Mammographic Parenchymal Patterns and Breast Cancer Natural History

A Case-Control Study

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The relationship between tumour size, malignancy grade and dense mammographic parenchymal patterns was evaluated by using a nested case-control design with 875 breast cancer cases and 2 601 matched controls. Wolfe's classification was used to assess mammographic parenchymal patterns. The dense P2/DY mammographic parenchymal patterns were significantly associated with invasive ductal grade 3 carcinoma (OR = 2.03; 95% CI 1.13–3.62; p = 0.016). Stratified by tumour size, we found that the odds ratio for grade 3 invasive ductal NOS breast cancer measuring 15–19 mm associated with P2/DY mammographic parenchymal patterns was 3.46 (95% CI 1.12–10.68). For tumours larger than 30 mm, the odds ratio was 10.09 (95% CI 1.27–79.93). The highest risk of grade 3 cancers being in tumours measuring 30 mm + may be due to dedifferentiation of missed cancers, but there is some excess even in the < 20 mm tumours, suggesting an increased risk in association with dense mammographic patterns of some aggressive cancers which are grade 3 at inception. Our results are consistent with the model that breast cancer is a progressive disease, whose development can be arrested by screening, and that the point at which individual tumour progression is stopped is crucial for prognosis not simply in terms of stage of disease, but also of histological grade.

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The mammographic appearance of the female breast varies among individuals, and depends on the relative amounts of fat, epithelial and connective tissue of the breast (1). Typically, the radiographic appearance of normal, cancer-free breast tissue represents a continuum of breast types ranging from fatty breast tissue that is radiologically lucent (darker in appearance) to that displaying extensive regions of density (lighter in appearance). These variations in mammographic density of breast tissue can be classified by the parenchymal pattern of the breast (1).

The two most commonly used classifications of mammographic parenchymal pattern are Wolfe's scale (2, 3), and a coarse quantitative scale of the proportion of the breast composed of dense tissue: 'percentage breast density' (4, 5). Another classification that has features in common with the Wolfe scale is the Tabar scale (6, 7). Novel methods have been described that use magnetic resonance imaging (MRI) mapping (8) and ultrasound scans (9).

Wolfe described four different mammographic patterns: N1, P1, P2 and DY (2). Women with either P2 or DY patterns have been shown to have a greater risk of breast cancer than those with N1 or P1 patterns (2, 10–12).

In a previous paper (12) we showed that dense mammographic patterns are preferentially associated with the more aggressive, poorly differentiated grade 3 cancers than with the less aggressive grades 1 and 2 cancers. We also showed, however, that mammography was less sensitive for the detection of small cancers in dense breast tissue. The association of dense patterns and grade 3 cancers might therefore be the result of dedifferentiation, since cancers missed at screening have a greater opportunity to dedifferentiate. On the basis of this hypothesis, the increased risk associated with grade 3 tumours would be a product of tumours being allowed to develop further because of being missed at screening. If this were the case, one would expect the increased risk of grade 3 tumours to be confined to the larger tumours, since the missed tumours would have an equal opportunity to develop with respect to size as well as grade, whereas those tumours detected early, as evidenced by small diameter, would have

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had little time to dedifferentiate. Furthermore, if the increased risk of grade 3 tumours were entirely due to dedifferentiation of missed cases, there would be no excess increased risk of grade 3 tumours after adjusting for size, for the same reason.

On the other hand, if the excess increased risk of grade 3 tumours were due to a greater biological predisposition of dense tissue to grade 3 cancers than to grade 1–2 *ab initio*, there would be an excess increased risk of grade 3 tumours at all sizes, including small cancers. Also, the increased risk of grade 3 cancers would remain higher than that of grades 1–2 after adjustment for size.

Finally, if the excess increased risk of grade 3 tumours were due to dedifferentiation of missed cases, it would be largely confined to interval cancers. Estimation of relative risk by grade and detection mode (screening or interval) would therefore give some insight into the reason underlying the differing relative risks by grade.

These observed phenomena cannot prove conclusively whether or not dedifferentiation is occurring and, if so, to what extent it accounts for the excess increased risk of grade 3 cancers in dense breasts. They can at least be checked for consistency with either a universal hypothesis that the excess risk is due *entirely* to dedifferentiation or to an innate universal predisposition to grade 3 cancers. In addition, they might yield information about which process most of the excess increased risk of grade 3 tumours is attributable to. If it is mainly due to tumour progression, this suggests enhanced early detection procedures in dense breasts as a means of control. If it is mainly due to a universal predisposition to grade 3 tumours at inception, an emphasis on primary prevention might be more productive.

In this paper, we evaluate the relationship between tumour size, malignancy grade and dense mammographic parenchymal patterns. In addition, we estimate relative risks by grade and detection mode. We also investigate the consequences of the interruption of cancer progression by early detection with mammographic screening, suggesting tentative inferences on some aspects of the natural history of breast cancer.

MATERIAL AND METHODS

Study population

The study subjects were part of a cohort of women who attended the prevalence screening round at either Norwich Breast Screening Centre or Cambridge and Huntingdon Breast Screening Centre between April 1989 and December 1993, and between March 1991 and March 1995, respectively. A detailed description of this cohort has been published elsewhere (12).

Nested case-control study

Eligible subjects for this study were all cohort members who had newly diagnosed breast cancer between April 1989 and September 1996. Cases were defined as women who attended either centre and were diagnosed with a histologically verified unilateral breast cancer (ICD-9 174) at the prevalence screening round, or at the first incident screening round, or in the interval between two screens, and for whom readable mammograms were still available. Additional information regarding case selection is presented elsewhere (12). A total of 875 cases were eligible, of which 747 were invasive cancers and 128 were in situ.

Controls were defined as women free of breast cancer who attended either of the screening centres. For each case, we aimed to select three controls matched to the case by date of birth (within 3 months), screening centre and date of attendance to screening (within 3 months). We selected 2 601 controls.

We examined the screening records of each woman. Both mediolateral and craniocaudal views of the mammograms from the unaffected breast of the cases and of the laterality-matched breasts of controls were identified. They were independently reviewed by two of the authors: RW and ES. The review by RW was done without knowledge of the subject status and without access to any other information about the subjects. This was not possible for ES, since she conducted the data collection. We therefore used the classification by RW in this study. The mammographic parenchymal patterns of breast tissue were independently assessed according to Wolfe's classification by the two radiologists. Mammographic patterns in this study refer to the pattern observed on the most recent mammogram before diagnosis in the cases.

The pathological variables of interest included the histological type, malignancy grade and size of lesion in millimetres. We recorded the size of the invasive component in cases where both invasive and in situ cancers coexisted.

Statistical methods

Data analysis was performed using conditional logistic regression, which takes into account the matching of controls to cases and produces odds ratio estimates of relative risk and 95% confidence intervals on these (13). Statistical analysis was performed using the Stata statistical package (Stata Corporation, Texas, USA).

RESULTS

In our study, 68% of the mammograms of patients and 58% of the mammograms of controls were classified as of the P2/DY pattern. To examine the relationship between mammographic parenchymal patterns and the risk of rapidly progressing tumours, we carried out a subgroup analysis on the cases of invasive ductal carcinoma not otherwise specified (NOS) grouped according to the malignancy grade. The results are presented in Table 1. The odds ratios of having an invasive ductal grade 3 breast cancer associated with the P2 and DY patterns were 2.69 and 3.83, respectively. The corresponding values for grades

Table 1

Grades 1, 2 and 3 invasive ductal NOS breast cancer odds ratios (OR) associated with mammographic parenchymal pattern

Wolfe's parenchymal pattern	Malignancy grade					
	Grades 1 & 2			Grade 3		
	Cases	OR	95% CI	Cases	OR	95% CI
N1	60	1.00	–	8	1.00	–
P1	85	1.23	0.84–1.79	18	1.64	0.66–4.00
P2	234	1.56	1.12–2.16	56	2.69	1.19–6.05
DY	48	1.20	0.78–1.84	18	3.83	1.46–10.01
OR per step	1.12			1.58		
(95% CI)	(0.99–1.27)			(1.19–2.09)		
P for trend	0.06			0.002		

1 and 2 breast cancer were 1.56 and 1.20, respectively, i.e. the increased risk associated with the P2 and DY is mainly confined to grade 3 tumours.

We extended our analysis to evaluating the association between tumour size and parenchymal patterns. Table 2 shows the results. Relative to the N1 pattern, the odds ratio of having a breast cancer measuring 30 mm or more, associated with the P2 pattern, was 2.22. The corresponding values for breast cancer of less than 15 mm and for breast cancer of 15 to 29 mm were 1.63 and 1.86, respectively.

Table 3 presents the results on grades 1, 2 and 3 invasive ductal NOS breast cancer associated with P2/DY mammographic parenchymal patterns, adjusted for tumour size. The odds ratio of having a grade 3 invasive ductal NOS breast cancer associated with P2/DY mammographic parenchymal pattern, adjusted for tumour size, was 2.03 (95% CI 1.13–3.62; $p = 0.016$).

Table 4 shows size-specific effects of dense parenchymal patterns on risk of grade 3 tumours. No increased risk of grade 3 tumours was observed for the smallest category, 1–14 mm. The odds ratio of having a grade 3 breast cancer of size 15–19 mm associated with the P2/DY mammographic parenchymal pattern was 3.46 (95% CI 1.12–10.68). Women with denser breast patterns (P2/DY) were 10 times more likely to be diagnosed with a grade 3 invasive ductal NOS breast cancer larger than 30 mm compared with those with non-dense patterns (N1/P1).

Table 5 presents the odds ratios of grade 3 invasive ductal breast cancer associated with mammographic parenchymal pattern, according to the detection mode (screen-detected or interval cancer). Women with very dense breast patterns (DY pattern) were at a significantly increased risk of having a grade 3 invasive ductal breast cancer diagnosed at either screening or in the interval between two screens (OR = 4.25, and 3.37 respectively). These findings were also observed in women with P2 patterns, but the risk magnitude was smaller (OR = 2.62 and 2.81, respectively) and the OR did not reach statistical significance.

DISCUSSION

In our study the increased risk of breast cancer associated with the dense P2 and DY patterns was concentrated in invasive ductal grade 3 cancers rather than in grade 1 and

Table 2

Invasive breast cancer odds ratios (OR) associated with mammographic parenchymal pattern, according to tumour size

Wolfe's parenchymal pattern	Tumour Size								
	1–14 mm			15–29 mm			30 + mm		
	Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
N1	46	1.00	–	41	1.00	–	9	1.00	–
P1	74	1.50	0.98–2.27	61	1.22	0.78–1.90	10	0.99	0.38–2.56
P2	171	1.63	1.11–2.36	180	1.86	1.27–2.71	52	2.22	1.00–4.93
DY	36	1.35	0.82–2.19	38	1.51	0.90–2.50	11	1.36	0.50–3.67
OR per step	1.13			1.24			1.24		
(95% CI)	(0.98–1.30)			(1.07–1.43)			(0.92–1.67)		
P for trend	0.08			0.004			0.14		

Table 3

Grades 1, 2, and 3 invasive ductal NOS breast cancer odds ratios (OR) associated with P2/DY mammographic parenchymal pattern, adjusted for tumour size

Wolfe's parenchymal pattern	Malignancy grade			
	Grades 1 & 2		Grade 3	
	OR	95% CI	OR	95% CI
N1+P1	1.00	–	1.00	–
P2+DY	1.31	1.04–1.66	2.03	1.13–3.62
OR per step	1.12	1.58		
(95% CI)	(0.99–1.27)	(1.17–2.12)		
P for trend	0.06	< 0.001		
		All tumours		
OR per step		1.19		
(95% CI)		(1.09–1.31)		
P for trend		<0.001		

2 cancers. This was independent of the tumour size. In addition, the P2 and DY patterns had stronger association with the larger tumour sizes than the smaller tumours. This was not observed in the study by Boyd et al. (14), which may be due to differences between the two studies, including the fact that the latter study uses clinically referred breast cancer patients and xeromammograms.

How consistent are these results with the two conflicting hypotheses (I) that the excess increased risk of grade 3 cancers is due to dedifferentiation or (ii) that the excess increased risk is due to an innate increased predisposition to grade 3 tumours in dense breasts? The observation that the relative risk of grade 3 tumours associated with dense patterns is extremely high (in excess of 10) in the large tumours, measuring 30 mm or more, compared to no increased risk at all in tumours of size 1–14 mm suggests that at least some of the excess is due to dedifferentiation as the tumour grows (Table 4). The fact that the association of dense patterns with increased risk of grade 3 tumours is stronger in interval cancers (Table 5) is also consistent with this observation.

There is also, however, some evidence from these results that the dense patterns increase the risk of cancers that are of grade 3 at inception. This is evidenced by the fact that the relative risks of grade 3 tumours after adjustment for size are similar to the unadjusted relative risks (Table 3), and by the high relative risk (3.46) of grade 3 cancers in tumours of size 15–19 mm (Table 4). Finally, although the increased risk of grade 3 tumours with dense patterns is stronger in interval cancers, it is definitely present, albeit slightly attenuated, in the screen-detected tumours, which under the dedifferentiation hypothesis would have had little time to dedifferentiate.

Thus, our results do not support either dedifferentiation alone or increased risk of grade 3 at tumour inception alone as explanations for the excess increased risk of grade 3 tumours in dense breasts. The results do not prove or disprove the existence of dedifferentiation, but they suggest that at least some of the excess risk is due to this phenomenon. They also clearly show that the excess risk cannot be entirely due to dedifferentiation of missed tumours. Interpretation of the results on histological grade is always complicated by the fact that grade 3 tumours will tend to be faster growing, and therefore larger, in any case. The results here at least strongly suggest that both phenomena, an increased risk of grade 3 tumours *ab initio* and a tendency to dedifferentiation in some tumours missed at screening, tend to occur in women with mammographically dense breasts.

This interpretation is consistent with the results of the Swedish Two-County trial, which showed that tumour dedifferentiation tended to occur before growth to 20 mm or more in the under 50 year-olds but tended to occur after growth to 20 mm+ in the over-50s (15, 16). Thus the highest risk of grade 3 being found in tumours measuring 30 mm+ is probably due to dedifferentiation of missed cancers, but there is some excess even in the <20 mm tumours, suggesting an increased risk of some cancers which are grade 3 at their inception. This is also supported by the fact that women with a DY mammographic pattern have a similarly increased risk of having either a screen-detected or an interval, grade 3 invasive ductal cancer compared to women with N1 patterns (Table 5).

Table 4

Odds ratios (OR) of having a Grade 3 invasive ductal NOS breast cancer associated with P2/DY relative to N1/P1 mammographic parenchymal pattern, within different tumour size

Tumour size	OR	95% CI
1–14 mm	1.07	0.39–2.87
15–19 mm	3.46	1.12–10.68
20–29 mm	1.72	0.62–4.77
30+ mm	10.09	1.27–79.93

Table 5

Grade 3 invasive ductal breast cancer odds ratios (OR) associated with mammographic parenchymal pattern, according to the detection mode

Wolfe's parenchymal pattern	Screen-detected		Interval	
	OR	95% CI	OR	95% CI
N1	1.00	–	1.00	–
P1	2.22	0.72–6.81	1.03	0.23–4.53
P2	2.62	0.93–7.32	2.81	0.75–10.47
DY	4.25	1.18–15.22	3.37	0.76–14.90
N1+P1	1.00	–	1.00	–
P2+DY	1.77	0.89–3.48	2.89	1.24–6.69

Several features of our study design should have minimized the possibilities of bias and increased the validity of our results. Bias in classification of mammographic appearance was avoided, as both the craniocaudal and mediolateral-oblique view mammograms of the opposite breast of the patients and the laterality-matched breasts of the controls were classified in a blinded manner, making it impossible for the radiologist to be influenced by the disease status of the women. In addition, the possibility of underestimating our risk estimates through using symptomatic controls referred for diagnostic evaluations was precluded since our controls were cancer-free women from screening centres.

In conclusion, our results support recent published findings (16) indicating that breast cancer is a progressive disease whose development can be arrested by screening, and that the point at which individual tumour progression is stopped may have a bearing on histological grade as well as on tumour size and lymph node status.

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