk associated with sclerosing adenosis or radial scar. Reasons for these discrepancies could be differences in the study populations as the calendar periods for all three of the cohorts overlap; the Nurses BBD cohort were women who reported a first diagnosis of BBD between 1976-1998; the Mayo BBD cohort is a hospital-based referral center that may see more high-risk women but with a similar calendar period to our study with BBD diagnoses occurring between 1967-2001. As our study was embedded in a health care organization where the women are actively followed and had access to mammography screening, breast cancers detected in our study may be found earlier than in other cohorts which makes direct comparisons difficult.

Columnar cell lesions

While its generally accepted that ADH, lobular neoplasia and ductal carcinoma in situ (DCIS) are precursor lesions for breast cancer [30, 31], evidence is accumulating that CCLs may also be a precursors, although conveying lower risk particularly among populations with access to mammography screening [32-34]. Our data support CCLs as a common risk factor for both ER-positive and ER-negative breast cancers with relative risk estimates of around 1.5 after accounting for BBD histology, for both tumor types. Molecular analyses of CCLs suggest that some alterations occur early and mimic those observed in coincident established precursor lesions such as DCIS [3, 8, 23, 33, 35-42]. There are three other studies that have evaluated CCLs in BBD cohorts, Nashville, Nurses, and Mayo and our data are consistent with the findings of all three [23, 35, 36, 40]. Only the Nurses BBD cohort obtained tumor characteristics on cases and also did not find any significant differences by ER status or grade, which is consistent with our data. Current management of CCL, according to the Mayo Clinic review, suggests that these patients should be managed with annual clinical breast exams and mammography [3]. Our data suggest CCL might be a risk factor for both ER+ and ER- disease, which has not been observed previously and requires further investigation.

Involution status

Reduced lobular involution has been previously shown to be a significant factor associated with elevated breast cancer risk among women with BBD [19, 43, 44]. In the present study, we found that involution was weakly inversely related with breast cancer risk for ER+ disease. Further, higher levels of lobular involution were inversely and significantly associated with risk for well-differentiated tumors, a finding which was not observed for moderately or poorly differentiated tumors. As there were relatively few hormone negative cases in this population, we had limited power to test for differences by ER status. A limitation of this study is the absence of data on menopausal hormone therapy (MHT) use after BBD diagnoses, as MHT uptake was rising at the same time that mammography screening was increasingly being adopted [16]. Given previous studies showing that recent MHT use reduces involution levels among current but not former users [45], we hypothesize that MHT use post BBD diagnosis may be an unmeasured

negative confounder attenuating involution associations towards the null. Overall, it is unclear whether screening practices, unmeasured MHT use, or/and both might confound observed associations with involution. Additional contemporary studies in other populations with managed health care might help clarify the relationship of involution with future breast cancer risk.

This is a unique cohort of women enrolled in a general community health care plan, providing the population access to screening and preventative services that may not be typical for other subsets of the US population. It is not currently known whether women with BBD are followed and screened more closely compared to women without BBD diagnoses. Current data from a study of over 42,000 screened women in Spain found that women with a previous benign breast disease diagnosis had a higher cumulative risk of screen-detected cancer and interval cancers, consistent with data supporting BBD as a risk factor for breast cancer regardless of mode of detection [46]. Whether women with BBD in our cohort are more likely than the general population to participate in screening is not known but could be the subject of future research.

Strengths/Limitations

A limitation of our study is that risk estimates are based on a BBD patient population diagnosed on excisional biopsies during a calendar period spanning the adoption of widespread mammography screening, which became more commonplace in KPNW around 1993; thus, associations may not be reflective of BBD diagnosed in more recent years. Since 1995, advances in breast imaging technologies have resulted in a shift in diagnostic biopsy procedures to core needle biopsies, which currently comprise about 80% of biopsies in the US [47]. Based on data from the US Breast Cancer Surveillance Consortium, risks associated with high-risk ADH lesions on excisional biopsy were lower when diagnosed via core biopsy (6.7% vs 5.0%), perhaps reflecting the size of the ADH focus [47]. Another limitation as noted earlier, was the absence of risk factor data after BBD diagnosis and in particular on MHT use, which has been noted to be prevalent at KPNW at this time [16] and could have biased the results, especially with respect to the findings for involution. The small number of patients with ER-negative breast cancers is another limitation. Our study had multiple strengths: it was a nested-case control study embedded within a large, well-characterized BBD cohort with lengthy follow-up and access to archival BBD tissues and well-established detailed tumor registry data, the latter aspect allowing us to provide one of the most detailed analyses to date of tumor characteristics of breast cancers diagnosed among the vast majority of patients. Moreover, because we studied women in a healthcare management organization we could also evaluate temporal changes in access to mammography screening, data that are limited in other cohorts.

Summary and conclusions

Within this BBD cohort, the largest to date with longitudinal follow up, we provide breast cancer risk factor associations within an HMO patient population [7]. Our data provide further evidence that PDWA is associated with both ER-positive and ER-negative disease. Further, we show CCLs are associated with moderate increases in breast cancer risk, independent of BBD histology, and irrespective of ER status, in agreement with previous studies. Given the predominance of low-stage ER-positive tumors that developed among this cohort, our findings suggest that invasive cancers that develop subsequent to a BBD diagnosis are likely highly treatable with low mortality. Histologic evaluation of BBD biopsies is a promising avenue for the identification of new risk factors for different molecular subtypes of breast cancer and could inform the natural history of disease; however, given complex relationships between screening and diagnosis, along with secular changes in risk factor prevalence, contemporary prospective studies are needed to clarify the relationships of factors that may influence progression of BBD to cancer.

Declarations

Ethics approval and consent to participate

The study used routinely collected data and archival BBD tissue no longer needed for treatment or clinical care. Hence, no verbal or written consent was obtained. All data were anonymized, and the study was approved by the Committee on Clinical Investigations of the Albert Einstein College of Medicine, the Kaiser Permanente Northwest Biospecimen Review Committee and the National Institutes of Health (NIH) Office of Human Subjects Research (OHSR).

Consent for publication

Not applicable

Availability of data and material

The datasets generated or analyzed during the current study are not publicly available due to data privacy of patients but are available from the corresponding author on reasonable request.

Competing interests

None to declare

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Authors' contributions

Conception and design of the study: JDF, GLG, TR, AGG; Interpretation of data: all authors. Drafting of the paper: JDF, GLG, SF, TR; Pathologic review and interpretation MAD, YW, OL; Data abstraction and analysis SF, TMK, MG, RF; Statistical input RMP; Revised work and provided important intellectual content: all authors. Final approval of the paper: all authors

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Figures

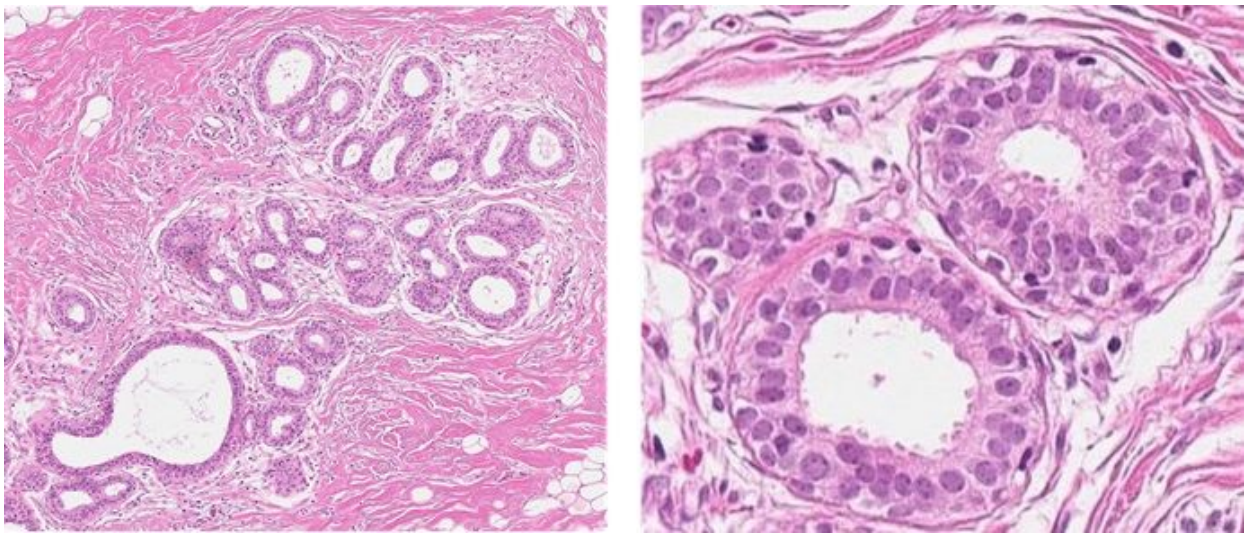

Figure 1

A representative hematoxylin and eosin x200um image of columnar cell change showing dilated acini lined by a columnar epithelium demonstrating apical cytoplasmic snouts

Supplementary Files

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