

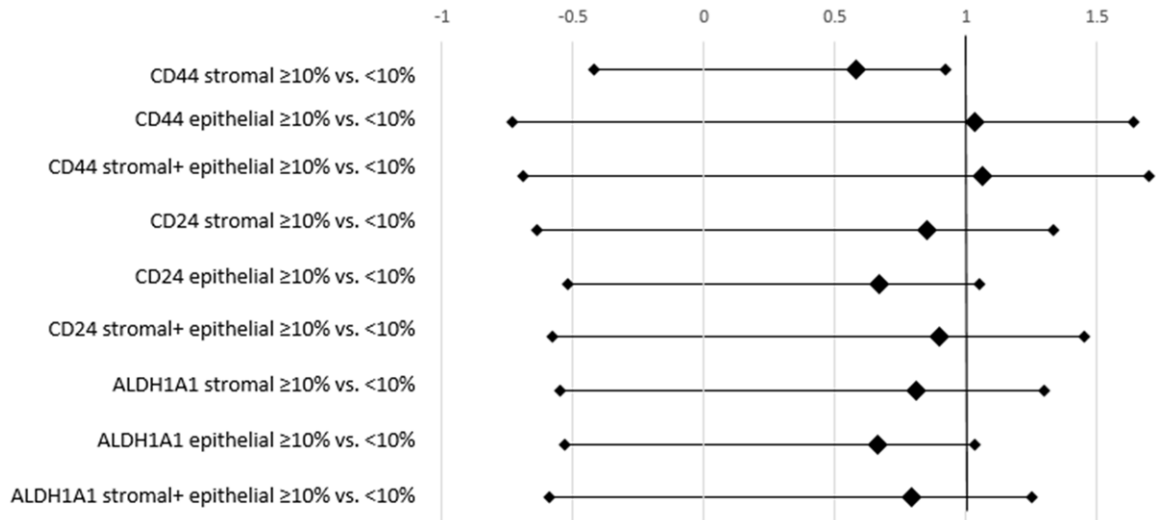
Stem cell markers and breast cancer

Supplementary Table 1. Distribution of stem cell markers in normal terminal duct-lobular units by case-control status and benign breast disease subtype (mean [SD] and range)

Stem cell marker expression	BBD subtype			Cases			Controls		
	Non-proliferative n=141	Proliferative without atypia n=257	Proliferative with atypia n=78	Non-proliferative n=24	Proliferative without atypia n=48	Proliferative with atypia n=29	Non-proliferative n=117	Proliferative without atypia n=209	Proliferative with atypia n=29
CD44 stroma	18.6 (28.5) 0-96.2	17.4 (27.4) 0-94.9	21.2 (27.7) 0-93.8	14.3 (26.9) 0-80.8	16.5 (28.1) 0-90.5	17.6 (28.2) 0-93.6	19.5 (28.9) 0-96.2	17.6 (37.3) 0-94.9	23.5 (27.5) 0-94.8
CD44 epithelium	27.4 (37.4) 0-100	38.4 (35.9) 0-100	49.0 (33.1) 0.9-100	30.5 (36.1) 0-98.9	35.6 (33.6) 0-98.8	42.8 (32.5) 0.9-100	39.0 (37.6) 0-100.0	39.1 (36.5) 0-100.0	52.9 (33.3) 1.1-99.8
CD44 stroma + epithelium	27.0 (32.1) 0-98.6	25.8 (30.4) 0-99.1	32.4 (30.0) 0.2-96.7	21.2 (30.5) 0-91.3	25.3 (29.8) 0-92.5	27.4 (29.1) 0.4-96.7	28.3 (32.5) 0-98.6	22.9 (30.6) 0-99.1	35.5 (30.5) 0.2-96.7
CD24 stroma	6.9 (12.8) 0-63.5	8.4 (13.4) 0-83.6	12.2 (15.6) 0-73.0	5.4 (8.5) 0-37.1	5.7 (8.8) 0-46.2	10.9 (12.7) 0-42.3	7.2 (13.6) 0-63.5	9.1 (14.2) 0-83.6	13.1 (17.3) 0-73.0
CD24 epithelium	28.0 (22.6) 0.5-98.1	28.2 (23.1) 0-97.6	33.5 (23.0) 0.7-82.5	27.8 (23.3) 0.5-85.4	25.5 (20.8) 0-87.9	32.8 (23.1) 4.4-78.8	28.0 (22.5) 1.7-98.1	28.9 (23.6) 0-97.6	33.9 (23.3) 0.7-82.5
CD24 stroma + epithelium	17.4 (16.9) 0.2-91.6	18.3 (17.7) 0-93.2	22.8 (17.8) 0-74.1	16.3 (14.7) 0.2-64.4	16.4 (14.6) 0.3-63.2	20.9 (15.2) 0-49.7	17.7 (17.4) 0.2-91.6	18.7 (18.4) 0-93.2	23.9 (19.3) 0.8-74.1
ALDH1A1 stroma	11.1 (12.0) 0-85.0	10.4 (12.0) 0-67.2	17.3 (17.8) 0-64.6	7.1 (8.6) 0-34.5	12.4 (14.3) 0-67.2	12.9 (16.1) 0.5-64.6	11.9 (14.2) 0-85.0	9.9 (11.4) 0-56.8	20.0 (18.4) 0-64.6
ALDH1A1 epithelium	28.0 (21.1) 0.5-90.8	26.0 (19.3) 0.5-93.4	28.4 (17.1) 0.9-67.9	24.5 (26.2) 2.2-85.1	27.8 (19.6) 0.7-85.5	28.6 (18.8) 0.9-67.9	28.8 (20.0) 0.5-90.8	25.5 (19.3) 0.5-93.4	28.3 (16.2) 1.6-59.5
ALDH1A1 stroma + epithelium	21.0 (15.9) 0.4-88.5	19.5 (14.2) 1.0-70.1	23.9 (15.1) 1.1-56.8	17.4 (17.5) 1.8-62.3	21.7 (14.7) 1.0-70.1	21.7 (14.4) 1.1-55.4	21.7 (15.5) 0.4-88.5	18.9 (14.1) 1.2-67.0	25.1 (15.6) 1.3-56.8

Abbreviations: BBD, benign breast disease; SD, standard deviation.

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Supplementary Figure 1. Associations of binary stem cell marker expression with subsequent breast cancer risk (ORs and 95% CI).

Supplementary Table 2. Associations of stem cell markers in normal terminal duct-lobular units with subsequent breast cancer risk, adjusted for benign breast disease subtype (odds ratios and 95% confidence intervals)^a

Stem cell marker expression	CD44		CD24		ALDH1A1	
	N cases/controls	OR (95% CI)	N cases/controls	OR (95% CI)	N cases/controls	OR (95% CI)
Stroma						
Continuous, per 10% increase	94/394	0.95 (0.86; 1.04)	95/333	0.83 (0.67; 1.03)	90/350	0.87 (0.72; 1.07)
<10%	67/197	Ref	71/248	Ref	59/191	Ref
$\geq 10\%$	27/127	0.53 (0.31; 0.93)	24/85	0.69 (0.39; 1.25)	31/124	0.74 (0.44; 1.26)
0-10%	67/197	Ref	71/249	Ref	59/191	Ref
>10-50%	13/76	0.40 (0.19; 0.83)	24/67	0.90 (0.49; 1.65)	29/114	0.81 (0.47; 1.38)
>50%	14/51	0.74 (0.36; 1.52)	0/17	NE	2/10	0.27 (0.04; 1.74)
p-trend		0.25		0.04		0.12
Epithelium						
Continuous, per 10% increase	91/300	0.95 (0.88; 1.02)	92/312	0.95 (0.85; 1.07)	90/299	1.02 (0.90; 1.17)
<10%	30/93	Ref	26/63	Ref	26/67	Ref
$\geq 10\%$	61/207	0.94 (0.55; 1.62)	66/249	0.62 (0.35; 1.11)	64/232	0.63 (0.35; 1.13)
0-10%	30/93	Ref	26/63	Ref	26/67	Ref
>10-50%	35/96	1.29 (0.70; 2.39)	48/188	0.63 (0.34; 1.15)	52/196	0.59 (0.32; 1.09)
>50%	26/111	0.66 (0.34; 1.27)	18/61	0.59 (0.27; 1.29)	12/36	0.85 (0.35; 2.04)
p-trend		0.11		0.28		0.67
Stroma + epithelial						
Continuous, per 10% change	94/325	0.95 (0.88; 1.04)	93/335	0.92 (0.79; 1.07)	96/326	0.98 (0.83; 1.16)
<10%	43/144	Ref	38/129	Ref	29/90	Ref
$\geq 10\%$	51/181	0.96 (0.58; 1.61)	58/206	0.83 (0.50; 1.38)	67/236	0.77 (0.44; 1.35)
0-10%	44/144	Ref	38/129	Ref	29/91	Ref
>10-50%	28/99	1.05 (0.58; 1.90)	56/177	0.95 (0.56; 1.58)	64/220	0.80 (0.46; 1.40)
>50%	22/82	0.78 (0.41; 1.48)	2/29	0.18 (0.04; 0.85)	3/15	0.54 (0.13; 2.20)
p-trend		0.42		0.03		0.32

Abbreviations: CI, confidence interval; OR, odds ratio; NE, not estimable. ^aAdjusted for age (continuous), BMI (continuous), a family history of breast cancer (Yes/No), menopausal status/postmenopausal hormone use (premenopausal, postmenopausal/no hormones, postmenopausal/past hormones, postmenopausal/current hormones, postmenopausal/unknown hormone use status, unknown menopausal status), age at menarche (<12, 12, 13, >13, unknown), combined parity/age at first birth (parous with first birth before age 25, parous with first birth at or after age 25, nulliparous, unknown), alcohol use (none, >0-<5, ≥ 5 g/day), BBD subtype (non-proliferative, proliferative without atypia, and proliferative with atypia), and NHS cohort.

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Supplementary Table 3. Associations of stem cell markers in normal terminal duct-lobular units with subsequent breast cancer risk, adjusted for percent breast density (odds ratios and 95% confidence intervals)^a

Stem cell marker expression	CD44			CD24			ALDH1A1		
	N cases/ controls	OR (95% CI)	% mediated	N cases/ controls	OR (95% CI)	% mediated	N cases/ controls	OR (95% CI)	% mediated
Stroma									
Continuous, per 10% increase	20/137	0.82 (0.64; 1.06)	Not mediated	20/143	0.80 (0.48; 1.33)	6.4% (P=0.28)	19/138	0.76 (0.45; 1.31)	Not mediated
<10%	16/77	Ref		15/112	Ref		11/84	Ref	
≥10%	4/60	0.20 (0.05; 0.86)		5/31	1.09 (0.29; 4.12)		8/54	1.14 (0.38; 3.44)	
0-10%	16/77	Ref		15/112	Ref		11/84	Ref	
>10-50%	1/35	0.11 (0.01; 1.04)		5/26	1.39 (0.37; 5.27)		8/50	1.18 (0.39; 3.59)	
>50%	3/25	0.35 (0.06; 2.08)		0/54	NE		0/4	NE	
p-trend		0.12			0.40			0.91	
Epithelium									
Continuous, per 10% increase	19/129	0.85 (0.71; 1.01)	Not mediated	20/136	1.04 (0.78; 1.38)	Not mediated	20/130	1.32 (1.00; 1.75)	3.5% (P=0.29)
<10%	7/38	Ref		4/17	Ref		2/32	Ref	
≥10%	12/91	0.46 (0.14; 1.53)		16/119	0.27 (0.06; 1.29)		18/98	2.74 (0.51; 14.78)	
0-10%	7/38	Ref		4/17	Ref		2/32	Ref	
>10-50%	7/37	0.74 (0.19; 2.97)		11/97	0.23 (0.05; 1.15)		14/84	2.43 (0.44; 13.49)	
>50%	5/54	0.28 (0.06; 1.26)		5/22	0.54 (0.08; 3.78)		4/14	6.19 (0.67; 57.49)	
p-trend		0.09			0.80			0.11	
Stroma + epithelial									
Continuous, per 10% change	20/137	0.82 (0.66; 1.03)	Not mediated	21/144	0.94 (0.66; 1.34)	30.7% (P=0.21)	21/139	1.23 (0.83; 1.82)	7.7% (P=0.23)
<10%	12/53	Ref		7/46	Ref		3/39	Ref	
≥10%	8/84	0.32 (0.11; 1.01)		14/98	0.70 (0.22; 2.22)		18/100	1.97 (0.47; 8.27)	
0-10%	12/53	Ref		7/46	Ref		3/40	Ref	
>10-50%	4/44	0.35 (0.09; 1.38)		13/88	0.77 (0.24; 2.43)		18/93	2.12 (0.51; 8.93)	
>50%	4/40	0.30 (0.07; 1.40)		1/10	NE		0/6	NE	
p-trend		0.12			0.18			0.69	

Abbreviations: CI, confidence interval; OR, odds ratio; NE, not estimable. ^aAdjusted for age (continuous), BMI (continuous), a family history of breast cancer (Yes/No), menopausal status/postmenopausal hormone use (premenopausal, postmenopausal/no hormones, postmenopausal/past hormones, postmenopausal/current hormones, postmenopausal/unknown hormone use status, unknown menopausal status), age at menarche (<12, 12, 13, >13, unknown), combined parity/age at first birth (parous with first birth before age 25, parous with first birth at or after age 25, nulliparous, unknown), alcohol use (none, >0-<5, ≥5 g/day), percent breast density (continuous), and NHS cohort.