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Size, node status and grade of breast tumours: association with mammographic parenchymal patterns

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Abstract. A case-control study was designed to assess the association of mammographic parenchymal patterns with the risk of in-situ and invasive breast cancer. In addition, the relationship between tumour characteristics and mammographic patterns were also investigated. A total of 875 patients with breast cancer were selected and matched with 2601 controls. Mammographic parenchymal patterns of breast tissue were assessed according to Wolfe's classification, and statistical analysis was by conditional logistic regression. Relative to the N1 pattern, the odds ratios of having an invasive breast cancer associated with the P2 and DY patterns were 1.8 and 1.4, respectively. In addition, the odd ratios of having an invasive grade 3 breast cancer associated with the P2 and DY patterns were 2.8 and 3.9, respectively. Relative to the combined N1/P1 pattern, the odd ratios of having a breast cancer smaller than 14 mm, 15–29 mm, or larger than 30 mm associated with the combined high-risk P2/DY pattern (P2 + DY) were 1.2, 1.6, and 2.0, respectively. Finally, women with the P2/DY pattern were twice as likely to have a breast cancer which had already spread to the axillary nodes, compared to women with women with the N1/P1 pattern (odds ratios of 2.1 and 1.4, respectively). Our results confirm previous findings suggesting that mammographic parenchymal patterns may serve as indicators of risk for breast cancer. Our results also suggest that mammographic parenchymal patterns are associated with the stage at which breast cancer is detected.

Key words: Parenchymal patterns – Breast neoplasms – Mammography

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Introduction

Breast cancer is the most common malignancy among women in the Western society. Over the past decades it has become apparent that breast cancer incidence rates are increasing steadily [1, 2]. Based on evidence from studies including randomised trials [3, 4, 5, 6], mammography is recognised as the most sensitive screening modality for the detection of breast cancer. In addition, screening with mammography is well accepted as the most effective means of early detection of breast cancer, and its use has been associated with reduction in breast cancer mortality among women aged 40 years and older [4, 7, 8]. In addition to early detection of breast cancer, mass screening programmes offer an opportunity to study aspects of mammographic appearances other than purely diagnostic features and their effect on risk of subsequent cancers. Of particular interest are the mammographic parenchymal patterns and related measures of radiographic density of breast tissue.

There is steadily accumulating evidence that the mammographic pattern of the breast is an important risk factor for breast cancer. 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 [9]. Typically the radiographic appearance of a normal cancer free breast tissue represents a continuum of breast types ranging from fatty breast that is radiologically lucent (darker in appearance) to those displaying extensive regions of density (lighter in appearance). These variations in mammographic density of the breast tissue are known as the parenchymal pattern of the breast [10].

The two most commonly used classifications of mammographic parenchymal pattern are the Wolfe's grade scale [11, 12] and a coarse quantitative scale of the proportion of the breast composed of dense tissue-percentage breast density [10, 13]. A relationship between mammographic parenchymal patterns and the risk of breast cancer was first proposed by Wolfe [11, 12],

whose classification consists of four patterns of breast parenchyma, which Wolfe named N1, P1, P2 and DY. It is postulated that the four patterns – N1, P1, P2 and DY– are associated with a stepwise increase in breast cancer risk with the highest risk observed in P2 and DY patterns. Recently, Tabar's modification of Wolfe's system was described [14, 15] and this is based on anatomic mammographic correlations rather than simple pattern reading as in the Wolfe system [14, 15]. This classification ranged from patterns I through V, where Tabar patterns I, II and III are thought to be low-risk patterns, while IV and V are high-risk patterns. Presently there is no consensus on which method to use when classifying mammographic parenchymal patterns to assign risk of breast cancer.

To date, most studies that have evaluated the association between parenchymal pattern and breast cancer risk differ in their conclusions. Methodological differences in design and analysis are likely to be partly responsible for the broad range of reported findings [16]. Despite these differences, however, the relative risk estimates are consistent in most studies, with an approximately three-fold increase in risk for women with radiologically dense breasts compared with those with normal or fatty breasts that are radiologically lucent [3, 16, 17].

Despite the level of evidence of an independent association with breast cancer, mammographic density is perhaps the most undervalued risk factor in studies investigating the causes of breast cancer. The radiological appearance of high-risk patterns suggests that the detection of small cancers would be difficult. Frequent screening of such women might be of value, especially in this study population in which the prevalence of high-risk patterns is high. Moreover, since there are no prescribed measures that a woman can employ to prevent the occurrence of breast cancer, early detection remains the most effective means of reducing the burden of the disease in terms of morbidity and mortality [16].

Selection of high-risk groups for breast cancer could be used to reinforce and possibly enhance the effectiveness of breast cancer screening programmes [16]. A possible criterion by which to select such groups is the mammographic parenchymal pattern. In this paper we report on a nested case–control study within a screening programme. We assessed the effects of mammographic parenchymal patterns on the risk of in situ and invasive breast cancer. In addition, we investigated the relationship between tumour characteristics and mammographic patterns.

Material and methods

Study population

Study subjects were part of a cohort of women who attended the prevalence screening round at either Norwich Breast Screening Programme or Cambridge and Huntingdon Breast Screening Programme between April 1989 and December 1993, and between March 1991 and March 1995, respectively. Detailed description of this cohort has been published elsewhere [18].

Nested case–control study on breast cancer

Subjects eligible for this study included all those newly diagnosed as having breast cancer between April 1989 and September 1996. This included 973 women identified with histologically confirmed unilateral breast cancer (ICD-9 174) either at the prevalence screening round, at the first incident screening round, or between the two screenings, and for whom readable mammograms were still available. Additional information regarding case selection is presented elsewhere [18]. A total of 875 patients were thus eligible, of whom 747 had invasive and 128 in situ cancers.

Controls were defined as women free of breast cancer who attended either screening centre. 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). When more than three controls were available for a given case, three were selected at random. We selected 2601 controls.

We examined the screening records of each woman. Both medio-lateral and cranio-caudal views of the mammograms from the unaffected breast of the cases and of the side-matched breasts of controls were identified. They were reviewed independently by two of the authors: a radiologist with experience in assessing mammographic features of breast tissue (R. W.) and a breast physician with previous training in reading the mammographic pattern of breast tissue (E.S). R. W. carried out the review without knowledge of the subject's status and without access to information from any other data on the women. This was not possible for E. S. since she conducted the data collection. The mammographic parenchymal patterns of breast tissue were assessed independently according to Wolfe's classification [11, 12] by the two radiologists. The pathological variables of interest included the histological type, malignancy grade, axillary node status and size of lesion (in millimetres). We recorded the size of the invasive component in cases in which invasive and in situ cancers co-existed. These were obtained by review of the pathology reports.

In this contribution we report the results for invasive and in situ cancers separately to evaluate the relationship between Wolfe's mammographic parenchymal patterns and breast cancer risk. When assessing the association between parenchymal patterns and breast cancer risk according to malignancy grade, tumour size and axillary node status, we present our findings only for invasive cancers. Presented here are the results of the analyses based on the film reading (R. W.), as the agreement between the two readers was 95 % on the four pattern categories, and 99 % when the P2 and DY categories were combined.

Table 1. Distribution of mammographic parenchymal patterns (percentages)

	Invasive cases		In situ cases		Overall cases	
	Patients	Controls	Patients	Controls	Patients	Controls
N1	13	19	14	18	13	19
P1	20	22	16	25	19	23
P2	55	46	57	48	56	46
DY	12	13	13	9	12	12
N	747	2221	128	380	875	2601

Table 2. Odds ratios of breast cancer (invasive and in situ) by mammographic parenchymal pattern (95% CI)

	Total		Screen-detected cancers only	
	Invasive	In situ	Invasive	In situ
N1	1.0	1.0	1.0	1.0
P1	1.3 (0.9–1.7)	0.8 (0.4–1.6)	1.4 (1.0–1.9)	0.9 (0.4–2.0)
P2	1.8 (1.4–2.3)	1.5 (0.8–2.8)	1.7 (1.2–2.3)	1.7 (0.8–3.1)
DY	1.4 (1.0–2.0)	2.0 (0.8–4.3)	1.1 (0.7–1.7)	1.7 (0.6–4.1)
N1 + P1	1.0	1.0	1.0	1.0
P2 + DY	1.5 (1.2–1.8)	1.8 (1.2–1.8)	1.3 (1.2–1.8)	1.7 (1.1–2.6)

Statistical methods

Results were modelled by 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 [19]. Statistical analysis was performed using the STATA statistical package (Stata Corporation, Tex., USA).

Results

The distribution of cases and controls by Wolfe's mammographic parenchymal pattern is shown in Table 1. The most common pattern was the P2 pattern, with 56% of cases and 46% of controls showing this pattern. There was no substantial difference in parenchymal pattern distribution between patients with invasive and those with in situ cancers.

Table 2 presents the odds ratios for the association between Wolfe's mammographic parenchymal pattern and breast cancer risk in women, with invasive and in situ cancers shown separately. Relative to the N1 pattern, the odds ratios of invasive breast cancer associated with the P2 or DY patterns were 1.8 and 1.4, respectively. Analysis of the total study population and of the screen-detected set, which includes prevalent and incident cases, was also performed, and similar results were obtained.

To examine the relationship between mammographic parenchymal patterns and the risk of rapidly progressing tumours we carried out a subgroup analysis on the invasive cancers grouped according to the malignancy grade. Table 3 shows the results. The odd ratios of having an invasive grade 3 breast cancer associated with the P2 and DY patterns were 2.8 and 3.9, respectively. The increased risk associated with the P2 and DY patterns is almost exclusively for the most malignant histological grade.

We extended our analysis to evaluating the association between tumour size/axillary node status and parenchymal patterns. Tables 4 and 5 show the results. Relative to N1 pattern, the odds ratios of having a breast cancer 30 mm or larger, associated with the P2 pattern, was 2.2. The corresponding value for breast cancer 15–29 mm in size was 1.9. Relative to the combined N1/P1 pattern, the odds ratios of having a breast cancer 15–29 mm or 30 mm or larger, associated with the combined high-risk P2/DY pattern are 1.6 and 2.0, respectively.

Women with the high-risk P2/DY pattern were twice as likely as those with the N1/P1 pattern to have breast cancer that had already spread to the axillary nodes. Women with a P2/DY pattern were more likely to develop a node-positive breast cancer than a node-negative one (odds ratios 2.1 and 1.4, respectively). Relative to the N1/P1 pattern, there was a significantly higher correlation of grade 3 cancers, cancers 30 mm or larger (also those 15–29 mm), and node-positive cancers with patterns P2 and DY.

Discussion

In our study 68% of cancer patients and 58% of controls were classified as showing the P2/DY mammographic pattern. These results are consistent with reported findings using Wolfe's classification criteria, which range from 30% to 70% [16, 20, 21]. The higher prevalence of P2/DY breasts in our population needs explanation. One possible explanation is hormone replacement therapy (HRT). In the late 1970s very few women used HRT. Although we do not have complete data on HRT, a subset of our study population had reported HRT use in another study. In this subset 35% were users of HRT. The Wolfe P2 pattern was the most frequent amongst both patients and controls. The prin-

Table 3. Odds ratios grades 1, 2, and 3 invasive breast cancer by mammographic parenchymal pattern (95 % CI)

	Grade 1		Grade 2		Grade 3	
	n	OR	*n*	OR	*n*	OR
N1	30	1.0	32	1.0	8	1.0
P1	35	0.9 (0.5–1.7)	63	1.8 (1.1–2.9)	18	1.6 (0.6–4.0)
P2	124	1.7 (1.1–2.7)	143	1.7 (1.1–2.7)	57	2.8 (1.2–6.2)
DY	23	1.1 (0.5–1.9)	31	1.5 (0.8–2.7)	18	3.9 (1.4–10.2)
N1 + P1	65	1.0	95	1.0	26	1.0
P2 + DY	147	1.6 (1.1–2.2)	174	1.2 (0.8–1.6)	75	2.2 (1.2–3.7)

Table 4. Odds ratios of breast cancer (invasive cancers only) by mammographic parenchymal pattern and tumour size (95 % CI)

	1–14 mm		15–29 mm		30 + mm	
	n	OR	*n*	OR	*n*	OR
N1	46	1.0	41	1.0	9	1.0
P1	74	1.5 (1.0–2.3)	61	1.2 (0.7–1.9)	10	0.9 (0.3–2.6)
P2	171	1.6 (1.1–2.4)	180	1.9 (1.2–2.7)	52	2.2 (1.0–4.9)
DY	36	1.3 (0.8–2.2)	38	1.5 (0.9–2.5)	11	1.4 (0.5–3.7)
N1 + P1	120	1.0	102	1.0	19	1.0
P2 + DY	207	1.2 (0.9–1.6)	218	1.6 (1.2–2.1)	63	2.0 (1.1–3.7)

cipal interest in mammographic features of the breast arises from their possible use in breast cancer screening programmes for determining the frequency of screening and in the identification of individuals at higher risk of breast cancer.

Our study provides additional evidence that mammographic parenchymal patterns are indicators of risk for the subsequent development of breast cancer. The relative risk estimates shown in Table 2 are in agreement with the findings of others [5, 11, 12, 13, 16, 17, 21, 22].

As expected, grade 3 invasive cancers were consistent in their relationship to denser patterns (Table 3). For instance, women with the P2 or DY pattern were more likely to have a grade 3 tumour than one of grade 1 or 2, and the greatest proportion of those with the N1 or P1 pattern had tumours characterised as either grade 1 or grade 2 tumours. It could be argued that the higher proportion of grade 3 tumours in women with denser breasts is due to the fact that the radiological appearance of the high-risk denser patterns renders difficult the detection of small cancers. In addition, these high-risk patterns may be associated with more rapidly progressing tumours.

It might also be expected, with regard to tumour characteristics, that individuals with the poorer prognosis [23], those with tumours larger than 14 mm, those with positive nodal status, and those with grade 3 tumours should all be found in greater proportion amongst women with denser patterns and in cancers detected between two screenings. In our study the combined high-risk P2/DY pattern had a definite association with the larger tumour sizes than the combined N1/P1 patterns, which were associated with the smaller tumours (Table 4). The same relationship was found with the axillary node involvement, where the node-positive tumours were found to be associated with high-risk P2/DY pattern (Table 5).

Another study that has investigated the association between tumour diameter and axillary node involvement found neither tumour size nor axillary lymph node involvement to be associated with any particular mammographic pattern [24]. However, this study is not comparable to the current study as there are methodological differences between the two: namely, it uses clinically referred breast cancer patients and xero-mammograms.

It should be noted that the increased risk of large, node positive or grade 3 tumours associated with the high-risk patterns may be a product of a poorer sensitivity of screening in breasts with a denser (i.e. high-risk) pattern. If the sensitivity were indeed lower, one would expect that a higher proportion of the tumours would be missed at screening and would therefore have more time to grow larger, invade the regional lymph nodes and possibly de-differentiate [25].

Several features of our study design should have minimised the possibilities of bias and increased the validity of our results. Bias in classification of mammographic appearances was avoided as both the cranio-caudal and mediolateral-oblique view mammograms of the opposite breast in patients and the side-matched breasts of controls were classified in a blinded manner, making it impossible that the radiologist was influenced by the disease status of the women. In addition, possibilities of underestimating our risk estimates by use of symptomatic controls referred for diagnostic evaluations was excluded since our controls were cancer-free women from screening centres.

The results from our study indicate that mammographic parenchymal patterns may serve as indicators of risk for breast cancer. The findings also suggest that mammographic parenchymal patterns are associated with the stage at which breast cancer is detected. The above-mentioned issues have implications for future

Table 5. Odds ratios of breast cancer (invasive cancers only) by mammographic parenchymal pattern and axillary node status

	Node negative		Node positive	
	n	OR	*n*	OR
N1	54	1.0	18	1.0
P1	84	1.4 (0.9–1.9)	21	0.9 (0.4–1.8)
P2	202	1.7 (1.2–2.2)	110	2.1 (1.2–3.7)
DY	44	1.4 (1.0–2.3)	16	1.2 (0.5–2.6)
N1 + P1	138	1.0	39	1.0
P2 + DY	246	1.4 (1.1–1.7)	126	2.1 (1.3–3.1)

studies on breast cancer epidemiology in the hope of expanding our knowledge to continue to make progress in understanding the aetiology and mechanisms of the disease.

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References

1. Quinn M, Allen E (1995) Changes in incidence of and mortality from breast cancer in England and Wales since introduction of screening. BMJ 33: 1391–1395
2. Parkin DM, Laara E, Muir CS (1988) Estimates of the worldwide frequency of sixteen major cancers in 1980. Int J Cancer 4: 184–197
3. Miller AB (1988) Screening for breast cancer: a review. Eur J Cancer 24: 49–53
4. Tabar L, Gad A, Holmberg L H, et al (1985) Reduction in breast cancer mortality by mass screening with mammography: first results of a randomised trial in two Swedish counties. Lancet I:829–832
5. Kato I, Beinart C, Bleich A, et al (1995) A nested case-control study of mammographic patterns, breast volume and breast cancer (New York, NY, United States). Cancer Causes Control 6: 431–438
6. Brekelmans CT, Westers P, Faber JA, et al (1996) Age specific sensitivity and sojourn time in a breast cancer screening programme (DOM) in the Netherlands: a comparison of different methods. J Epidemiol Community Health 50: 68–71
7. Shapiro S, Venet W, Strax P, Venet L, Roeser R (1982) Ten-to-fourteen-year effect of screening on breast cancer mortality. J Natl Cancer Inst 69: 349–355
8. Hendrick RE, Smith RA, Rutledge JH, Smart CR (1997) Benefit of screening mammography in women aged 40–49: a new meta-analysis of randomized controlled trials. J Natl Cancer Inst Monogr 22: 87–92
9. Byrne C, Schairer C, Wolfe J, et al (1995) Mammographic features and breast cancer risk: effects with time, age and menopause. J Natl Cancer Inst 87: 1622–1629
10. Byng JW, Boyd NF, Little L, et al (1996) Symmetry of projection in the quantitative analysis of mammographic images. Eur J Cancer Prev 5: 319–327
11. Wolfe JN (1976) Breast patterns as an index of risk for developing breast cancer. AJR Am J Roentgenol 126: 1130–1139
12. Wolfe JN (1976) Risk for breast cancer development determined by mammographic parenchymal patterns. Cancer 37: 2486–2492
13. Brisson J, Merletti F, Sadowsky NL, et al (1976) Mammographic features of breast and breast cancer risk. Am J Epidemiol 115: 428–437
14. Gram IT, Funkhouser E, Tabar L (1997) The Tabar classification of mammographic parenchymal patterns. Eur J Radiol 24: 131–136
15. Gram IT, Funkhouser E, Tabar L (1995) Reproductive and menstrual factors in relation to mammographic parenchymal patterns among perimenopausal women. Br J Cancer 71: 647–650
16. Saftlas AF, Szklo M (1987) Mammographic parenchymal patterns and breast cancer risk. Epidemiol Rev 9: 147–171
17. Waard F de, Rowbach JJ, Colletle HJA, et al (1984) Breast cancer risk associated with reproductive factors and breast parenchymal patterns. J Natl Cancer Inst 72: 1277–1282
18. Sala E, Warren R, McCann J, Duffy S, Day N, Luben R (1998) Mammographic parenchymal patterns and mode of detection: implications for the breast screening programme. J Med Screen 5: 180–185
19. Breslow NE, Day NE (1980) Statistical methods in cancer research, vol 1. The analysis of case-control studies. IARC, Lyon
20. Tabar L, Dean PB (1982) Mammographic parenchymal patterns: risk indicator for breast cancer? JAMA 247: 185–189
21. Ciatto S, Zappa M (1993) A prospective study of the value of mammographic patterns as indicators of breast cancer risk in a screening experience. Eur J Radiol 117: 122–125
22. Warner E, Lockwood G, Math M, et al (1992) The risk of breast cancer associated with mammographic parenchymal patterns: a meta-analysis of published literature to examine the effect of method of classification Cancer Detect Prev 16: 67–73
23. Duffy SW, Tabar L, Fagerberg G (1991) Breast screening, prognostic factors and survival – results from the Swedish-two county study. Br J Cancer 64: 1133–1138
24. Boyd NF, O'Sullivan B, Campbell JE, et al (1982) Mammographic patterns and bias in breast cancer detection. Radiology 143: 671–674
25. Tabar L, Fagerberg G, Chen HH, Duffy SW, Gad A (1996) Tumour development, histology and grade of breast cancers: prognosis and progression. Int J Cancer 66: 413–419