

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)		P ^a	ER+ (N=391)		ER- (N=64)		P ^a
	N	%	N	%	N	%		N	%	N	%	
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 ^b					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 ^b					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 ^b				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. ^aP 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. ^bP values from Fisher exact test. ^cPatients with tumor grade as "Not determined" were excluded from analysis. ^dPatients 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

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-hett†
	N ^a	% ^a	N ^a	% ^a		N ^a	% ^a		
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 ^b					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. ^aAveraged frequencies and percentages. ^bWomen with zero-TDLU observed were not included in trend tests or heterogeneity tests. ^cTwo 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.

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

Variable	Premenopausal women, N= 449 (43.6%) ^a					Postmenopausal women, N= 579 (56.4%) ^a					P-het [†]
	Control N= 217 (21.1%)		Case N= 233 (22.5%)		Multivariable model* OR (95% CI)*	Control N= 297 (28.9%)		Case N= 282 (27.5%)		Multivariable model* OR (95% CI)*	
	N ^a	% ^a	N ^a	% ^a		N ^a	% ^a	N ^a	% ^a		
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^b											
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	

^aAveraged frequencies and percentages. ^bTwo controls (all premenopausal women) and two cases (1 pre- and 1 postmenopausal women) were missing for columnar cell lesions. *OR and 95% CI estimates were calculated using unconditional logistic regression models adjusted for continuous age at BBD and follow-up period from BBD diagnosis to breast cancer diagnosis, categorized BBD calendar year as a trend, family history of breast cancer in 1st degree relatives, BBD

histology, and parity. Postmenopausal women were additionally adjusted for history of bilateral oophorectomy. †P-heterogeneity were calculated from multivariable analyses comparing pre- versus post-menopausal women. BBD, benign breast disease; CI, confidence interval; OR, odds ratio.