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Life course breast cancer risk factors and adult breast density (United Kingdom)⋆

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Abstract

Objective: To determine whether risk factors in childhood and early adulthood affect later mammographic breast density.
Methods: Subjects were 628 women who attended a medical examination at the University of Glasgow Student Health Service (1948–1968), responded to a questionnaire (2001) and had a screening mammogram in Scotland (1989–2002). Mammograms (median age of 59 years) were classified using a six category classification (SCC) of breast density percent. Logistic regression was used to determine associations between risk factors and having a high-risk mammogram ($\geq$ 25% dense).
Results: In multi-variable analyses, high-risk mammograms were associated with parity (adjusted odds ratio (OR) per child: 0.77 (95% confidence interval (CI) 0.61–0.99)), age at first birth, OR per year: 1.05 (0.99–1.11), smoking at university, OR smokers *versus* non-smokers: 0.58 (0.36–0.92) and body mass index (BMI) while at university, OR per 1 kg/m^2 0.75 (0.69–0.82). No associations with SCC were found for age at menarche, birth weight, oral contraceptive (OC) use, height, leg length or exercise at age 20.
Conclusions: We confirm previous findings that breast density is affected by reproductive events and some anthropometric measures, however most of the risk factors acting throughout the life course which we examined were not closely related to adult breast density.

Introduction

During a woman's lifetime, breast size and composition change, primarily in response to reproductive events. The rapid sequential cell divisions during puberty diminish the time available for DNA repair between replications [1]. The breast cells remain as stem cells until a woman's first pregnancy, when extensive, although not complete, cellular differentiation occurs, thus reducing the pool of multiplying stem cells. These biological observations have led some to suggest that during the time period between menarche and first birth, the breast may be at its most vulnerable to potentially carcinogenic insults [2]. Epidemiological evidence points to the importance of considering early life exposures to further understand breast cancer risk [3]. This evidence includes reports on the association with age at migration [4, 5] and studies of markers of exposures such as age at menarche [6] and height [7], both of which influence subsequent breast cancer risk.

Quantifiable measures of mammographically defined breast composition are related to breast cancer risk [8, 9]. There are several methods used to measure so-called 'breast density', each of which is associated with a four-to sixfold increase in the risk of breast cancer, when comparing the extremes of the breast density distribution.

The aim of the current study was to investigate relationships between exposures in early life and young adulthood and later breast density in a cohort of women who attended the University of Glasgow between 1948 and 1968.

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Materials and methods

The women included in the study are part of the Glasgow Alumni Cohort [10]. Students who were registered at the University of Glasgow at some time between 1948–1968 were invited to an annual medical examination at the Student Health Service. Approximately 50% of students attended, including 3584 women. We have previously shown that those who attended were broadly representative of the total student population [10]. Substantial medical data were collected at this examination, including age at menarche (self-reported approximately 6 years after the event), smoking behaviour and social class in childhood (assigned using the Registrar General's occupational classification of father's job, ranging from I ('professional') to IV/V ('semi-/un-skilled')). The examining physician measured height and weight from which we calculated body mass index (BMI), in kg/m^2.

Women were traced through the NHS Central Register and those who were successfully traced and still alive (n = 2169, 61%) were contacted by postal questionnaire in 2001. The response rate was 59% (n = 1285). Women provided self-reported information on details of all pregnancies, lifetime use of oral contraceptive (OC) and hormone replacement therapy (HRT), physical activity at age 20 years (categorised as: very physically active, fairly physically active, not very physically active, not at all physically active), self-reported birth weight and current weight in 2001. Menopausal status was elicited using the questions developed for the National Survey on Health and Development (UK 1946 birth cohort). Women were sent a tape measure and instructions of how to measure their inside leg length. Because of marked digit preference in these data, the results are presented in inches to the nearest inch. (Note that 1 in. = 2.54 cm.)

Questionnaire respondents who were living in Scotland (n = 935, 73%) were asked for consent to access mammograms taken under the Scottish Breast Screening Programme (1989–2002). Two hundred and seventy seven women (30%) had never had a screening mammogram, and two women refused access to their films, leaving 656 women in the study. Both the questionnaire survey and mammogram study received full ethical approval.

Mammograms were retrieved from the relevant breast screening centre and were digitised on site with a Canon FS 300 digitiser scanner at a resolution of 100 μm with 8 bit precision by a single radiographer. Scanned images were displayed at 300 micron resolution on a flat-panel display system. No adjustment or image post-processing was applied. Digitisation was performed because the main focus of the study was to allow volumetric modelling of breast density from digitised screen-film mammograms. Only area-based measures are reported here. We have previously reported the similarity in density measures obtained from the digitised image compared to those from the original film [11]. Data on HRT use at the time of the mammogram were abstracted from the medical records of the screening centre.

Outcome measures were made by one radiologist experienced in density assessment (RW) using a six-point categorical scale (0%, 1–10%, 11–24%, 25–49%, 50–74% and $\geq$75%) of the percentage of the breast area that appeared dense, which has previously been used [9, 12]. All mammograms for each woman were presented to the radiologist ordered by the date on which they were performed, earliest first. In previous studies, RW has demonstrated good inter-rater [13–15] and intra-rater [16, 17] agreement of density assessment. Mammograms were also classified using the Wolfe system [8], but due to the close agreement (94% agreement between the two rankings) we only present findings in relation to the six category classification (SCC).

All mammograms taken at the screening round closest to age 60 were included for analysis, to minimise the effect of age on the results. Analyses were restricted to medio-lateral oblique (MLO) views, since density tended to be over-estimated from cranio-caudal (CC) mammograms compared to MLO views, which accounted for 82% of all films. Since breast density in healthy women ought to be similar between left and right breasts, we attempted to increase the precision of the density assessment by using the median of all readings (both left and right) taken on the same day to estimate one value of density for each woman, thereby avoiding non-independence of multiple observations per women. The median SCC category was estimated as the category defining the point at which half of the woman's included mammograms were more dense and half were that category or less dense. In instances where the median value fell between two categories, the lower (less dense) value was used.

Logistic regression was used to determine the relationship between exposure variables and high-risk *versus* low-risk breasts ($\geq$25% *versus* <25%). Reference groups for the analysis of categorical variables were chosen as the group with the largest number of women, to maximise the stability of the estimated OR. The exceptions to this were for anthropometric variables, where the second lowest category was used, to avoid the inclusion of outlying variables in the baseline group, which could distort the interpretation of all other groups. Likelihood ratio tests were used to test for a linear trend of effect across levels of exposure.

All results are adjusted for age (linear variable, measured in years), birth cohort (categorical variable: 1923–1938, 1939–1945, 1946–1951) and an approximation of menopausal status (see below). Our variable for menopausal status indicated whether or not the mammogram was taken prior to the woman's last menstrual period. Because of bleeding associated with HRT use, this variable only approximates menopausal status. The 37 women for whom we did not have a date of their last menstrual period were coded to a separate group, to avoid their exclusion. Potential confounding by OC ever use, HRT use at the time of the mammogram and self-reported BMI at the time of the 2001 questionnaire was investigated by comparison of the magnitude of the ORs estimated from models with and without these variables.

Twenty three of the 656 women were excluded as they reported having had breast cancer in the 2001 questionnaire. A further five women (51 mammograms) were excluded because the digitised image was too pale to assign density to any of their mammograms. The results presented here are based on mammograms of 628 women. Because of incomplete data on some variables, not all 628 women were included in all analyses, but comparisons of crude and adjusted results were always based on the same women. Where height (n = 24) and age at menarche (n = 28) were missing from the Student Health Service record, values were substituted with recalled data from the self-reported postal questionnaire. Women with missing data were excluded from relevant analyses. Exclusions from leg length analyses included women who did not provide a leg length measure (n = 9) as well as women who measured their trousers not their leg (n = 49) and those who did not specify how they performed the measurement (n = 37), because the mean reported leg length among women who measured their trousers was significantly higher than that of women who measured their leg (28.4 *versus* 27.5 in. $P = 0.001$).

Results

There were 628 of the original 3584 cohort members included in the study. The included women did not differ from the remainder of the women in terms of father's social class ($P = 0.94$) or birth order ($P = 0.89$). Respondents had similar mean age at menarche (both 12.9 years, $P = 0.45$), height (both 163.1 cm, $P = 0.93$) and weight at university (57.4 *versus* 56.9 kg, $P = 0.14$). Respondents were more likely to come from smaller families (proportion who were only children 22% *versus* 19%, $P = 0.04$), more likely to be smokers at university (83% *versus* 79%, $P = 0.030$) but less likely to drink alcohol at university (68% *versus* 62%, $P = 0.009$).

The median age of the 628 included women when they attended the Student Health Service was 18.7 years (inter-quartile range (IQR) 18.2–19.9 years); nine women were over the age of 25. In 2001, at the time of collection of the recalled exposure data, the median age was 60.6 years (IQR 55.1–68.3 years). The median age at breast screening was 58.9 years (IQR 55.3 – 60.6 years). There was an inverse relationship between age at mammography and breast density. The mean age was 59.3 years in the 0% dense category compared to 56.2 years in the >75% dense category. Other characteristics of the study participants, by mammographic density category, are shown in Table 1. Higher density was seen in women were younger at mammography, whose last period was after her mammogram (*i.e.*, were pre-menopausal at the time), those who had lower BMI at university and those who had ever used an OC (in particular prior to first birth).

Age-adjusted and further-adjusted associations between the explanatory variables and breast density are shown in Table 2. The 20 women with missing data on current BMI or ever use of OC were excluded from these tables. Parous women had a lower odds of high-risk mammograms, with an inverse linear relationship between number of children and density. Later age at first birth was positively related to density, with the odds of high-risk mammograms being over three times higher in women who first gave birth over the age of 35 compared to those who first gave birth under the age of 25 years. None of these effects were explained by the potential confounding of HRT use at the time of the mammogram, OC ever use or BMI in adulthood.

There was no association between age at menarche, own birth weight, height, leg length, exercise at age 20 or social class in childhood. Body mass index in young adulthood (at university) was inversely related to density, and this effect was strengthened following adjustment for change in BMI from young adulthood to later adulthood. Women who smoked while at university tended to have lower breast density, and this was not explained by confounding by BMI either at university (data not shown) or in 2001, nor by parity, OC use or HRT use.

There was a suggestion that OC use at a young age (20 years or under) was related to a lower odds of high-risk mammograms, although this did not reach conventional levels of statistical significance. Women who had ever used an OC were also more likely to have had a child (OR for having had a child, comparing people who had ever used OC compared to never-users: 4.83, 95%

Table 1. Distribution of exposure variables among 628 women in Scotland

	Total	SCC Category						p-Value[a]
		0% No (%)	1–10% No (%)	11–24% No (%)	25–49% No (%)	50–74% No (%)	≥75% No (%)	(χ^2)
Age at mammography (years)								
49–54	288	9 (6%)	14 (9%)	24 (15%)	37 (23%)	41 (25%)	37 (23%)	
55–59	180	31 (12%)	46 (17%)	40 (15%)	60 (22%)	55 (21%)	36 (13%)	
60–71	160	26 (13%)	31 (16%)	37 (19%)	59 (30%)	30 (15%)	15 (8%)	< 0.001
Last menstrual period								
Prior to mammogram	535	59 (11%)	81 (15%)	83 (16%)	137 (26%)	104 (19%)	71 (13%)	
After mammogram	56	6 (11%)	3 (5%)	9 (16%)	9 (16%)	16 (29%)	13 (23%)	0.053
Not reported	37	1 (3%)	7 (19%)	9 (24%)	10 (27%)	6 (16%)	4 (11%)	
HRT use at the time of mammography								
Yes	122	12 (10%)	14 (11%)	13 (11%)	25 (20%)	32 (26%)	26 (21%)	
No	148	18 (12%)	18 (12%)	27 (18%)	36 (24%)	32 (22%)	17 (11%)	0.15
Unknown	358	36 (10%)	59 (16%)	61 (17%)	95 (27%)	62 (17%)	45 (13%)	
Age at menarche (years)								
10–12	228	25 (11%)	32 (14%)	32 (14%)	66 (29%)	36 (16%)	37 (16%)	
13	211	28 (13%)	25 (12%)	39 (18%)	44 (21%)	52 (25%)	23 (11%)	
14	135	13 (10%)	24 (18%)	17 (13%)	33 (24%)	28 (21%)	20 (15%)	
15–18	54	0 (0%)	10 (19%)	13 (24%)	13 (24%)	10 (19%)	8 (15%)	0.062
Ever had a live birth								
Yes	419	46 (11%)	64 (15%)	70 (17%)	95 (23%)	88 (21%)	56 (13%)	
No	192	19 (10%)	24 (13%)	26 (14%)	57 (30%)	36 (19%)	30 (16%)	0.40
Missing	17	1 (6%)	3 (18%)	5 (29%)	4 (24%)	2 (12%)	2 (12%)	
No. of children								
0	192	19 (10%)	24 (13%)	26 (14%)	57 (30%)	36 (19%)	30 (16%)	
1	45	5 (11%)	7 (16%)	5 (11%)	10 (22%)	10 (22%)	8 (18%)	
2	185	19 (10%)	21 (11%)	29 (16%)	42 (23%)	43 (23%)	31 (17%)	
3	130	13 (10%)	23 (18%)	25 (19%)	30 (23%)	26 (20%)	13 (10%)	
4+	59	9 (15%)	13 (22%)	11 (19%)	13 (22%)	9 (15%)	4 (7%)	0.53
Missing	17	1 (6%)	3 (18%)	5 (29%)	4 (24%)	2 (12%)	2 (12%)	
Age at first birth[b]								
19–24.9	80	11 (14%)	10 (13%)	18 (23%)	17 (21%)	16 (20%)	8 (10%)	
25–29.9	237	27 (11%)	42 (18%)	35 (15%)	52 (22%)	50 (21%)	31 (13%)	
30–34.9	76	8 (11%)	10 (13%)	12 (16%)	18 (24%)	17 (22%)	11 (14%)	
35–43	26	0 (0%)	2 (8%)	5 (19%)	8 (31%)	5 (19%)	6 (23%)	0.69
Own birth weight (kg)								
2–2.9	51	4 (8%)	6 (12%)	1 (25%)	7 (14%)	1 (22%)	1 (20%)	
3–3.49	148	11 (7%)	22 (15%)	21 (14%)	35 (24%)	36 (24%)	23 (16%)	
3.5–3.9	64	8 (13%)	10 (16%)	8 (13%)	13 (20%)	16 (25%)	9 (14%)	
4+	33	2 (6%)	6 (18%)	6 (18%)	10 (30%)	5 (15%)	4 (12%)	0.76
Missing	332	41 (12%)	47 (14%)	53 (16%)	91 (27%)	58 (17%)	42 (13%)	
Height (cm)								
147–160.0	199	20 (10%)	25 (13%)	35 (18%)	46 (23%)	45 (23%)	28 (14%)	
160.1–165.0	203	25 (12%)	32 (16%)	29 (14%)	46 (23%)	44 (22%)	27 (13%)	
165.1–170.0	173	13 (8%)	28 (16%)	29 (17%)	52 (30%)	29 (17%)	22 (13%)	
170.1–179	52	8 (15%)	6 (12%)	8 (15%)	12 (23%)	8 (15%)	10 (19%)	0.70
Missing	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	
BMI at university (kg/m^2)								
14–19.9	163	8 (5%)	14 (9%)	23 (14%)	43 (26%)	44 (27%)	31 (19%)	
20–21.9	222	18 (8%)	30 (14%)	36 (16%)	54 (24%)	44 (20%)	40 (18%)	
22–24.9	159	26 (16%)	31 (20%)	26 (16%)	39 (25%)	25 (16%)	12 (8%)	
25–33	58	13 (22%)	14 (24%)	8 (14%)	15 (26%)	8 (14%)	0 (0%)	< 0.001
Missing	26	1 (4%)	2 (8%)	8 (31%)	5 (19%)	5 (19%)	5 (19%)	
Leg Length (inches)								
22–26.0	142	19 (13%)	22 (15%)	26 (18%)	37 (26%)	19 (13%)	19 (13%)	
26.1–27	112	9 (8%)	19 (17%)	18 (16%)	32 (29%)	20 (18%)	14 (13%)	
27.1–28	109	7 (6%)	18 (17%)	16 (15%)	30 (28%)	24 (22%)	14 (13%)	
28.1–29	90	10 (11%)	13 (14%)	10 (11%)	13 (14%)	26 (29%)	18 (20%)	
29.1–34	80	10 (13%)	8 (10%)‘	15 (19%)	19 (24%)	19 (24%)	9 (11%)	0.25
Missing	9	1 (11%)	0 (0%)	1 (11%)	3 (33%)	2 (22%)	2 (22%)	

Table 1. (Continued).

	Total	SCC Category 0% No (%)	1–10% No (%)	11–24% No (%)	25–49% No (%)	50–74% No (%)	≥75% No (%)	*p*-Value[a] (χ^2)
Ever used OC								
Yes	335	39 (12%)	39 (12%)	55 (16%)	66 (20%)	76 (23%)	60 (18%)	
No	273	27 (10%)	49 (18%)	41 (15%)	83 (30%)	47 (17%)	26 (10%)	0.001
Missing	20	0 (0%)	3 (15%)	5 (25%)	7 (35%)	3 (15%)	2 (10%)	
Age at starting OC								
15–20	21	4 (19%)	3 (14%)	3 (14%)	4 (19%)	5 (24%)	2 (10%)	
21–24	129	12 (9%)	11 (9%)	21 (16%)	20 (16%)	32 (25%)	33 (26%)	
25–29	90	13 (14%)	9 (10%)	13 (14%)	18 (20%)	19 (21%)	18 (20%)	
30–47	88	10 (11%)	13 (15%)	18 (20%)	22 (25%)	19 (22%)	6 (7%)	0.19
Missing	7	0 (0%)	3 (43%)	0 (0%)	2 (29%)	1 (14%)	1 (14%)	
OC prior to first birth[c]								
Yes	175	19 (11%)	16 (9%)	29 (17%)	30 (17%)	47 (27%)	34 (19%)	
No	100	13 (13%)	15 (15%)	19 (19%)	26 (26%)	17 (17%)	10 (10%)	0.050
Missing	5	0 (0%)	2 (40%)	0 (0%)	2 (40%)	1 (20%)	0 (0%)	
Smoking while at university								
Yes	101	11 (11%)	23 (23%)	16 (16%)	24 (24%)	17 (17%)	10 (10%)	
No	495	54 (11%)	66 (13%)	77 (16%)	126 (25%)	101 (20%)	71 (14%)	0.23
Missing	32	1 (3%)	2 (6%)	8 (25%)	6 (19%)	8 (25%)	7 (22%)	
Age at starting smoking[d]								
10–18	99	15 (15%)	16 (16%)	17 (17%)	17 (17%)	19 (19%)	15 (15%)	
19–22	81	8 (10%)	19 (23%)	9 (11%)	20 (32%)	12 (15%)	7 (9%)	
23 +	40	5 (13%)	4 (10%)	8 (20%)	1 (28%)	6 (15%)	6 (15%)	0.27
Missing	7	2 (29%)	0 (0%)	2 (29%)	1 (14%)	1 (14%)	1 (14%)	
Smoking prior to first birth[b, d]								
Yes	138	16 (12%)	23 (17%)	26 (19%)	32 (23%)	27 (20%)	14 (10%)	
No	7	0 (0%)	1 (14%)	1 (14%)	5 (71%)	0 (0%)	0 (0%)	0.11
Missing	3	1 (33%)	0 (0%)	0 (0%)	1 (33%)	0 (0%)	1 (33%)	
Exercise at age 20 years								
Not at all physically active	16	1 (6%)	2 (13%)	3 (19%)	2 (13%)	3 (19%)	5 (31%)	
Not very physically active	144	15 (10%)	18 (13%)	26 (18%)	34 (24%)	30 (21%)	21 (15%)	
Fairly physically active	344	34 (10%)	53 (15%)	55 (16%)	89 (26%)	63 (18%)	50 (15%)	
Very physically active	115	16 (14%)	17 (15%)	15 (13%)	28 (24%)	29 (25%)	10 (9%)	0.64
Missing	9	0 (0%)	1 (11%)	2 (22%)	3 (33%)	1 (11%)	2 (22%)	
Childhood social class								
I ('professional')	137	13 (9%)	22 (16%)	20 (15%)	35 (26%)	27 (20%)	20 (15%)	
II	236	23 (10%)	42 (18%)	40 (17%)	54 (23%)	48 (20%)	29 (12%)	
III	195	25 (13%)	24 (12%)	31 (16%)	50 (26%)	36 (18%)	29 (15%)	
IV/V ('semi- /un-skilled')	31	4 (13%)	2 (6%)	5 (16%)	1 (35%)	8 (26%)	1 (3%)	
Missing	29	1 (3%)	1 (3%)	5 (17%)	6 (21%)	7 (24%)	9 (31%)	0.75

[a] Based on a χ^2 test between groups. Categories with missing data are excluded from these analyses.
[b] Amongst 419 women who had had a live birth.
[c] Amongst 280 women who had had a live birth and used the OC.
[d] Calculated among women who reported that they had ever smoked in the 2001 questionnaire.

CI: 3.32–7.03). Adjusting the association between age at first OC use and breast density for parity (as well as age and birth cohort) did not change the estimated ORs. In this study, OC use prior to first birth was not related to breast density.

We investigated the use of ordinal logistic regression in the analysis of our ordered categorical outcome (SCC). This approach has previously been used for the analysis of Wolfe patterns [18]. However, for several of the models, the assumption of proportional odds underlying models were violated. We have therefore chosen not to present these results. The interpretation of the results from the models in which the proportional odds assumptions were not violated were similar to those made from the high-risk mammogram analyses presented here. The main analyses were also repeated using Wolfe's four-category categorisation system. Our main findings/conclusions were essentially unchanged.

Table 2. Associations between breast density and exposure variables among 608 women in Scotland

	Model 1		Model 2	
Age at Menarche (years)				
10–12	1*		1*	
13	0.87	0.59–1.29	0.91	0.61–1.36
14	1.06	0.67–1.68	1.07	0.67–1.71
15–18	1.11	0.59–2.07	1.20	0.63–2.29
Per year	1.02	0.88–1.17	1.02	0.88–1.18
p (trend)		0.80		0.78
Ever had a live birth				
No	1*		1*	
Yes	0.67	0.46–0.97	0.62	0.42–0.91
Parity				
0	1.20	0.78–1.87	1.30	0.83–2.03
1	0.99	0.50–1.99	1.05	0.53–2.13
2	1*		1*	
3	0.72	0.45–1.15	0.69	0.43–1.12
4+	0.50	0.27–0.93	0.55	0.29–1.02
Per child[a]	0.77	0.61–0.98	0.77	0.61–0.99
p (trend)		0.032		0.038
Age at first live birth (years)[a]				
19–24	0.83	0.49–1.40	0.83	0.48–1.43
25–29	1*		1*	
30–34	1.06	0.61–1.83	1.01	0.57–1.78
35–42	2.69	1.01–7.19	2.83	1.03–7.79
Per Year	1.05	1.00–1.11	1.05	0.99–1.11
p (trend)		0.064		0.077
Own birth weight (kg)				
2–2.9	0.61	0.32–1.20	0.57	0.28–1.15
3–3.49	1*		1*	
3.5–3.9	0.83	0.45–1.54	0.89	0.47–1.70
4+	0.77	0.35–1.69	0.77	0.34–1.75
Per kg	1.03	0.66–1.62	1.05	0.66–1.68
p (trend)		0.89		0.82
Height (cm)				
Up–160	1.10	0.73–1.64	1.07	0.70–1.63
161–165	1*		1*	
166–170	1.11	0.73–1.69	1.01	0.66–1.57
Over 170	1.01	0.54–1.88	0.93	0.48–1.80
Per 5 cm	1.05	0.90–1.21	1.03	0.88–1.20
p (trend)		0.55		0.75
Leg length (inches)				
Up–26	0.84	0.50–1.39	0.85	0.50–1.43
26.1–27	1*		1*	
27.1–28	1.15	0.67–1.99	1.12	0.64–1.97
28.1–29	1.20	0.67–2.14	1.17	0.65–2.12
Over 29	0.99	0.55–1.78	0.98	0.53–1.81
Per Inch	1.04	0.94–1.15	1.05	0.94–1.16
p (trend)		0.41		0.40
BMI (kg/m^2) at University				See footnote b
Up–19.9	1.61	1.03–2.51	1.71	1.05–2.78
20.0–21.9	1*		1*	
22.0–24.9	0.58	0.38–0.88	0.50	0.32–0.80
25.0 or over	0.40	0.22–0.74	0.23	0.11–0.46
Per kg/m^2	0.81	0.76–0.88	0.75	0.69–0.82
p (trend)		< 0.001		< 0.001

Table 2. (Continued).

	Model 1		Model 2	
Age at starting OC (years)				
⩽20	0.41	0.15–1.09	0.41	0.15–1.12
21–24	1*		1*	
25–29	0.98	0.54–1.78	0.98	0.53–1.81
30 or over	0.72	0.35–1.69	0.78	0.34–1.76
Per year	1.01	0.95–1.07	1.01	0.95–1.07
p (trend)		0.71		0.78
OC prior–first birth[a]				
No	1*		1*	
Yes	1.13	0.58–2.19	1.31	0.66–2.62
Smoking while at university				
No	1*		1*	
Yes	0.62	0.40–0.96	0.58	0.36–0.92
Age at starting smoking (years)				
⩽18	0.78	0.42–1.45	0.69	0.36–1.32
19–22	1*		1*	
23 or over	1.14	0.51–2.51	1.17	0.51–2.68
Per year	1.06	0.99–1.15	1.08	0.99–1.16
P(trend)		0.099		0.058
Exercise at age 20 years				
Not at all active	0.91	0.32–2.63	0.89	0.30–2.66
Not very active	0.85	0.56–1.28	0.78	0.51–1.20
Fairly active	1*		1*	
Very active	1.03	0.67–1.59	1.02	0.65–1.60
Per category	1.09	0.86–1.38	1.12	0.88–1.43
p (trend)		0.47		0.35
Childhood social class				
I ('professional')	1.28	0.83–1.97	1.18	0.75–1.85
II	1*		1*	
III	1.15	0.78–1.70	1.01	0.67–1.51
IV/V ('semi-/un-skilled')	1.38	0.62–3.13	1.50	0.67–3.37
Per category	1.00	0.83–1.20	1.00	0.82–1.21
p (trend)		0.99		0.99

Values are odds ratios (95% confidence intervals) estimating the odds of high-risk ($\geq$ 25% versus < 25%) mammograms. The 20 women with missing data on current BMI or ever use of OC were excluded from these analyses.
Model 1: adjusted for age, birth cohort and menopausal status.
Model 2: also adjusted for HRT use at the time of the mammogram, OC ever use and BMI in 2001.
* Reference category.
[a] Excludes women who have not had a child.
[b] This model is adjusted for HRT use at the time of the mammogram, OC ever use and BMI change from university to 2001, because of the close correlation between the two BMI measures.

Discussion

Our study confirms previous reports of associations between breast density and reproductive factors. We observed higher risks of breast density in women who were nulliparous, had fewer children, had their first child at a later age and who were lean or were non-smokers while at university. None of age at menarche, birth weight, height, leg length, OC use of physical activity in young adulthood were related to breast density in later life.

Strengths and limitations

Contemporaneously recorded exposure measures from the Student Health Service are more accurate than recalled measures, as well as excluding the possibility of recall bias. Height and weight at university were measured not self-reported, and age at menarche was collected on average 6 years after the event. The available data on HRT use and menopausal status were limited. We relied on HRT data collected at the screening unit, which was incomplete. We only had an accurate estimation of menopausal status for women whose menopause had occurred prior to completing the questionnaire. Differential associations between breast density and breast cancer according to menopausal status have been described [19, 20]. The age range of the women in our study suggests that the majority were post-menopausal.

The sample of women included in the study were highly selected. Not only were they all university-educated, thus likely to have high socio-economic position in adulthood [21], but, furthermore, our analyses were based on the subset who could be traced, responded to our questionnaire and who had a screening mammogram in Scotland. These women comprise 18% of the original cohort. It is likely that the questionnaire respondents and women who have had breast screening are more health conscious than non-respondents. We know that uptake of screening mammography in Scotland differs by deprivation level [22]. These selective forces affected the women in the study, but are unlikely to have biased our results, since to do so would require there to be modification of the observed associations by socio-economic position. Any effect of socio-economic position on breast density is likely to be mediated through measurable reproductive, anthropometric and/or behavioural factors, rather than through contextual effects.

Main findings and interpretation

The results relating reproductive events (nulliparity, age at first birth, number of children) to breast density are in accordance with data previously reported [23–25]. Those studies demonstrate consistent patterns of association between these well-recognised breast cancer risk factors [6] and breast density, irrespective of the manner in which density is assessed (BI-RADS, Tabar, percent area density) across ethnically diverse populations.

Biological explanations of the observed relationships centre on the role of oestrogen, under the influence of which breast cells multiply. Rapid multiplication occurs during puberty, diminishing the time available for DNA repair between replications [1]. The anti-oestrogenic properties of cigarette smoke [26] could reduce the proliferation of breast tissue, thus reducing breast density. This would explain the inverse relationship between smoking in early adulthood and breast density we and others [27, 28] have observed. Our results suggest that starting smoking at a young age may influence breast density in later life to a greater degree than starting smoking at an older age, which is consistent with some [29] but not all [30] studies which have looked at associations between smoking at a young age and breast cancer risk.

If higher levels of cell division during a prolonged period between menarche and first birth contributes to breast density, early age at menarche would be related to higher breast density. Previous studies have found the opposite [23, 31] or no association [24, 25], as in the current study. The close proximity to reporting and occurrence of menarche in our study gives greater weight to our finding as its timing is likely to have been accurately recalled over the short period since its occurrence. One study found an association between age at menarche and breast density only following statistical adjustment for factors which included BMI [31]. The relationship between age at menarche and BMI [32] is important to consider when investigating breast density.

Associations between OC use and breast density are conflicting [31, 33]. Exposure measures such as those obtained by postal questionnaire in our study may be too crude to determine risks associated with certain preparations. Both the demographics of the users and the hormonal constituents of the preparations have changed since the introduction of OCs. The effects of OC use in early life/young adulthood may not become evident until the cohort of women to whom the OC was available from adolescence onwards reach an advanced post-menopausal age.

In conflict with previous studies [34, 35], we found no relationship between height at 19 years and breast density. We offer two explanations for these inconsistencies. Firstly, in our study height is measured in young adulthood, prior to any age-related height loss occurring. One study found greater height loss in women with less dense breasts [18], which would result in an association between breast density and height when measured in later life, but not when height in early adulthood is used. Secondly, most cohort members in the current study experienced a relatively high socio-economic position in childhood, and the determinants of height in this cohort may not be the same are those in the general population. We have previously suggested that this explains the null relationship observed between height and cancer mortality in this cohort [36]. Associations between growth patterns and breast cancer may be mediated through the effect of insulin-like growth factor-I (IGF-I) [37], which is also related to breast density [12, 38–40]. We found no relationship between birth weight or leg length and density. Previous reports also suggest no relationship between birth weight and mammographic features [18, 41]. Our data suggest that the possible effect of leg length on breast cancer risk [42] is not mediated through factors which influence breast density.

Height shows differing relationships with the absolute and relative (percentage) area of dense breast tissue (inverse and positive associations respectively) [35]. The amount of fat in the breast is a component of relative measures of breast density, resulting in an inevitable inverse relationship between breast density and BMI at various ages, as shown in this and several previous reports [18, 23–25, 27, 43]. This finding is paradoxical, since women with a higher BMI, particularly in post-menopausal years, have a higher risk of breast cancer. The inverse relationship between breast density and BMI is an artefact of the measurement techniques which we use. We propose that future studies ought to examine absolute as well as relative areas of the breast that are dense.

Given the strong relationships between BMI and density, the lack of an association between physical activity and breast density in this and previous studies [27, 31] seems surprising. A single measure of recalled activity from 40 years ago is unlikely to be very precise, although similar measures have been related to lowered risks of breast cancer in several case–control studies (reviewed in [3]).

In conclusion, we have replicated associations found by previous researchers in relation to associations between reproductive events and breast density. Few of the other early life and young adult exposures which we investigated were related to breast density in this cohort. Not all breast cancer risk factors, such as age at menarche and BMI, relate to breast density in the same way that they do to breast cancer. To understand these differences, studies with measures of both breast density and breast cancer outcomes are required.

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